

Management of Safety Information from Clinical Trials

Report of CIOMS Working Group VI



Geneva 2005

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Geneva, April 2005

Juhana E. Idänpään-Heikkilä, MD. PhD
Secretary-General, CIOMS

Dedication

This work is dedicated to the many thousands of patients and other volunteers who generously participate in clinical research programs so vital for the development and advancement of medicines.

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Vision

Patients and prescribers expect approved medicines to be “safe and effective.” The goal of those who produce and regulate proprietary medicinal products is to ensure that this expectation is met. This requires that clinical trials be planned and performed to provide good evidence that tested medicines are effective and that patients can be reassured that the benefits outweigh the risks, both during the development process and in general use.

This report has implications for all stakeholders in clinical medicinal research:

- 1) patients and other volunteers
- 2) investigators and their site staff
- 3) ethics review committees
- 4) data and safety monitoring boards
- 5) drug regulatory authorities and the public health community
- 6) pharmaceutical companies and other clinical research sponsors

The vision of the CIOMS VI Working Group is that this report will enhance awareness of the ethical and technical issues associated with safety in clinical trials and point out the need for increased care and scrutiny in the conduct of research. It is also hoped that this work will advance the methodology for collecting, analysing, evaluating and reporting information on product safety ascertained in clinical trials, and help to set standards in these areas. Establishing and maintaining standards by all involved groups will benefit all participants in trials and improve public health for those who take medicines.

Pharmacovigilance has traditionally focused on detection and evaluation of signals in the post-approval environment in order to secure early detection of new adverse reactions or patient subgroups of exceptional sensitivity, and to introduce measures to manage those risks.

However, we believe that there is a need not only to incorporate newer approaches for managing safety information in the clinical trial setting, but also to adapt the methods and tools used in post-approval pharmacovigilance to the early and late stages of pre-approval development of medicinal products. It is our vision that the practical approaches provided in this report will aid these processes and will enable a more seamless

transition in conducting high quality pharmacovigilance from the development stage to the post-approval period. We also hope that this work will stimulate research in several unresolved areas.

Finally, we recognize that new regulations have recently been enacted in the EU and are pending elsewhere, such as in the US. It is hoped that this book will stimulate the regulators to reconsider aspects of regulations pertaining to our proposals; we believe that our suggestions can help to improve the ability to generate and analyze useful safety data and to protect trial participants.

Preface

Since 1986, when they began a series of projects dedicated to important drug safety issues, the CIOMS Working Groups on drug safety have been recognized for creating the theoretical platforms and pragmatic suggestions to advance the debates leading to harmonization of international pharmacovigilance practices. The initiatives over the years, identified as CIOMS Working Groups I, IA, II, III, IV and V, have resulted in six major published reports.¹ The nature of their membership, senior drug safety officials from many major regulatory agencies and the regulated pharmaceutical industry, and their *modus operandi* as a “think tank” seeking practical solutions to important problems, have facilitated their unique contributions. All members have served less as representatives of any single organization or interest and more as motivated colleagues, with day-to-day responsibility in the drug safety field. All shared a commitment to think beyond their local practices even if such thinking were in disagreement with current rules and regulations, in order to optimize drug safety procedures, particularly in an international context. Although the Working Groups did not – indeed could not – develop regulations, its work has always been intended to inform and encourage those with rule-making responsibilities. Gratifyingly, many of the recommendations have been incorporated into regulations, not only in the countries of the participating regulators, but elsewhere as well.

The CIOMS I Working Group introduced definitions, criteria and a standard form (CIOMS I Form) for international reporting of medically important (“serious”) adverse drug reactions (ADRs) to marketed products. It also served as a model for the development of the International Conference on Harmonization (ICH) Guideline E2A on expedited ADR case reporting for clinical trials.

The result of the CIOMS II deliberations was a set of proposed standards for the format, content and frequency of periodic safety update reports (PSURs) which has been adopted by many regulatory authorities.

¹ *International Reporting of Adverse Drug Reactions* (CIOMS I) (1990); *International Reporting of Periodic Drug-Safety Update Summaries* (CIOMS II)(1992); *Guidelines for Preparing Core Clinical-Safety Information on Drugs*, First Edition (1995) (CIOMS III) and Second Edition, *Including New Proposals for Investigator’s Brochures* (1999)(CIOMS III/V); *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals* (CIOMS IV)(1998); *Current Challenges in Pharmacovigilance: Pragmatic Approaches* (CIOMS V)(2001). All published by the Council for International Organizations of Medical Sciences, Geneva.

It also formed the basis for the ICH Guideline on periodic reporting, E2C,² adopted in 1996 and subsequently implemented internationally. A recently adopted addendum to ICH E2C³ represents further refinement of the harmonization concepts espoused by the CIOMS V Working Group.

Coincident with CIOMS II and in recognition of the need for more efficient, automated techniques to document and report ADRs to regulators, the CIOMS IA subgroup worked on a proposal for a harmonized format for electronic submissions. The CIOMS IA recommendations were not published but formed the basis for the ICH Guideline E2B (Data Elements for Transmission of Individual Case Safety Reports, 1997).

The CIOMS III Working Group concentrated on best practices for applying the concept of “company core safety information” (CCSI) introduced in CIOMS II. The Working Group developed a set of what have conveniently been referred to as “good safety information/labeling practices” for post-approval drug safety data, including practical guidance on determining when the threshold has been reached for adding an adverse reaction to the CCSI. In the CIOMS III/V report, the second edition of the CIOMS III report, the concepts were extended to the pre-approval environment by recommending use of Development Core Safety Information (DCSI).

One of the most important aspects of post-marketing safety surveillance is the identification and analysis of new, medically important findings that might influence the use of a medicine. In recognizing that there existed at the time no guidance on a systematic approach for handling the emergence of a major safety issue, especially one that might lead to important regulatory action, CIOMS IV developed its proposals for approaches to comparative benefit-risk evaluation, analysis of options for action, and good decision making practices.

As acknowledged in the reports by each of the Working Groups, unresolved and un-addressed issues remained. Thus was born the CIOMS V Working Group which focused on several difficult aspects of day-to-day pharmacovigilance work that affect the management and interpretation of safety data. The proposals and their rationale are the subject of the CIOMS V report which has become a regular source of guidance to industry professionals engaged in the day-to-day management of safety reporting.

² ICH E2C *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*, Step 5 as of November 1996. (See <http://www.ich.org>)

³ Addendum to ICH E2C: *Periodic Safety Update Reports for Marketed Drugs*, Step 5 as of February 2003. (See <http://www.ich.org>)

Proposals emanating from CIOMS Working Groups I through V were principally focused on post-marketing surveillance regulations and activities. These are described in greater detail in published papers.^{4,5} The CIOMS Working Group reports themselves can be ordered by sending a request to cioms@who.ch.

The current report, that of the CIOMS VI Working Group, represents a shift from the management of post-marketing safety information, which relies heavily on spontaneous reports, to the management of clinical trial information, starting from the earliest clinical trials and extending to the post-marketing environment. The CIOMS VI Working Group also represents an expansion in membership to include regulatory, industry and academic representation with experience in the conduct of clinical trials and to include representatives from less developed regions of the world. This book introduces proposals for enhancing the collection, analysis, evaluation, reporting and overall management of safety information from clinical trials. It also discusses the importance of sponsors' having a systematic approach to managing risk during development, taking into account non-clinical as well as clinical data. CIOMS VI is not intended to be a reiteration of other available guidances and guidelines on these subjects^{6,7,8,9,10} or a rehash of closely related recent work.^{11,12} Rather, the proposals in this document should be considered along with the principles established in those authoritative documents.

The views and recommendations in this book are those of the CIOMS VI Working Group as a whole, generally reached through a consensus process, or in some cases by a majority vote. They do not necessarily represent the views of the participants' sponsoring organizations.

⁴ Castle, W. Overview of the CIOMS Pharmacovigilance Working Group. *Regulatory Affairs Focus*, April 2000 (Regulatory Affairs Professionals Society; see www.raps.org)

⁵ Tsintis, P. and LaMache, E. CIOMS and ICH Initiatives in Pharmacovigilance and Risk Management. Overview and Implications. *Drug Safety*, 27 (8):509-517, 2004

⁶ ICH E6 *Good Clinical Practice: Consolidated Guideline*, Step 5 as of May 1996. <http://www.ich.org>

⁷ ICH E9 *Statistical Principles for Clinical Trials*, Step 5 as of February 1998. <http://www.ich.org>

⁸ ICH E3 *Structure and Content of Clinical Study Reports*, Step 5 as of November 1995. <http://www.ich.org>

⁹ ICH E2A *Clinical Safety Data Management : Definitions and Standards for Expedited Reporting*, Step 5 as of October 1994. <http://www.ich.org>

¹⁰ *Guideline for the Format and Content of the Clinical and Statistical Section of an Application*, US FDA Center for Drug Evaluation and Research, July 1988. <http://www.fda.gov/cder/guidance>

¹¹ *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, and Premarketing Risk Assessment*. US Food and Drug Administration, March 2005. (See <http://www.fda.gov/cder/guidance/6357fml.htm> and <http://www.fda.gov/cder/guidance/6359OCC.htm>), respectively.

¹² ICH Guideline E2E. *Pharmacovigilance Planning (PvP)*, Step 4 as of November 2004. (See <http://www.ich.org>)

It is recognized that some of the proposals, in particular those found in Chapter 7, may be in conflict with existing regulations in various countries and in newly enacted legislation in Europe. However, it is the hope of the CIOMS VI Working Group that its recommendations may stimulate regulators to rethink some aspects of their regulations in terms of the practicality of implementation and the usefulness of the safety information provided to stakeholders. This book is primarily aimed at providing guidance to sponsors of clinical trials. The hope is that these proposals, once adopted by regulatory authorities, will enhance our ability to protect patient well-being and optimize the development and use of new medicines.

I

Introduction and Overview

a. Rationale for the CIOMS VI Project

Medical research on human subjects is capable of providing significant advances to benefit individuals and public health. The universally accepted motif for such endeavors is that all such research be designed to create important scientific knowledge, that it maximize the potential benefits to the subjects, and, most importantly, it minimize their risks. Thus, although this report focuses on the technical, medical and regulatory aspects of “drug safety” during clinical research, the foundation for all these activities must always be the respect for the rights and welfare of clinical trial participants. Some harm to individual patients or subjects may be considered tolerable – for after all, it is the proper balance between benefits and risks that drives not only the research process but the use of any marketed medicine.^{1,2}

Regulations and guidelines in most countries govern the conduct and requirements of clinical trial sponsors and, increasingly, investigators and their institutions. The collection, monitoring, and regulatory reporting of clinical safety information on trial subjects feature prominently in such regulations, usually in connection with Good Clinical Practice (GCP) requirements. In many cases, regulations pertaining to clinical trials have been based on or influenced by guidelines established under the ICH process. Among the most important are: timing of non-clinical studies in relation to clinical exposure (ICH M3), extent of population exposure to assess safety in a development program (E1), expedited regulatory safety reporting (E2A), presentation of safety data in clinical study reports (E3), dose response information (E4), ethnic factors (E5), good clinical practice (E6), studies in special populations (geriatrics, E7 and pediatrics, E11), statistical principles (E9), and choice of active or placebo control group(s) (E10).³

¹ For purposes of this report, the term medicine or drug refers to prescription or over the counter products, whether they are “drugs”, vaccines, or biotechnology products for prevention, prophylaxis or treatment of a disease or medical condition, and possibly for use in diagnosis.

² The benefit-risk relationship is commonly imprecisely summarized by referring to a product as “safe and effective,” a description that may be misleading. The words “safety” and “safe” in common usage infer the presence or absence of harm. The Working Group believes there is an erroneous perception, especially by the public, that once a drug reaches the market it is, or should be, risk-free. In clinical trials or in general product use, patients are monitored for the presence or absence of harm (not “safety”), and the data are assessed to evaluate the probability of such harm, in other words the risk associated with the treatment. Patients and trial subjects will have different “acceptable” levels of harm or risk, and in that sense risk and harm are relative concepts to the individual.

³ For full details and access to specific guidelines, see: <http://www.ich.org>

Historically, the CIOMS Working Groups on drug safety have concentrated on post-approval pharmacovigilance⁴ while recognizing that pharmacovigilance as a discipline and a science should be regarded as a continuum throughout the life of a product, beginning with exposure in humans during the first Phase 1 trials.⁵ Nevertheless, safety functions for new drug development and post-marketing are often separated, even to the point of maintaining different departments and responsibilities within some companies and most regulatory bodies. Although the separation of pre- and post-marketing clinical safety departments and responsibilities has been a standard model for drug regulation, it may introduce an unnecessary complication into the discipline of pharmacovigilance. There has been a trend in recent years toward more integration of the two organizational divisions. Even with organizational separation, the conduct of pharmacovigilance is best accomplished with close functional collaboration between the groups. One goal of this CIOMS VI project is to help bridge the gap between pre- and post-approval activities to understand and manage risk.

Although general responsibilities for managing drug safety issues are usually covered in GCP regulations or guidances, the details and increasing complexity of the field would benefit from the development of more specific, internationally based Good Pharmacovigilance Practices (GPP), something beyond the scope of this Working Group's efforts.

More than 130 pharmaceutical products have been withdrawn from various markets over the past 40 years because of actual or perceived safety concerns. An estimated third were withdrawn within two years of launch and half within 5 years.⁶ The most frequent problems are reported to be associated with hepatic, hematological and cardiovascular complications. It is unclear whether such problems could have been foreseen during the drugs' development and, if recognized early, managed sufficiently to preclude the harm done to individual patients and to establish a favorable benefit-risk profile for a specified target population. However, many lessons have been learned from these past experiences, among them the need to have a more

⁴ The term "pharmacovigilance" is not always used consistently among its practitioners. For example, there is some debate as to whether it should be used for pre-approval safety. We recommend that it should be. Detailed discussion on terminology and definitions for this and other concepts are covered in Appendix 1.

⁵ For the most recent CIOMS report, see "Current Challenges in Pharmacovigilance: Pragmatic Approaches," Report of CIOMS Working Group V, CIOMS, Geneva, 2001.

⁶ For example, see Fung, M., Thornton, A., Mybeck, K., Wu, J. H., Hornbuckle, K. and Muniz, E., Evaluation of the Characteristics of Safety Withdrawal of Prescription Drugs from Worldwide Pharmaceutical Markets – 1960 to 1999. *Drug Information Journal*, 35: 293-317, 2001 and Friedman, M. A., Woodcock, J., Lumpkin, M. M., Shuren, J. E., Haas, A. E. and Thompson, L. J., The Safety of Newly Approved Medicines. Do Recent Market Removals Mean there is a Problem? *J. Am. Med. Assoc.*, 281:1728-1734, 1999.

systematic and comprehensive approach to safety issues during the development process and beyond. Identifying and managing real or potential safety problems as early as possible during drug development might therefore be expected to help avoid premature termination of a development program and thereby prevent the loss of therapies whose benefits might indeed outweigh the risks when used appropriately in the right patients. Similarly, a systematic approach will also enable identification at the earliest possible time of a product that does *not* meet an acceptable benefit-risk profile, and therefore allow for cessation of the program with minimal risk to trial subjects.

Recent concerns have been raised by clinical researchers on possible inadequacies in adverse event reporting and on the interactions between parties with clinical safety oversight responsibilities.⁷ Some of their concerns and suggestions include: valid assessment of individual AE cases needs more information, including on efficacy, than that contained in the case itself; the use and roles of data and safety monitoring boards (DSMBs) need improvement, especially vis-à-vis their relationship with institutional ethics committees/institutional review boards (IECs/IRBs) (e.g., they should provide the ethics committees with a periodic summary on whether or not the safety and other parameters established for the trial are as expected). Many problems faced by IECs/IRBs were also identified, such as their inability to evaluate the overwhelming number and types of expedited reports in isolation from previous data; lack of access to data from sites other than their own to help place their data in proper perspective; confusing regulatory terminology; and often a focus on regulatory compliance at the expense of ongoing benefit-risk assessment at the local site.

From a different perspective, a review of safety reporting and reasons for patient withdrawal for toxic effects during randomized trials has found variability and inadequacies across several medical areas, with a call for improved standards.⁸

Although there are some important differences between pre-marketing and post-marketing safety monitoring and management, there is a growing realization that there should be a much stronger and closer relationship

⁷ Morse, M. A., Califf, R. M. and Sugerman, J., Monitoring and Ensuring Safety During Clinical Research, *J. Am. Med. Assoc.*, 285: 1201-1205, 2001 and a response to the article – Burman, W. J. and Schooley, R. The Role of Local Institutional Review Boards in Protecting Human Research Subjects. *ibid.*, 285: 2713, 2001.

⁸ Ioannidis, J. P. A. and Lau, J., Completeness of Safety Reporting in Randomized Trials. An Evaluation of 7 Medical Areas. *J. Am. Med. Assoc.*, 285: 437-443, 2001, and commentary on the publication, Safety Reporting in Clinical Trials, *ibid.*, 285: 2076-2078, 2001.

between them, for among other reasons, to learn from and use the tools and methodologies applied in the two environments. This same observation has been forcefully made by Vandenbroucke, who asserts that those who conduct randomized trials and pharmacoepidemiologists are needlessly “worlds apart” in their approaches to understanding drug benefits and harms.⁹ This connection is especially important for development programs on new uses or dosage forms of products already on the market. In an age when the “risk management” of medicines has almost become a discipline on its own, the development process must incorporate planning for managing risks early in a product’s life, and well before launch. Such planning will allow the transition from development to authorized use to be based on a systematic and comprehensive pharmacovigilance plan that involves not only clinical safety specialists (including pharmacoepidemiologists), but also toxicologists, clinical pharmacologists, statisticians, and clinicians.¹⁰

Although existing regulations form the framework for how clinical trial safety data should be monitored and reported to authorities and other involved parties, there is a considerable lack of consistency and completeness in the treatment of these issues. This is partly due to cultural and historical influences that have an impact on individual country requirements. There also are many important topics not even covered within regulations or supporting guidelines that perhaps should be, and it is our goal to stimulate discussion of these topics in the hope that consensus may be reached for change.

It is important to remind the reader that this book presents proposals and recommendations that may or may not be in agreement with current regulations and guidance from health authorities. Continued adherence to current requirements and guidances is obviously essential unless and until our recommendations are officially recognized and implemented.

All the principles and practices recommended throughout this report are summarized in Chapter 8 (Summary of Concepts and Proposals), which the reader may wish to consult for a convenient overview of the main points. We also believe that it would be very beneficial for the readers to familiarize themselves with the Glossary (Appendix 1), especially the introductory explanations.

⁹ Vandenbroucke, J. Benefits and harms of drug treatments. Observational studies and randomised trials should learn from each other. *British Medical Journal*, 329:2-3, 2004.

¹⁰ For example, see Perfetto, E. M., Ellison, R., Ackerman, S., Shorr, M., and Zaugg, A. M., Evidence-Based Risk Management: How Can We Succeed? Deliberations from a Risk Management Advisory Council. *Drug Information Journal*, 37: 127-134, 2003.

A listing of the Working Group members and their affiliations along with a summary of its activities over the nearly four years spent to bring this project to fruition are found in Appendix 2.

b. Results of the CIOMS VI Survey on Company Practices

In order to ascertain prevailing practices in the industry for many of the areas under consideration here, a survey was conducted via the Internet during February and March 2003. A summary of key findings follows, but for details a copy of the questionnaire and the complete results are found in Appendix 3. Of 19 European, 35 US and 5 Japanese companies, subsidiaries or other industry organizations approached, there was a total of 21 respondents: 9 from Europe, 8 from the U.S. and 4 from Japan. The names of the specific companies are given in Appendix 3; however, all results are anonymized as to origin of answers. The topics covered in the survey included broad organization and policy issues (regarding, e.g., risk management, Investigator's Brochure management) as well as case processing and data management issues (e.g., causality assessment, study/case blinding, use of AE terms and coding dictionaries, and much more).

Although there has been a tendency to create one safety/pharmacovigilance department covering both pre- and post-approval periods, 8 of 21 respondents reported separate organizations within their companies. It is clear that "risk management" as a discipline has taken hold, with 20 of 21 companies having incorporated this approach; 7 of 17 responding indicate that a distinct group is responsible for this area – 4 headed by the safety department, 3 by clinical development.

Most companies (14/21) regard the signing of informed consent as the starting point for collecting adverse event information on subjects/patients; 4 other respondents indicated that it was protocol specific. Only 4 of 21 required investigators to record signs and symptoms of an AE/ADR along with a suggested diagnosis on the study case report form; however, if signs and symptoms were provided, 13 of 21 code and enter the information in their database with the diagnosis.

The CIOMS Working Group has deliberated the appropriateness and practicality of using a single, standard form that all companies would use globally for investigators to record data on suspected serious adverse events/reactions; 16 of 21 support this idea. More discussion on this point is found

in Chapter 4. Another Working Group concept involves the introduction of periodic summary reports of serious suspected ADRs to investigators and ethics committees as a substitute for sending individual cases as they arise; this idea was supported by 19 of the 21 respondents. See Chapter 7 for more details. Some regulatory authorities or study sites already request some sort of periodic report along these lines (e.g., under the European Clinical Trials Directive or other country-specific requests (UK, Portugal, Spain), as reported by 5 companies).

Safety information is supplied to ethics committees directly by the company (9 of 21 responses) and/or to the investigators who then forward it to the ethics committees (12/21); however, this practice is country-dependent (11/21) and may vary from study to study (2/21).

“Introspection” was the choice for 12 of 21 with regards to what causality method is used by the company for assessing whether an AE is an ADR; 2 use a home-grown algorithm, 3 a published routine (e.g., Karch-Lasagna), and 4 indicated “no specific method.” Nearly all respondents (19/21) take the investigator’s causality assessment into account in their analyses and regulatory reporting of safety cases.

The CIOMS III/V recommendation on the Development Core Safety Information (DCSI) concept for the Investigator’s Brochure¹¹ has been (6/21) or will be adopted (7/21) by many of the respondent companies.

Perhaps surprisingly, not all companies conduct regular aggregation and review of all AE data from ongoing trial results; 16 of 21 do and 5 of 21 reportedly do not.

The results of the survey were helpful to the CIOMS Working Group in formulating its proposals.

c. Areas Covered by the CIOMS VI Project

The CIOMS VI Working Group has developed proposals based on scientific principles for harmonizing many aspects of the collection, monitoring, analysis, evaluation/interpretation, and communication to all relevant parties of clinical trial safety information. In so doing, it has

¹¹ See *Guidelines for Preparing Core Clinical Safety Information on Drugs. Second Edition, Including Proposals for Investigator’s Brochures*. Report of CIOMS Working Groups III and V. Council for International Organizations of Medical Sciences, Geneva, 1999.

developed an approach to “good clinical trial safety practices” that embraces an overall safety surveillance/risk management program that links pre-marketing to post-marketing safety environments.¹²

Underlying this effort was the need to explore the following specific areas, and others, which are not adequately addressed in regulations, yet are the subject of considerable uncertainty and debate:

- **Terminology and definitions:** How relevant are conventional safety terms, definitions and categories, largely developed for post-marketing regulatory reporting purposes, to the analysis and understanding of clinical trial safety data (for example, pharmacovigilance; serious, non-serious; adverse event, adverse drug reaction)? What is meant by a “signal” and “adverse events of special interest”? Are terms like effectiveness, risk, benefit-risk relationship clearly delineated and understood? Whose terms and definitions should be used among those issued by WHO, ICH, prior CIOMS groups, various regulatory authorities, and others? The Glossary in Appendix 1 as well as discussions within the Chapters attempt to answer these questions. The reader is urged to read the opening section of the Glossary for an important perspective on term usage, abbreviations and definitions. In addition to terminology related to pharmacovigilance and drug safety, the Glossary also covers important statistical terms as used in Chapter 6.
- **Ethical aspects of clinical trials:** Events of the recent past have led to changes in various rules and regulations governing proper ethical practices and behaviour. Revisions of the Declaration of Helsinki, modified roles and responsibilities of investigators, sponsors, ethics committees, and data and safety management boards (DSMBs), new privacy and data confidentiality laws, and other considerations affecting the rights and welfare of study subjects all require an expanded view of the role of ethics concepts in human drug research. Chapter 2 covers these matters.
- **Overall pharmacovigilance/risk management system:** Can general principles and practical guidance be developed for an overall product safety system as a basis for the identification, assessment, and management of potential and real safety issues for the product? How can it be applied to the transition between a development

¹² The reader will be interested in ICH guideline E2E (Pharmacovigilance Planning), that outlines a comprehensive approach to pharmacovigilance/risk management of newly introduced products. See <http://www.ich.org>.

program and introduction of a medicine after its marketing authorization? Chapter 3 provides guidance on a pharmacovigilance/risk-management process that can form the basis for any needed general or specific pharmacovigilance plans during drug development.

- **Collection and proper management of safety data:** Does traditional study protocol language satisfy the needs of safety management? When should data collection begin? Can standards be developed on what should be collected and when? Are there special issues with regard to the collection and documentation of laboratory data? What is the relationship between safety data and clinical efficacy endpoints (especially involving mortality or increased morbidity)? Who has the responsibility to ensure complete and timely data collection at the study site? Who is responsible at the sponsor's location (especially when work is outsourced to contract organizations or there are licensing relationships)? Is it feasible and practical to adopt a global, standard form or set of data elements for use by investigators to report serious adverse events to sponsors? What impact should an investigator's causality assessment for an adverse event have? How long after a patient withdraws from a study for safety reasons, or completes a study (or takes the last dose), should he/she be followed for potential adverse drug reactions or to monitor an existing ADR? Once data are retrieved, what is the appropriate way to ensure the proper choice and coding of AE/ADR terms to ensure accurate and informative analysis and evaluation? Chapters 4 and 5 deal with these and other issues.
- **Evaluation of safety data:** Can standard approaches be recommended for the detection, analysis and management of safety signals? What is the proper place of individual case report assessment vis-à-vis aggregate data analysis? How should blinded studies be managed with respect to safety monitoring, reporting and analysis? Among the various stakeholders, who should have responsibility for, or participate in, the ongoing analysis and interpretation of aggregate safety data (investigator, sponsor, Ethics Review Committees (ERCs)¹³, Institutional Review Boards (IRBs), data and safety monitoring boards/committees (DSMBs/DSMCs), regulatory authorities)? What factors should determine how often and to what depth safety data should be analyzed and evaluated during a

¹³ May also be called Independent Ethics Committees (IECs), or Research Ethics Committees (RECs). See Chapter 2 for more discussion on the roles and responsibilities of ERCs and IRBs.

development program? What options are available for action based on the findings, particularly those relating to stopping rules, emergencies, or changes to study protocols? What approaches are needed to assess the safety experience of special or sub-populations (such as the elderly, pediatrics,¹⁴ organ impaired, women of child bearing potential)? How precise and relevant are the medical terminology and definitions that are used to describe AEs/ADRs, including the use of specific coding dictionaries? What influence do they have on the information to be included in the Investigator's Brochure (IB) and the eventual authorized product information (data sheets)? Chapter 5 covers these topics in some depth.

- **Statistical analysis of safety data:** What is the appropriate use for inferential and descriptive statistics and when should they be used? Should “intention-to-treat” analyses be applied to safety data? What impact do statistical power, multiplicity (multiple analyses) and time dependency have on analysis and interpretation of the data from individual trials? Is one-sided or two-sided testing preferred? What are the correct approaches to analysis of continuous data (e.g., laboratory chemistries) vs binary data (e.g., present/absent)? Are survival analysis techniques (accounting for time on drug and discontinuations) important and if so, when? How can meta-analytic approaches be used to pool data from multiple studies? How can background data from various sources outside the trials be used for comparison of results? What are the best ways to express risk information for healthcare providers and patients? Chapter 6 provides details and guides to these and other statistical issues.
- **Regulatory reporting and communication to others of safety information during clinical trials:** Is there sufficient consistency between different countries' regulations to allow for standard global practices by industry? How do recent changes (e.g., the European Directive on Clinical Trials¹⁵) affect the monitoring, handling and reporting of safety data? What should be communicated to investigators, ERCs, IRBs, DSMBs, and ultimately study subjects, not

¹⁴ The EMEA issued a concept paper as evolving guidance in March 2003 on pharmacovigilance in children (<http://www.emea.eu.int/pdfs/human/phvwp/483802en.pdf>). Although it pertains directly to post-marketing conditions, it could serve as a useful reference for clinical trials as well.

¹⁵ See <http://europa.eu.int/eur-lex/en/oj/index.html> for the Directive and <http://pharmacos.eudra.org/F2/pharmacos/new.htm> for the associated Guidances, two of which relate directly to pharmacovigilance during clinical trials.

only as a trial progresses or at its completion, but prior to its initiation? When should the information be communicated? Whose responsibility is it to communicate such information to the various affected/involved parties? Chapter 7 addresses these issues in detail and makes some recommendations for new approaches.

It is important that we rely on a more comprehensive and transparent approach to risk management than in the past; our understanding of a product's safety profile evolves throughout its study and use. This CIOMS report covers all the issues discussed above (and more) in an attempt to provide practical guidance for the design and execution of a rational drug safety surveillance plan during any clinical research program. It is directed not only to pharmacovigilance/clinical safety specialists, but to all those involved in the planning, design, and execution of the clinical research process for the development of new medicines, as well as new uses and preparations of already available products.

Another aspect of product safety that deserves careful consideration is the possibility of medication errors – mistakes made in the prescribing, dispensing, administration, and use of medicines – which can lead to adverse reactions, sometimes serious. Although not usually associated with clinical trials, there have been instances of such errors during development programs. In addition, it behooves a sponsor to try to anticipate what kinds of errors might occur once the product reaches the general population and to take steps to minimize their possibility (e.g., avoid possible name, appearance, and packaging similarity/confusion with other products).¹⁶ Similarly, it would be prudent for a sponsor to attempt to foresee what if any off-label (unapproved) uses might be made of the medicine once it is in general use; different or unusual safety considerations might pertain in such circumstances. For a discussion and some recommendations on these issues, see Chapter 3.

d. Limitations of Clinical Trials for Understanding Safety

The development process for virtually all new medicines represents a compromise between two extremes: (1) acquiring a minimum, basic data set on a drug's properties in animals and humans, and (2) the desire to learn as much as possible about a product's safety (and efficacy) prior to its

¹⁶ For a set of definitions and a taxonomy of medication errors, see www.nccmerp.org (the US National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP)).

approval and general use. In order to enable the introduction of new medicines within a reasonable time and at acceptable cost, the regulatory and scientific requirements must be practically achievable. As a result, there are limitations of typical clinical development programs which are familiar and include: small numbers and homogeneity of study subjects relative to the much larger and diverse population that may use the product; statistical aspects of study designs focus on efficacy (power calculations, etc.) rather than on safety; a controlled, experimental environment that may not reflect the “real world” (concomitant treatments, number of treatment visits, extent of intervention and measurements, concurrent conditions, etc.); uncertain generalizability of the data;¹⁷ and a relatively short duration of treatment (e.g., latent effects may not be observable). With certain categories of medicines, such as anti-HIV drugs, there may be additional pressure to shorten development time to satisfy urgent public health needs, in which case our knowledge and understanding of the safety profile will be even less complete and will be confounded or made more complicated, especially by polypharmacy and the use of fixed combination products. In principle, randomization during clinical trials will mitigate such confounders, unlike the situation in most post-marketing trials and observational studies.

Compliance with ICH GCP Guideline (E6), the most widespread standard in use for the conduct of clinical trials, provides assurance that the rights, safety and well being of trial subjects are protected, and that the trial data are credible. General principles and guidance are given on the roles and responsibilities of sponsors and investigators for collection and reporting of safety information. Another ICH Guideline, General Considerations for Clinical Trials (E8), summarizes key principles and practices that govern scientific excellence and explains the connection between the various ICH clinical guidelines. However, the field has become increasingly complex and many aspects require renewed attention in spite of such widely agreed standards and the availability of published treatises on pharmaceutical clinical research.¹⁸ While it is believed that companies strive to establish internal global standards for the collection, monitoring, processing, analysis, assessment, presentation and reporting of safety data, some new thinking and practices are deemed advisable by the Working Group.

¹⁷ For a recent analysis of clinical trial vs “real world” ADR profiles that highlights the problems with attempting to generalize results from trials, see Dieppe, P., Bartlett, C., Davey, P., Doyal, L., and Shah, E. Balancing benefits and harms: the example of non-steroidal anti-inflammatory drugs, *British Medical Journal*, 329:31-34, 2004.

¹⁸ For example, see *Guide to Clinical Trials* by B. Spilker. Lippincott Williams & Wilkins, Philadelphia, 1991 and *Handbook of Phase I and II Clinical Drug Trials*, Edited by J. O’Grady and P. H. Joubert. CRC Press, LLC, 1997.

e. Scope of the Project

The concepts and proposals developed here are applicable to prescription drugs, biotechnology products, diagnostic agents and over-the-counter (non-prescription) products, as well as prophylactic therapies. The focus of this work is on new product development programs, conventionally Phase I through III trials, but it also is relevant for Phase IV trials (generally regarded as post-authorization therapeutic use studies).¹⁹ This work also applies to programs involving the use of pharmacogenetics. An added complication for biological and biotechnology-derived products is their greater sensitivity to quality (manufacturing) issues; the presence of foreign antigens, specific DNA content or DNA contamination, pyrogens, and/or viral contaminants all can play a crucial role in establishing a safety profile. Such technical details are beyond the scope of the present work.

Although gene-therapy research and programs involving genetically modified organisms are still highly exploratory and may be somewhat controversial, we believe that the guidance provided in this report can be applied to these areas. However, evolving knowledge pertaining to the underlying science and potential quality issues must be taken into account.

The material here is also applicable to prophylactic and therapeutic vaccines, although each represents a somewhat special situation, with the former involving potential major public health implications. The testing of huge populations is often involved, increasingly with a requirement to assess immunological markers. In many cases, most of the confirmatory research will take place in a post-authorization environment. The fact that most vaccine programs are directed at infants and children heightens the sensitivity to ethical considerations and informed consent.

This report does not address the increasingly frequent attempt under some regulatory jurisdictions to include cost effectiveness of products when prescribed within defined clinical situations. This concept involves many perspectives and controversies within the regulation of medicines and may be seen as a sociopolitical or economic rather than (or in addition to) a scientific issue. Approaches to benefit-risk-cost analyses and decisions are still in their infancy.

¹⁹ ICH Guideline E8 (General Considerations for Clinical Trials) has proposed that studies be categorized according to their objectives (human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use), as distinct from the temporal phases of drug development (I through IV). For example, human pharmacology studies (traditionally referred to as Phase I) can be and often are conducted throughout a product's lifetime.

Although this work deals with medicinal products, it is believed that the principles and practices invoked can apply to medical devices as well, although it is recognized that there are some special issues associated with their study and use.

This effort is directed not only at pharmaceutical companies as clinical trial sponsors along with their agents (contract research organizations, CROs), but also to independent clinical researchers and others not involved in commercially-based medicines development, since the pursuit of enhanced safety standards is principally concerned with the protection of patients. It is hoped that this report will be read and used by academic clinical researchers who are as important as any other stakeholders in the conduct of clinical trials.

Finally, it is important to acknowledge that the risks of a drug cannot and should not be considered in isolation from the established benefits. In any development program, the ultimate goal is to evaluate and provide a measure of the benefit-risk relationship for the anticipated conditions of use, something that is critical to its approval and use in the general population. A rational assessment of the benefit-risk (or benefit-harm) relationship is notoriously difficult, whether done by regulators for populations or by patients and healthcare professionals for individuals. There are many potential biases and influences that affect decisions surrounding the relationship, decisions that are usually based on what is often referred to as “subjective expected utility theory”.²⁰ This report only indirectly addresses the benefit side of the relationship and does not deal in a major way with the evolving methodologies for qualitative and quantitative aspects of benefit-risk weighing.^{21,22} No matter what method is used to derive and describe the benefit-risk relationship for a specific product, it must be recognized that

²⁰ For a thoughtful treatment of this subject with suggestions on how to understand why different stakeholders interpret the benefit-harm balance of medicines differently, and how to form a basis for strategies to counter cognitive and other influences, see: Greenhalgh, T., Kostopoulou, O., and Harries, C. Making decisions about benefits and harms of medicines, *British Medical Journal*, 329:47-50, 2004.

²¹ For more details on benefit-risk considerations, see: Spilker, B., Incorporating Benefit-to-Risk Determinations in Medicine Development, *Drug News and Perspective*, 7 (1), February 1994, 53-59; Chuang-Stein, C. A., New Proposal for Benefit-less-Risk Analysis in Clinical Trials, *Controlled Clinical Trials*, 15: 30-43, 1994; and “Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals,” CIOMS, Geneva, 1998. Although this last reference focuses on marketed drugs, the principles and process described are valid for drugs in development.

²² Holden, W.L., Juhaeri, J. and Dai, W. Benefit-risk analysis: a proposal using quantitative methods, *Pharmacology and Drug Safety*, 12:611-616, 2003, and *idem*, Benefit-risk analysis: examples using quantitative methods, *ibid.*, 12: 693-697, 2003. Also, see Eriksen, S. and Keller, L. R. A Multiattribute-utility-function Approach to Weighing the Risks and Benefits of Pharmaceutical Agents, *Medical Decision Making*, 13:2, April-June 1993, 118-125.

over time, especially once a product is in general use, it can change for the better or worse. As new and improved products are authorized for clinical use, subsequently developed products in similar therapeutic classes will need to meet increasingly stringent benefit-risk requirements, which can have a significant impact on new development programs.

II

**Ethical Considerations
for Clinical Trial
Safety Management**

a. Background

Most countries or regions have rules and regulations on safety surveillance during clinical trials that address the responsibilities of sponsors, investigators and ethics committees but the details are continuously evolving. The ethical underpinnings of all the regulations are based on several regional and international guides that set out principles of research on humans. The most widely known and applied is the Declaration of Helsinki,¹ which is incorporated or referenced within most countries' regulations. However, there are several other valuable works that can be consulted and that have had an impact on standards in this area. The CIOMS International Ethical Guidelines² provide guidance on how the ethical principles of the Declaration of Helsinki can be applied effectively. The topic has also been receiving increased attention in specific parts of the world, such as Latin America³ and in developing countries.⁴ It should also be noted that the Council of Europe has been preparing a "Protocol for Biomedical Research," a comprehensive regulation intended to be legally binding and that Member States must ratify.⁵ Independently, UNESCO plans to develop a "Universal Instrument on Bioethics," to include a section on biomedical/clinical research.⁶

For anyone designing and conducting a clinical trial, the fundamental principle should be that any study that is not scientifically sound can be considered unethical. The basic ethical principles universally accepted for dealing with the potential risks and benefits for human subjects are: autonomy of the individual (respect for persons and their dignity), beneficence (do good), nonmaleficence ("do no harm"), and justice (benefits and burdens of research distributed fairly among all groups and classes).⁷ These

¹ For the latest edition, see Appendix 4 or www.wma.net/ethicsunit/DeclarationofHelsinki

² *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, Geneva, 2002 (a guide to the application of the Declaration of Helsinki, particularly for research in developing countries; available in several languages, including Japanese, Spanish, Italian, German, etc.); also, see *Ethical Considerations in Clinical Trials*, Proceedings of an EMEA Workshop, 26 November 2001 (www.emea.eu.int).

³ Cavazos, N., Forster, D., Orive, O., Kaltwasser, G. and Bowen, A. J. The Cultural Framework for the Ethical Review of Clinical Research in Latin America, *Drug Information Journal*, 36:727-737, 2002.

⁴ Zumla, A. and Costello, A. Ethics of Healthcare Research in Developing Countries, *J. Roy. Soc. Med.*, 95:275-276, 2002.

⁵ See www.coe.int/T/E/legal-affairs/legal_co-operation/bioethics.

⁶ For an interim report, see www.unesco.org/ibc/en/actes/s10/index.

⁷ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. US Department of Health, Education and Welfare, Washington, DC, 1979 (see <http://ohsr.od.nih.gov/mpa/belmont.php3>).

principles apply to actions by researchers and investigators, which have a direct impact on the potential risks and benefits experienced by patients and normal volunteers. Neutel⁸ has examined in detail the complicated issues surrounding the ability of investigators to apply the principles of beneficence and nonmaleficence so as to effectively minimize risk and maximize benefit; improvements in the informed consent process play a key role.

The purpose of this Chapter is to discuss current thinking and regulations associated with ethical aspects of clinical medicinal research, with particular focus on clinical safety. This is a complicated and culturally dependent topic and examination of clinical research ethics is an active process by different groups.⁹ Thus, the Working Group believes it is currently beyond its scope to make any firm proposals on possibly controversial matters of ethics. However, in a few areas it does provide recommendations and provides information and ideas it hopes will inform ongoing debates.

New laws or regulations and new perspectives have expanded the application of ethical concepts in clinical trials beyond the usual themes of informed consent and indemnification (insurance) against study subject injury. There is growing importance and sensitivity not only for patient rights generally, but for clinical trials in non-industrialized, developing countries,¹⁰ vulnerable and socially underprivileged patients,¹¹ transparency (including on payments to investigators and to trial subjects), and the availability of results of all trials, including those with “negative” findings.

Conflicts of interest (professional as well as financial) also represent a source of concern. Potential conflicts of interest with respect to clinical trials may compromise the integrity of the research and human research participant protection, and therefore must be considered carefully. They may involve the institution, the investigator, and independent ethics committees (IECs) and their individual members. In addition to the obvious conflicts such as financial benefits that might accrue to individuals and/or institutions, there are subtle influences, such as professional recognition and promotion. For example, when ethics committees are constituted within the

⁸ Neutel, C. I. The Dilemma of Using Humans as Research Subjects: An Assessment of Risks and Benefits, *Drug Information Journal*, 38:113-126, 2004.

⁹ For example, see Emanuel, E. J. *et al.* Oversight of Human Participant Research: Identifying Problems to Evaluate Reform Proposals, *Ann. Intern. Med.*, 141: 282, 2004.

¹⁰ Idanpaan-Heikkila, J. E. Ethical principles for the guidance of physicians in medical research – the Declaration of Helsinki, *Bulletin of the World Health Organization*, 79(4):279, 2001.

¹¹ Vrhovac, B. Chapter 2. Ethical Considerations in *Basic Guidelines for Pharmacological Research in Humans*, IUPHAR, August 2004 (Brisbane, Australia).

institution that is scheduled to conduct the research, they must be careful not to let the often large amounts of funding the institution might receive influence their review and approval of the protocol and the subject protection measures.¹² There is increased scrutiny of the potential undue influence of monetary compensation to investigators and patients, something that has to be managed carefully.¹³

Transparency with all affected parties is paramount when faced with any potential conflicts of interest. Each institution, investigator, IEC/IRB and its members should have a conflict of interest policy that ensures independence from undue external influence of any kind that could cast doubt on their ability to make unbiased decisions and fulfill their mandate to protect the rights, safety and welfare of human research participants. This would entail the clear separation of the approval, audit and oversight functions of the IEC/IRB from the operational functions of the institution and investigator(s), i.e., those involved with funding, initiating and conducting the research, and who might stand to gain from its positive outcome. The IEC/IRB and its members should be unaffiliated with both the research sponsor and the trial subjects.

It is useful to consider the broad subject of ethics in the current context under two headings: stakeholder roles and responsibilities, and regulatory considerations.

b. The Stakeholders

The monitoring and management of pre-authorization clinical safety data involve many parties, with their own perspectives and expectations, as well as roles and responsibilities.

- **Patients.** Their willingness to accept risk is based on their perception of safety (“Is this study safe?”) and is tempered with expectations of a favorable safety and, aside from normal volunteers, efficacy outcome. They should always be regarded as full partners in the research and thereby be kept well informed so that they understand their role and importance. In this way, patients/volunteers will be in

¹² For a detailed discussion and suggestions for dealing with conflicts of interest, see *Responsible Research: A Systems Approach to Protecting Research Participants*, Institute of Medicine (US), Washington, DC, October 2002 (<http://www.iom.edu/report.asp?id=4459>).

¹³ See Reiser, S.J. Research Compensation and the Monetization of Medicine, *J. Am. Med. Assoc.*, 293:613-615, 2005.

a better position to make decisions regarding their participation and continuation in a study, and can enhance their willingness to adhere to all protocol requirements. This makes it all the more important that they be given as much information as possible in a way that maximizes comprehension, through the informed consent process and throughout a study.¹⁴ These issues represent a significant challenge to sponsors, investigators and ethics committees.¹⁵ There has been evidence for some time that consent documents in use are too long and too difficult to read by many patients.^{16,17} This aspect is beyond the scope of the CIOMS VI project. Patient privacy and the confidentiality of their data are also of considerable importance (see part c. of this chapter for more details).

- **Regulatory Authorities and the Public Health Community.** Governments through their regulatory bodies¹⁸ have a statutory responsibility to authorize the use of medicines only if they can be demonstrated to be “safe and effective” and when they have the required manufacturing quality. They develop the regulatory framework to ensure that their scientific evaluation is based on reliable data obtained from well conceived and conducted clinical trials. The regulatory and public health communities protect the public through their ongoing monitoring of the safety of a wide range of both experimental and authorized medicines. During clinical development programs, the authorities have several options available to protect trial subjects and ensure the scientific quality and integrity of the research – from routine monitoring and audits to “clinical holds” (temporary cessation/suspension of one or more trials), mandatory protocol and/or informed consent adjustments, periodic safety assessment reports from sponsors, complete discontinuation of the program, and other mechanisms. Once the products are authorized and used in the

¹⁴ See Guideline 5, “Obtaining informed consent: essential information for prospective research subjects,” in *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, Geneva, 2002.

¹⁵ For example, see Hochhauser, M. Why You Can’t Write a Consent Form at a Sixth-grade Reading Level, *DIA Forum*, October 2002, p. 22-25 and DeMillo, L. Working with Institutional Review Boards and Informed Consent, *ibid.*, July 2002, p. 16-20.

¹⁶ Sharp, S. M. The Problem of Readability of Informed Consent Documents for Clinical Trials of Investigational Drugs and Devices: United States Considerations, *Drug Information Journal*, 38:353-359, 2004.

¹⁷ Recently, the US Office for Human Research Protection (OHRP) has provided guidelines and sample documents for obtaining and documenting informed consent for non-English speaking subjects. Go to <http://www.hhs.gov/ohrp/policy/index.htm/#informed> for links to the information.

¹⁸ For example, U.S. Food and Drug Administration (FDA), U.K. Medicines and Healthcare Products Regulatory Agency (MHRA), Japan Ministry of Health, Labor and Welfare (MHLW), European Medicines Agency (EMA).

general population, the authorities must continue to monitor product use to ensure that an acceptable balance between benefits and risks is sustained for each authorized indication and sub-population.

- **Investigators.** Whether they are independent researchers or are conducting trials on behalf of a company or other sponsor, the investigator and his/her staff play the most important role in ensuring the rights and safety of subjects and in the collection of complete, accurate, protocol-required data. They are also pivotal in establishing and maintaining effective communications with ethics and data and safety monitoring committees, sponsors, and when required, with the health authorities.
- **IECs and IRBs.**¹⁹ Responsibilities and membership for these bodies are generally articulated in national and international regulations for clinical research.²⁰ However, new issues have arisen that affect their governance and their roles. It has become increasingly difficult for clinical research ethics committees to cope with ethical and technical complexities involving, for example, use of placebos, equivalence vs non-inferiority trials, use of the appropriate comparative agent, proper dosing, and therapeutic endpoints.²¹ Increased scrutiny of IECs/IRBs by government and public groups has also emerged as a result of serious injury or death to some trial patients over the past few years and efforts are being made to strengthen subject safety, including by legislation.²²

¹⁹ In common usage, the names IRB (Institutional Review Board), ERC (Ethics Review Committee) and Independent Ethics Committee (IEC) generally represent the same or similar bodies which are expected to have the expertise to maintain study oversight and protection of the subjects. However, in some cultures and institutions, ethics committees and review boards may interpret their roles differently and perform different functions. IRBs are usually limited to an institution as the name implies, but are expected to be capable of reviewing and approving study protocols. For example, some may include statisticians and trial methodologists to ensure that studies will obtain data of value; however, IECs focus on assuring that patients are not exposed to undue risk and may not have scientific expertise. Furthermore, an ethics committee may be responsible for all ethical issues within an institution, including issues related to clinical trials, whereas a separate IRB might be established within the same institution for a specific purpose, especially for oversight of clinical research. Because of the use of “centralized” IRBs or IECs for multi-site studies, some institutions have redefined and separated the local boards’ roles and responsibilities (e.g., data privacy, animal research review, ethical considerations). See the Glossary (Appendix 1) for more discussion.

²⁰ For example, see Article 6 in the EU Directive on good clinical practice and conduct of trials (<http://europa.eu.int/eur-lex/en/oj/index.html>). Official Journal of the European Communities, 1 May 2001, L 121/34 – L 121/44.

²¹ Garattini, S., Bertele, V. and Li Bassi, L. How can research ethics committees protect patients better?, *British Medical Journal*, 326:1199-1201, 2003.

²² For example, see (a) *Responsible Research: A Systems Approach to Protecting Research Participants*, Institute of Medicine (US), National Academies Press, Washington, DC, 2003 (see <http://www.iom.edu/report.asp?id=4459>). (b) *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*, US Department of Health and Human Services Office of Inspector General, September 2001 (Report Number OEI-01-00-00190, available at <http://oig.hhs.gov/oei>) and (c) Bailey, V. J., *New Directions for IRBs, Food and Drug Law Institute Update*, November/December 2001 (www.fdpi.org).

Steps have also been taken to introduce accreditation of IECs and IRBs.²³ In the US, a new accreditation program (Partnership for Human Research Protection, Inc, PHRP) began in 2003.²⁴ Another new organization, the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in the US has also created an accreditation system.²⁵ Its mission is to provide a process of voluntary peer review and education among institutions, IRBs, and investigators concerned with research involving humans, in order to promote preservation of the rights and welfare of subjects in research, and compliance with relevant ethical and regulatory standards.

Other developments include the use of centralized IRBs, whereby local site IECs/IRBs would accept a review of a multi-center trial from an authorized (preferably accredited) body in lieu of individual reviews by each local group.²⁶ Under the EU Clinical Trial Directive, each Member State must establish a mechanism for a single opinion on approving clinical trials within that country.

Guidelines have been developed for auditing of ethics committees in Europe.²⁷ A practical proposal has been published for an investigator's checklist to ensure proper IEC/IRB review of the protocol and subject protection mechanisms for each study.²⁸ Finally, there

²³ *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs*, National Academy of Sciences, Washington, DC, 2001 (see www.nap.edu). Also, see the EU Clinical Trial Directive approach to accreditation: <http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004>

²⁴ This is a collaborative effort by JCAHO (Joint Commission on Accreditation of Healthcare Organizations) and the NCQA (National Committee for Quality Assurance). For details, see www.phrp.org.

²⁵ The overall goal of accreditation is to improve protection of human research subjects by developing performance standards that encourage programs to adopt "best practices" in this area, and by recognizing the programs that meet those standards. See www.aahrpp.org/ for details.

²⁶ A few examples of centralized and independent IRB models operating in the US include: MACRO (Multi-center Academic Clinical Research Organization), a reciprocal IRB approval process for several academic medical centers (www.ccs.wustl.edu); WIRB (Western Institutional Review Board), www.wirb.com, which offers international ethics review services; CIRB (Consortium of Independent IRBs), a group associated with the US National Cancer Institute (www.ncicirb.org); Midlands L.L.C. IRB, which has the ability to review studies in all States of the US (see www.midlandsirb.com); Coast Independent Review Board (www.coastirb.com); The Copernicus Group (www.copernicugroup.com). For the UK, see Multicentre Research Ethics Committee (MREC) and Local Research Ethics Committee (LREC) requirements (www.corec.org.uk and www.eric-on-line.co.uk/index.php). Also, see www.irb-irc.net for information on Independent Review Consulting, an organization that provides IRB services and ethics review consultation.

²⁷ See "European Guidelines for Auditing Independent Ethics Committees," European Federation for Good Clinical Practice (EFGCP) at www.efgcp.org.

²⁸ Spilker, B. Creating an IRB Checklist to Protect Human Subjects in Clinical Trials, *Applied Clinical Trials*, September 2002, p. 34-36.

are associations dedicated to clinical research ethics that publish and hold conferences on the roles of IRBs and IECs.²⁹

- **Data and Safety Monitoring Boards.**³⁰ The use of data monitoring boards for randomized clinical trials has increased in recent years and different approaches have been taken as to their responsibilities and interactions with other stakeholders. Such committees can play a critical role in the new drug development process, and their regulatory status is changing.³¹ There is some debate, from a scientific as well as an ethical perspective,³² regarding whether or when DSMBs should have access to unblinded efficacy and safety data, and with whom such data should be shared. Many of the underlying principles of such committees, their roles and responsibilities, and levels of access to blinded data have been established by some regulatory bodies. The FDA has issued a Draft Guidance for sponsors on the operations of clinical trial monitoring committees.³³ The EU Pharmacovigilance Guidelines for the Clinical Trials Directive address such issues as well.³⁴ The WHO through its Special Program for Research and Training in Tropical Diseases has also created a draft operational guideline for DSMBs.³⁵ The underlying challenge for such boards/committees is to seek the proper balance between maximizing the scientific value and validity of trials, and their obligation to protect participating and future patients.³⁶ Under

²⁹ PRIM&R (Public Responsibility in Medicine and Research, www.primr.org); ARENA (Applied Research Ethics National Association, www.aamc.org/research/primr/arena); ACRP (Association of Clinical Research Professionals), a very large membership of research professionals (www.acrpnnet.org).

³⁰ An independent body with oversight for the monitoring and assessment of data from clinical trials to protect study participants and to protect the validity and credibility of the trial. They may be referred to variously as data monitoring boards or committees (DMBs, DMCs), data and safety (monitoring) boards (DSMBs), and other terms. See the Glossary (Appendix 1) under Independent Data-Monitoring Committee for more discussion, and Appendix 5 for a detailed description.

³¹ Ellenberg, SS, Fleming, TR and DeMets, DL. *Data Monitoring Committees in Clinical Trials: A Practical Perspective*, John Wiley (Chichester, England), 2002. Also, see Ellenberg, S.S. Independent Data Monitoring Committees: Rationale, Operations and Controversies, *Statistics in Medicine*, 20: 2573-2583, 2001.

³² Fleming, T.R., Ellenberg, S., and DeMets, D.L. Monitoring Clinical Trials: Issues and Controversies Regarding Confidentiality, *Statistics in Medicine*, 21: 2843-2851, 2002.

³³ Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees, November 2001 (www.fda.gov/cber/guidelines.htm).

³⁴ See ENTR/6422/01 at <http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm>

³⁵ Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards, UNICEF/UNDP/World Bank/Who Special Program for Research and Training in Tropical Diseases (TDR), 31 March 2004 draft (WHO, Geneva). For details, write to Dr. Juntra Karbwang, the clinical coordinator of TDR, at karbwangi@who.int.

³⁶ Slutsky, A. S. and Lavery, J. V. Data Safety and Monitoring Boards, *New England Journal of Medicine*, 350:1143-1147, 2004.

the auspices of the DAMOCLES project³⁷ a comprehensive review has been published on the use of DSMBs with recommendations as to best practices.

- **Pharmaceutical Companies and Their Representatives.** It is incumbent on companies and their contractual partners (CROs, laboratories, licensors/licensees) to work with investigators to ensure that all needed steps will be taken to ensure that trials will be conducted under the best scientific and ethical conditions so as to maximize the quality of the work and to minimize the risk to subjects – all while adhering to local and international regulations. Multinational sponsors should strive for implementation of global safety standards for their clinical trial practices and operations, including the assurance that all study protocols adequately address safety surveillance and reporting.

In addition to the above stakeholders, other participants in the clinical research process, namely, statisticians and epidemiologists,³⁸ have developed their own ethical and related guidelines. Although not directly related to the clinical trial process, journalists for the professional and lay media also have an ethical obligation to provide accurate and balanced reports on information available to them on clinical research results.

c. Evolving Regulatory and Societal Demands

The ethical, technical and administrative requirements in regulations governing the conduct of clinical trials are many and complicated and may depend on the country or region where trials are conducted. A detailed discussion is beyond the scope of this project, but access to information on the continuously changing picture is available.³⁹ One of the more important requirements relates to the expedited reporting to regulators of medically important (serious) adverse events during clinical trials. Periodic (status)

³⁷ **Data Monitoring Committees: Lessons, Ethics and Statistics (DAMOCLES).** For details, see Sydes, M. R. *et al.*, Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials, *Clinical Trials*, 1:60-79, 2004.

³⁸ For example: Ethical Guidelines for Statistical Practice, American Statistical Association (for information, asainfo@asa.mhs.compuserve.com), and Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States, *Pharmacoepidemiology and Drug Safety*, 5:333-338, 1996.

³⁹ A useful source of current regulations and guidelines for many countries throughout the world is found at: www.regsource.com

reports during development programs are also required in some countries, such as under US IND Rules and the EU Clinical Trials Directive.⁴⁰

(1) Privacy and Confidentiality of Personal Data

Over the past several years, there has been considerable attention paid to confidentiality and the protection of personal data. New laws and regulations introducing increased subject data rights and data safeguards have been mandated in the EU and its Member States, the US, Canada, Australia, Japan, Argentina, and several other countries, all of which have an impact on the collection, access to, and handling of personal data from clinical trials, as well as the ability to transfer such data outside the source country.⁴¹ The increasing use of pharmacogenetics and DNA typing of tissue samples in clinical research programs represent an especially sensitive area.⁴² Some analyses of these laws and their impact on clinical research and pharmacovigilance have been published.⁴³ Adherence by investigator sites to the new provisions may fall under the scrutiny of IRBs and IECs, thereby increasing their responsibilities; however, this is an evolving area and no international standards have been established.⁴⁴

⁴⁰ For US IND Rules, see 21CFR312 (www.fda.gov) and for the EU CT Directive, see *Directive 2001/20/EC of the European Parliament and of the Council* (4 April 2001), Official Journal of the European Communities, L121/34, 1 May 2001 (<http://europa.eu.int/eur-lex/en/oj/index.html>). Implementation guidelines for the CT Directive are available on the European Commission website at <http://pharmacos.eudra.org/F2/pharmacos/docs.htm#news>.

⁴¹ For example, see European Parliament and the Council of the European Union “Directive on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data,” (Directive 95/46/EC), Official Journal of the European Communities, No. L 281, 31-50 (November 23, 1995). Also available on the Internet at: http://europa.eu.int/eur-lex/en/lif/dat/1995/en_395L0046.html. The Directive has been transposed into local law within the Member States of the European Economic Area. In the US, the Department of Health and Human Services (DHHS) released its final rule on Standards for Privacy of Individually Identifiable Health Information on 20 December 2000 for implementation in April 2003; see <http://www.hhs.gov/ocr/hipaa.html>.

⁴² Anderson, D.C. *et al.* Elements of informed consent for pharmacogenetic research; perspective of the pharmacogenetics working group, *The Pharmacogenomics Journal*, 2:284-292, 2002. Also, see *Pharmacogenetics – Towards Improving Treatment with Medicines*. Report of a CIOMS Working Group, CIOMS, Geneva, 2005.

⁴³ M. Barnes and J. Kulynych, *HIPAA and Human Subject Research: A Question-and-Answer Reference Guide*, Barnett International, Media, PA, 2003 (for information, see www.barnettinternational.com/edu-pubs.cfm); The Effect of the New Federal Medical-Privacy Rule on Research, *N. Eng. J. of Med.*, 346:201-220, 2002; and Knudsen, L. E., Theilade, M. D., Gordon, A., Mascaro, J. and Bruppacher, R. Will Data Privacy Impact Health Research?, *Drug Information Journal*, 36:465-4809, 2002.

⁴⁴ National standards have been defined in the UK and were of a statutory nature from 1 May 2004 under the new UKECA (United Kingdom Ethics Committee Authority). UKECA will authorize, inspect and certify standards for all research ethics committees in the UK. See “MRC Ethics Series: Human Tissue and Biological Samples for Use in Research” (April 2001) at <http://www.mrc.ac.uk>. In the US, the Office of Human Research Protection (OHRP) has issued a Guidance on Research Involving Coded Private Information or Biological Specimens (August 10, 2004) which deals with the anonymization of data (<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>).

(2) Informed Consent

Although gaining informed consent is the cornerstone of all human subject clinical research, there are situations where it may not be possible or appropriate. This raises a dilemma: is a trial unethical if informed consent was not obtained in advance?⁴⁵ There are settings which do justify such exceptions, including use of anonymized tissue samples, some types of epidemiological research, and certain kinds of survey research (to avoid biased results).⁴⁶ For example, observational studies rarely require informed consent, and it would be highly impractical if not impossible if it were needed.

Conducting clinical trials on medicines for emergency-case patients (in ambulance or hospital emergency room) represents a circumstance in which the patient is rendered incapable of providing informed consent, and a legally authorized patient-representative is often not available. Examples are many, such as acute MI, stroke, sepsis, grand mal seizure, accident trauma, and alcohol and related intoxications by poisons, resulting in the need for emergency treatment. The available guidances for such trial situations call for prior approval of the protocol by an ethics committee as usual, and inclusion in the protocol of the detailed reason(s) for the inability to secure informed consent, as well as details on how consent to remain in the study will be obtained as soon as possible from the trial subject, or if not possible, from a family member or a legally authorized representative.⁴⁷

A topic that must be considered carefully by all parties conducting clinical research relates to the need for “re-consenting” of trial subjects. Under what circumstances and how should new, important safety information be conveyed to trial subjects who have already given their informed consent to participate? Situations that must be considered include subjects who are still in the trial, those who are in a post-treatment follow-up period, and those who have completed the trial. There are several factors that must be considered in deciding what the

⁴⁵ Dogal, L. Informed Consent in medical research: journals should not publish research in which patients have not given fully informed consent with three exceptions, *British Medical Journal*, 314:1107-1111, 1997.

⁴⁶ Dawson, A. J. Commentary: Methodological reasons for not gaining prior informed consent are sometimes justified, *British Medical Journal*, 329:87, 2004.

⁴⁷ (1) Guidance 6 in *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOIMS, Geneva, 2002. (2) Article 26 of the Declaration of Helsinki (Appendix 4, this report). (3) Code of Federal Regulations (US), Title 21, Part 50, Subpart B, Section 50.24. Exception from informed consent requirements for emergency research. (4) See Chapter 14. Research and innovative treatment, in *Medical Ethics Today. The BMA's handbook of ethics and law*, Second Edition, British Medical Association, London, 2004.

obligations are of the investigators, ethics committees and sponsor. For example, for how long after a patient leaves a trial should new information be provided? Does it depend on the nature of the information? Although some aspects of re-consenting are covered in Chapter 7, the details of this topic were considered beyond the scope of the Working Group; however, this issue has become the subject of debate within and between companies and must be addressed.

(3) **Transparency in Availability of Clinical Trial Results**

One of the more complicated and controversial issues facing the biopharmaceutical industry and the biomedical research community is whether results of all completed clinical trials should be made available to interested parties, and if so what information and how. ICH Guideline E6 (GCP) states that there should be a written publication policy for trials, either as part of the protocol or as a separate agreement. It calls for both positive and negative results to be made available for other researchers so that lessons learned in trial design can be shared. Similar guidance is provided in the Declaration of Helsinki and in the CIOMS Ethics Guidelines. However, critics have pointed to underreporting of clinical research by company sponsors, which allegedly leads to bias, especially because “negative results” (e.g., lack of, or poor, efficacy) are rarely published or otherwise made publicly available.⁴⁸ One of the problems in this area is the reluctance of journals to publish reports of studies with negative findings. The absence of complete data not only compromises the ability of independent researchers to conduct proper meta-analyses, but also it has been opined that it denies practitioners and possibly the public from information needed to make good treatment decisions.

The medical publishing community has a cooperative group (CONSORT) that has made proposals for improving the quality of papers, reducing publication bias, and making transparent any conflicts of interest.⁴⁹ Many published papers reporting clinical trials, however, do not comply with their guidelines and apparently most are deficient in the

⁴⁸ Chalmers, I. Drug companies should be forced to publish all the results of clinical trials. How else can we know the truth about their products?, *New Scientist*, 6 March 2004, p. 19; Herxheimer, A. Open access to industry’s clinically relevant data, *British Medical Journal*, 329:64-65, 2004.

⁴⁹ The **Consolidated Standards of Reporting Trials** Group (CONSORT) has developed a checklist and flow diagram for the reporting of randomized clinical trials (<http://consortstatement.org>). See Moher D, Schulz KF, Altman D, *et al.* The CONSORT Statement: Revised. Recommendations for improving the quality of reports of parallel-group randomized trials. *Journal of the American Medical Association*, 285:1987-1991, 2001.

reporting of adverse events.⁵⁰ There have been proposals from various groups, journals included,⁵¹ that a special database be created to contain the results of all studies. Contrary to claims made by many parties that development and use of such a database is straightforward, we believe that it is actually very complicated; the details must be carefully considered to preclude possible unintended consequences of making very large amounts of unfiltered data available to inexperienced parties.

CIOMS Working Group VI is sensitive to and concerned about this subject and endorses the concept of transparency of results and outcomes for all clinical research, especially safety data; however, it is not in a position to make concrete proposals or recommendations on this continuously evolving subject. Nevertheless, we make the following points with the hope that they help contribute to a logical and rational solution.

- (a) In a global research and development environment, care must be taken to avoid unilateral legislation or other requirements for the creation of a master database of clinical research results; a harmonized effort would be highly desirable.
- (b) It is important that all parties understand the distinction between a database of results and a registry of ongoing trials that is informational for prospective patients and their health care providers. There is evidence of confusion on the difference by both the public and many journalists.
- (c) There are legitimate concerns regarding possible proprietary information associated with study designs and methodologies; premature disclosure in the absence of a public health need would not be appropriate.
- (d) It is vital to take into account the huge number of clinical medicinal trials conducted by independent clinicians, academic institutions, managed care organizations, and public agencies.⁵²
- (e) Deciding on the structure and contents of a database requires consideration of many parameters: Should it cover both pre- and post-approval studies? Include all protocols used for the trials? Include full data sets for individual patients? When some trial study reports can reach hundreds or even thousands of pages in

⁵⁰ Ioannidis, J. P. A. and Lau, J. Completeness of safety reporting in randomized trials – an evaluation of seven medical areas, *Journal of the American Medical Association*, 285:437-443, 2001.

⁵¹ See Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors, *New Eng. J. of Med.*, 312:12, 2004.

⁵² By one recent estimate, drug manufacturers sponsor only about one-third of drug trials in the US.

- length, of how much practical value will they be to practicing physicians, let alone patients? Should results of only prospective trials be included or should observational study results be covered? What is the best form and focus for result summaries?
- (f) Who will design, create and maintain the database and who will pay for it?
 - (g) How should access by the public to such complicated data be arranged? How can they, or even healthcare professionals, evaluate the quality of the study and interpret the statistics provided?
 - (h) How much useful information can be gleaned from individual study reports without placing them in the context of a full research program?
 - (i) Drug regulatory authorities have access to all the clinical study results (from companies) and use their expertise to judge their value and application for product information, including official labeling. When many agencies make available to the public their summary reviews of marketing application data along with considerable details, is it necessary to create new or different systems?⁵³ Is there a risk in bypassing or usurping the role of the regulators?
 - (j) If a database is required for all studies, how does this affect the peer review process for journal publication? Does it prejudice the ability to publish such disclosed results?
 - (k) Will availability of results of studies covering unapproved uses of medicines lead to increased off-label use and serve as an implicit (but unintended) form of “promotion” for such use?
 - (l) There is at least one group that maintains a comprehensive register of well-reviewed trials that meet certain minimum standards of quality (Cochrane Central Registry of Clinical Trials).⁵⁴ Can lessons be learned from its experience and methods?
 - (m) There may be liability issues for companies when there are differences between the official product information (data sheets) for marketed products and the full panoply of data found within

⁵³ The US FDA posts summaries of the medical reviews for new drug approvals on the drugs@FDA website: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. For results of pediatric studies: www.fda.gov/cder/pediatric. Other sources for results of trials conducted in the US are: clinicaltrials.gov (service of the National Institutes of Health), cancer.gov (National Cancer Institute), centerwatch.com (industry and government sponsored trials) and trialscentral.org (web site of Brown University’s Center for Clinical Trials and Evidence-Based Medicine covering worldwide trials). In Japan, the MHLW posts the results of studies in their summary basis of approval after a drug is approved; further details on individual studies can then be accessed from the companies on request. In the UK, there are at least two repositories of trial results: <http://www.cancerhelp.org.uk/trials/trials/> and <http://www.controlled-trials.com/mrct/>

⁵⁴ See www.cochrane.org

multiple study reports, even though those differences may be perfectly understandable.

Some individual pharmaceutical companies have taken steps to make results of all their trials available, some through their own web sites, others through public institutional sites, such as the NIH in the US. The US pharmaceutical industry, through its professional association, has established a principle for all its members to make study results available on a voluntary basis.⁵⁵ It has also established a central database to contain the results of hypothesis-testing trials completed since October 2002 by member companies, mainly Phase III and IV trials, whether published or unpublished.⁵⁶ A “Joint Industry Position on Clinical Trial Information Disclosure” was issued by EFPIA, IFPMA, JPMA and PhRMA that commits to making publicly available the results of all clinical trials (other than exploratory) on a drug marketed in at least one country, and completed after the date the position paper was published (6 January 2005).⁵⁷ The Association of the British Pharmaceutical Industry (ABPI) sponsors a clinical trial database.⁵⁸ Also in the UK, the British Medical Journal publishes *Clinical Evidence*, an international source of the “best available evidence for effective health care” to foster informed decision making by summarizing what’s known and not known about the treatment and prevention of nearly 200 medical conditions.⁵⁹

Some leading medical journals have announced an initiative that would require listing of a trial in a public registry of the results before a paper would be accepted for publication.⁶⁰

Much more debate and work will be required before a useful and validated system for widespread documentation of clinical trial results can be achieved.

⁵⁵ See Updated Principles For Conduct Of Clinical Trials And Communication Of Clinical Trial Results, PhRMA, June 2004 (<http://www.phrma.org/mediaroom/press/releases/30.06.2004.427.cfm>).

⁵⁶ This Internet database is publicly available free (www.clinicalstudyresults.org).

⁵⁷ See www.ifpma.org

⁵⁸ See <http://www.cmrinteract.com/clintrial>.

⁵⁹ See <http://www.clinicalevidence.com>

⁶⁰ *British Medical Journal*, 329:637-638, 2004.

(4) Other Issues

Another sensitive issue relates to clinical trials in resource-poor and developing countries. Development of new treatments or new uses of old treatments for “neglected diseases” or conditions prevalent in developing countries, such as HIV/AIDS, malaria and other tropical diseases, requires that trials be conducted in those locations. Guidance for the ethical aspects of studies in such locations is available.⁶¹ The potential study populations are often vulnerable and socially underprivileged, and the issue often arises as to whether study medication should be provided to the subjects after trial completion; an important clarification on this issue has been made to the Declaration of Helsinki.⁶² Many companies have a process for deciding under what circumstances, and how, such treatment continuation should be implemented. Limited financial and infrastructure resources have an impact on the choice of authorized medicines used in such areas.

Among other difficult ethical and scientific questions that do not have easy answers, and for which no regulations or guidance is available, is the following: If a new, significantly safer and/or more efficacious drug is approved after beginning a development program that uses the previous standard therapy as a comparator, how should a sponsor proceed? The strategy will likely depend on how far along the development program is (Phase I, II, III) and on other factors. It would be prudent for the sponsor to discuss the situation with appropriate regulators.

⁶¹ *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, Geneva, 2002. See Guidelines 3, 10, 11, 20 and 21. Also, see http://europa.eu.int/comm/european_group_ethics/docs/avis17_complet.pdf

⁶² The Declaration of Helsinki covers this issue under Paragraph 30. For the update (Tokyo 2004), see www.wma.net.

III

Good Pharmacovigilance and Risk Management Practices: Systematic Approach to Managing Safety during Clinical Development

a. Introduction

Although most of this CIOMS report focuses on the technical aspects of safety surveillance, analysis and reporting, the Working Group believes it important to consider first an overall framework for a pharmacovigilance process for any clinical program. It is hoped that such a perspective can help sponsors elucidate a thorough, systematic and disciplined approach to clinical trial patient safety. The purpose of this chapter is to suggest some important aspects of such an approach that should be taken into account perhaps even before initiating the first Phase I study but certainly throughout the clinical program. It is also recommended that a formal risk management plan be created. While the tone of the chapter tends to address large pharmaceutical company research and development, the principles can be adapted to other environments. For example, in a smaller organization one person may serve multiple roles otherwise served by several in a larger company. In addition, certain functions (e.g., clinical data management or clinical expertise) may be covered internally by a larger company and externally by a smaller one. Likewise the same principles that apply to pharmaceutical company sponsors should apply to all other sponsors of clinical trials.

Regardless of the setting, it is important to ensure that a well-defined and well-structured process is in place that will allow sponsors to readily identify, evaluate and minimize potential safety risks relative to potential benefits for study subjects in pre-approval trials. Such a process should start before initiating the first Phase I study and continue through post-approval use of the drug or biologic in the general population. In establishing the process, it is important to consider and define, in advance, the roles and responsibilities of individuals within the organization who are expected to participate.

Depending on the business processes and organizational structure of the company a formal plan should probably be created, and modified as needed during a clinical program. In the initial planning stages of a new clinical development program, one goal is to gather the necessary knowledge and information to adequately plan the optimum program from the standpoint of safety. This would be a good time to create the team that will be responsible for the process and if desired prepare the initial risk management plan.

In contrast to the post-marketing phase, little guidance is available on the pharmacovigilance process during development.

Although the term “pharmacovigilance” has traditionally been associated with post-marketing activities, the CIOMS VI Working Group recommends that the term be applied to the pre-marketing process for collecting, managing and assessing safety information during development. Likewise, the concepts of risk assessment and risk minimization, components of risk management, are terms that are as applicable to the pre-marketing environment as they are to the post-marketing environment. (See Appendix 1 for more details on terminology.)

Concurrently with CIOMS VI, guidelines are being developed that address the planning of post-marketing pharmacovigilance and risk management activities for newly licensed/approved products. These include a set of guidance documents by the FDA¹ and ICH E2E (Pharmacovigilance Planning)². In both cases, a major focus is on the creation of a document, to be submitted to health authorities prior to approval, that describes the company’s plan for gathering additional information to fill remaining gaps in knowledge or for interventions to minimize the known risks in the patient population, once the product is approved/licensed and marketed. These guidance documents complement each other, appropriately reinforcing the growing recognition of the importance of maintaining a proactive stance toward safety surveillance throughout a product’s life. The CIOMS VI Working Group suggests that such written plans might be a natural outgrowth of a process that starts at the earliest stages of development. It is not recommending any particular format for a development risk management plan since this will likely vary depending on the circumstances and would evolve as development progresses. Early in development, documentation of risk considerations and planned steps to deal with them would most logically be part of the overall Clinical Development Plan. As risks are better understood, they would be included in the Investigators Brochure as part of the Development Core Safety Information. In later stages of development, documentation would eventually evolve into a stand-alone Risk Management Plan. (See section c. below.)

¹ The FDA issued three guidance documents for industry in March 2005: (1) *Premarketing Risk Assessment* (<http://www.fda.gov/cder/guidance/6357fnl.htm>), (2) *Development and Use of Risk Minimization Action Plans* (<http://www.fda.gov/cder/guidance/6358fnl.htm>), and (3) *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (<http://www.fda.gov/cder/guidance/6359OCC.htm>).

² ICH Guideline E2E: *Pharmacovigilance Planning*, Step 4 as of November 2004 (<http://www.ich.org>).

b. Principles of a Systematic Approach

- (1) **Begin early.** Consideration of patient safety is the most important first step in clinical development. As a matter of principle, the process for managing risk during development should start no later than when a decision is made to begin human trials. The sponsor's decision to proceed with development of a medicinal product will certainly need to take into account a broad range of factors including but not limited to safety. However, a determination of whether and under what conditions it is safe to proceed should always be made independent of other considerations and the safety review team should be involved in that decision. For new chemical entities, the decision regarding safety will be made based on non-clinical safety data and information on closely related compounds, and therefore requires careful assessment and advice from qualified toxicology specialists as well as careful and deliberate planning for safety monitoring during early clinical trials.

- (2) **Establish a procedure.** The first step in establishing a systematic approach to identify and manage risk during development is the creation of a procedure that defines how it will:
 - ❑ ensure the regular and timely review and evaluation of all available safety information in order to identify potential risks
 - ❑ clearly define roles and responsibilities
 - ❑ enable timely and effective decision-making to minimize risks to study subjects
 - ❑ assure consistent implementation of risk minimization actions across protocols and study locations
 - ❑ enable realization of the implications for the intended target population after approval so that appropriate post-marketing pharmacovigilance and risk minimization activities can be designed and implemented.

Sponsors should establish standard operating procedures that define a framework for a process that can be applied consistently across all development programs, but which allows enough flexibility to meet the needs of what will inevitably be a diversity of products and a broad range of safety issues associated with them. In some cases it may be appropriate to supplement standard operating procedures with product-specific procedures.

- (3) **Establish a Multidisciplinary Safety Management Team (SMT).** The procedure should clearly define the makeup and charter of a multidisciplinary team that will be responsible for the timely review, assessment and evaluation of incoming safety data. The core team should include a representative from each of the medical functions that play a role in the development and post-marketing monitoring of the product. Other members should be available on a regular or *ad hoc* basis depending on the issues, e.g., epidemiologist, clinical pharmacologist, toxicologist, chemist, biostatistician, regulatory affairs expert. Roles and responsibilities should be clearly defined, for the team as well as for each individual on the team. Each member of the team must have responsibility and accountability for raising issues, in particular those emanating from their respective disciplines. The team should be empowered to make decisions that will accomplish the goal of minimizing risk while maximizing benefits to subjects in clinical trials, as well as anticipating the use of the product once marketed. Decisions should take into account the need to update the IB, DCSI, CCSI and/or informed consent, modify or add new monitoring procedures, implement protocol amendments or initiate prompt communications to investigators, ethics committees and regulators. When applicable, consideration should also be given to when and how prescribers and patients should be informed for a product already marketed in one or more countries.

The composition of such a team will vary depending on a number of factors such as:

- ❑ Structure and size of the company
- ❑ Development stage of the compound
- ❑ Type of compound under development
 - First in class
 - Follow-up compound within the company
 - Line extension

Although it will depend on the product and the size and complexity of the program, the following is an example of how such a team can be composed and function:

- ❑ Global project/product physician has the overall medical responsibility for the project, including assessment of the benefit-risk profile of the product
- ❑ Global safety physician has the responsibility for identifying and evaluating the risks relating to the product
- ❑ Global regulatory affairs director/manager has the responsibility for advising the team on regulatory policy

- ❑ Project manager, specifically assigned to track and manage the team's decisions, ensuring appropriate follow-up and completion of assigned tasks
- ❑ Other disciplines on an as needed basis

The leader of the multidisciplinary SMT can be made accountable for the creation and appropriateness of the plan and for ensuring that the plan is implemented. Responsibility for drafting the plan should be shared among all members of the team.

As necessary, the SMT would work with appropriate staff (e.g., epidemiologist and toxicologist) in the quantitative assessment of identified risks, the characterization of the safety profile of the substance under development, the identification of signals, and the determination of changes in the safety profile.

The global regulatory affairs director or manager is responsible for ensuring that a plan is included with regulatory submissions (e.g., New Drug Application or Marketing Authorization Application) when required, or when the global project team determines that it represents an essential element of the application.

When internal resources are limited, e.g., for smaller companies or for sponsors in developing countries, teams may be smaller and individuals may play more than one role. In these situations, greater consideration might be given to involving outside experts or establishing an external DSMB with a role wider than for one specific study. (See Appendix 5 for more detailed discussion on the role of the DSMB.)

When licensing partners are involved, a joint safety review process, including clear roles and responsibilities of the respective companies, should be defined in advance with timelines for exchange and joint review of data. Ideally the terms should be part of the initial contract, but at the very least should be incorporated into a follow-on agreement on safety matters.

- (4) **Establish a project management function.** Key to the successful implementation of a consistent and systematic approach is the establishment of a mechanism for scheduling meetings, tracking issues and timelines, and assuring completion of action items. The CIOMS VI Working Group recommends establishing a project management function to manage these tasks, document any decisions, and ensure compliance with internal procedures.

- (5) **Determine background data.** Although there will generally not be an abundance of data for the team to review early in clinical development, it is at those stages, if not sooner, that the team should begin to formulate an understanding of the target population. It is advantageous to involve epidemiologists to help describe the natural history of the disease being treated, to aid in defining endpoints, especially for Phase III studies, and to anticipate important adverse events of interest (e.g., serious, severe, frequent or otherwise of clinical importance) that might be observed as part of the background. It is also a good time to consider the target benefit-risk profile, taking into account the natural history and associated risks of the disease as well as the benefits and risks of available alternative therapies. For more details, see section d. Role of Epidemiology, below.
- (6) **Ensure accessibility of data.** Also key to successful implementation is the accessibility of all relevant data. It should be a top priority to make safety and other pertinent data readily available to the safety team from the clinical trial and safety databases as well as from other relevant sources, such as the pre-clinical toxicology department (e.g., carcinogenicity and development and reproductive toxicology), *in vitro* mutagenicity studies, and pharmacokinetic and drug-interaction studies. In doing so, it would be important to identify who is responsible for accomplishing the retrieval and presentation of data in a format that can be readily evaluated by the core team. If data management is being handled by another party, e.g., a contract research organization (CRO), it is important for the sponsor to define in the contractual obligations the mechanism for timely accessibility to accurate data.
- (7) **Develop a proactive approach.** During early stages of development it is also advisable to begin formulating components of risk assessment and risk minimization plans. If there are adverse events of particular interest or concern, for example based on knowledge of the therapeutic or pharmaceutical class, on animal toxicology studies, or on the known mechanism of action, then consideration should be given to special monitoring procedures.³ If there are populations that are considered to be potentially at higher risk, then plans should be made for addressing the risk through

³ The CIOMS VI Working Group considers the term “known risk” to refer to a risk that has been observed and is reasonably established for the investigational product itself; the term “anticipated risk” to refer to a risk that has not yet been observed or established for the product but is expected to occur based on knowledge of the class of drugs; and the term “potential risk” to refer to a risk that has not yet been observed in humans for the investigational product itself or for other drugs in the class but for which there is reason to suspect it might occur, based on animal toxicology studies or the known pharmacologic properties. In other contexts (e.g., ICH E2E), what we refer to as anticipated risks are usually placed in the potential risk category.

exclusions or special studies. The size, components and nature of the development program will in large part be driven by anticipated or potential safety issues. It is therefore important to identify those issues as early as possible to ensure the adequacy of the program. For example, if there is a special population that is expected to be at high risk but that risk is not yet well characterized, there may be a need to plan for special studies in that population or to ensure their sufficient representation in the pivotal trials. If drug metabolism studies suggest a propensity for drug interactions, it would be important to understand the likelihood that the target population would be using concomitant therapies that might be of concern, and to plan accordingly. ICH Guideline E1 provides guidance on the size of the safety database for drugs intended for chronic use in non-life threatening conditions.⁴ The FDA Draft Guidance for Industry on Premarketing Risk Assessment includes a discussion of other factors to consider, such as the value of long-term controlled safety studies, the diversity of the clinical trial population, and exploration of dose effects (see footnote 1). See also Chapter 5 for a discussion of the safety review process.

- (8) **Establish timeframes and milestones.** Monitoring of safety during development should be viewed as an intensive continuous process, especially in Phase I and II when little may be known about the risks. However, the procedure should establish regular timeframes for review of safety data by the multidisciplinary SMT. The CIOMS VI Working Group recommends quarterly review of safety data as a reasonable standard. More frequent reviews might be necessary in some circumstances, in particular very early in development when little is known about the risks or benefits, or when a specific issue has arisen. On the other hand, less frequent reviews might be appropriate for continuing development of an approved product with a fairly well established safety profile, or when the pace of new data acquisition from trials is very slow. Whatever the cycle of reviews it would be important to coordinate the timing with that of pre-approval periodic reports such as the annual IND report or the newly proposed Development Safety Update Report (see Chapter 7 for detailed discussion). If the product is approved, such reviews should also be coordinated with PSURs, where applicable. It would also be important to coordinate the review with milestones such as end-of-Phase II, completion of pivotal trials, or writing of the integrated summary of safety.

⁴ ICH E1: *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*, Step 5 as of October 1994 (<http://www.ich.org>).

The CIOMS VI Working Group recommends that sponsors create a dedicated Safety Management Team (SMT) to review all the available safety information on a regular basis so that decisions on safety can be made in a timely manner. It also recommends that these reviews take place usually at least quarterly pre-approval and be coordinated with pre-approval and, if applicable, post-approval periodic reporting. Quarterly and ad hoc safety reviews should consider the overall evolving safety profile of the investigational product, make necessary changes to the IB/DCSI, and determine if any changes to the conduct of the trials need to be considered.

- (9) **Decision making:** The focus of safety reviews should be on the identification of issues, a determination of their implications, what actions should be taken, and monitoring and assessing the results of those actions. For each safety review meeting, there should be a clear determination of whether or not there are any new issues that warrant close attention or any new developments on issues identified earlier. For any ongoing or newly identified potential risk, consideration should be given to the implications for the DCSI, informed consent, communications to investigators, ethics committees or regulatory authorities, any changes to monitoring procedures, amendments to protocols or the IB, or to the overall development plan itself.
- (10) **Advisory bodies:** The SMT should have advisors readily available to call upon when issues of significant concern arise. These might be in the form of an internal safety committee, an issue-specific external advisor or advisory board, or an independent monitoring board for a trial or program.

There will be situations where the SMT might benefit from a higher level of internal review, to ensure awareness of the issue by more senior management, to obtain support for decisions that may have a significant impact on the overall clinical development program, and to ensure consistency of the timeliness and content of communications on a global basis. Hence, establishment of an internal senior safety committee of executives with expertise in managing safety issues from a scientific, medical and regulatory perspective might be considered. This would generally be a single committee that would review and respond to issues presented by the product-specific SMT. This senior safety committee would provide scientific advice, consider implications for the overall development program, and expedite decisions and their resultant actions through liaison with other parts of the organization, where timeliness and consistency across regions is of utmost importance.

If not available internally, it may be necessary to obtain the advice of outside experts on an *ad hoc* basis when issues arise. Expert advisors or advisory panels may provide advice regarding the significance of findings, make suggestions regarding usefulness and interpretation of diagnostic or screening tests, develop decision rules for discontinuation of study drug, or provide input on other risk minimization actions. Expert advisory panels are particularly useful if there is a need for ongoing review of accumulating cases. The advisory panel may also provide overall advice regarding implications for the viability of the program based on the emerging product profile as it relates to standard of care and other available therapies.

There may also be circumstances where the use of a DSMB is advisable. Although DSMBs are generally responsible for a particular trial, it would be important to ensure that they have access to any and all information external to the trial that might have a bearing on its role of monitoring safety. In exceptional circumstances, consideration might be given to establishing a DSMB to monitor safety across the entire program rather than just one or more trials. For example, if a new class of oncology drugs is being tested in multiple tumor sites across a number of protocols with survival as an endpoint, it would be reasonable to establish a DSMB to monitor safety in all the trials.

c. Components of a Development Risk Management Plan (DRMP)

The CIOMS VI Working Group fully recognizes the demanding workload and pressures on companies, and the many committees, working groups and reports that are already involved in drug development. Thus, it does not take lightly the recommendation to create another plan and process. However, high quality pharmacovigilance is an essential component of any clinical program. A natural outgrowth of the systematic approach described above is the creation of a formal Development Risk Management Plan. Such a plan would need to be compound-specific and perhaps form a section of the overall Clinical Development Plan. It should include early documentation of known, anticipated or potential risks along with plans for addressing them during development and, where appropriate, the DRMP would eventually evolve into a post-marketing risk management plan that will accompany the registration application.

The DRMP is not intended to be a legal or regulatory document, but rather a guide for safety surveillance during development. However, it must be recognized that these documents may be subject to legal discovery. Therefore, there are two actions which should be considered in the development of the process. First, the company's legal department should ensure appropriate language is considered for a general statement that this is a working document. Second, the company should ensure that processes including project management are in place to make sure that action plans are followed through. The plan should not be a place for speculation, theoretical explanations or potential action plans. Any action which is written in the document should be followed.

The DRMP should include, at a minimum, the following sections; many of them are expected to be addressed routinely in any development plan, from the perspective of efficacy as well as safety:

(1) Introduction and Objectives

(2) Anticipated Product Profile

- Indications
- Intended population
- Expectations for new product (prevention vs symptomatic treatment vs cure) and associated threshold for tolerating risk (see also Chapter 5)
- Anticipated benefit and/or risk advantages over existing therapies, if any

(3) Epidemiology (see Section d. below for details)

- Definition of disease and diagnostic criteria
- Natural course of disease, including likely concurrent conditions and concomitant medications
- Quantification of burden of disease (incidence, prevalence, morbidity, mortality, percentage of patients diagnosed)
- Consideration of special populations, such as:
 - pediatrics (ICH Guideline E11)
 - elderly (ICH Guideline E7)
 - ethnicity (ICH Guideline E5)
 - women of child-bearing age, pregnancy⁵
 - organ impaired patients (e.g., decreased hepatic or renal function)

⁵ The Committee for Human Medicinal Products (CHMP) in the EU issued (June 2004) a draft Note for Guidance on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorization Data (www.emea.eu.int/pdfs/human/phvwp/188904en.pdf; document EMEA/CHMP/1889/04/Consultation). Comments to the CHMP were due in December 2004. Although focused on the post-authorization period, this document, still draft as of this writing, would be useful to consult regarding data requirements and other considerations.

(4) Non-clinical safety experience⁶

- ❑ Pharmacokinetics/Pharmacodynamics
- ❑ Acute and chronic toxicity
- ❑ Developmental and reproductive toxicology
- ❑ Mutagenicity and carcinogenicity
- ❑ *In vivo* and *in vitro* drug interactions
- ❑ Special safety pharmacology studies (e.g., cardiac conduction, neurotoxicity)

(5) Clinical safety experience (see footnote 6)

- ❑ Clinical pharmacology
 - Absorption, distribution, metabolism, excretion (ADME)
 - Drug interactions
 - Dosing and dose-response information
 - Efficacy
 - Safety
 - Safety profile of class
 - Safety profile of new product
 - Extent of exposure to date
 - Evaluation of adverse events, including frequency
 - Safety in demographic groups and special populations
 - Effects on different body systems
- ❑ Benefit-risk profile of new product

(6) Identification and assessment of known or anticipated risks

- ❑ Known or anticipated adverse events might warrant special attention if special measures need to be taken. For example, if there is the potential for gastrointestinal bleeding, it would be important to define what would be considered a clinically significant bleed that should be reported promptly to the sponsor even if not considered serious for regulatory purposes (such an event could be considered an “AE of special interest”). It would also be important to ensure that informed consent documents include early signs and symptoms for patients to be aware of so that bleeding can be detected early. Consideration might also be given to developing coding guidelines for adverse events of special interest.

⁶ The non-clinical and clinical sections should be consistent with the IB/DCSI (see Chapter 7), but may include more. For example, there may be a discussion of an evolving, but still uncertain, safety issue that has not yet reached the threshold for inclusion in the DCSI or IB.

- ❑ There may also be obvious compound-specific or known therapeutic class-specific issues, such as drug-drug, food-drug or disease-drug interactions. For biologics, the issue of immunogenicity should always be considered. There are also certain special populations that should always be considered, for example, women of child-bearing potential, pediatric patients, elderly patients or patients with renal or hepatic insufficiency. Specific issues and special populations are described below.

(7) Identification and assessment of potential new risks

- ❑ In developing a systematic approach to managing safety during development, one can identify a handful of specific issues that should always be “on the radar screen,” e.g., QT prolongation, hepatotoxicity and potential for abuse. (See Section e. below.)
- ❑ Potential high risk populations or circumstances
- ❑ Potential for medication errors during treatment in clinical trials or during general use once the product is approved/licensed
- ❑ Potential for off-label use once the product is on the market

(8) Actions and/or plans for evaluating and mitigating risk

Routine as well as compound- or protocol-specific steps should be described, including data that will be monitored and the time frames for conducting safety reviews.

As specific signals or issues are identified, action plans should be made describing the specific activities that will be conducted in order to assess and/or control them. An action plan for each issue will generally include either a plan for further assessment (risk evaluation), or a plan to decrease the risk to patients (risk minimization). The action may range from relatively simple, e.g., monitoring during the ongoing trials, to relatively complex, e.g., development of a special data collection form or the conduct of a targeted study. From a practical point of view, this list will usually include actions developed by the product team and be specific to the product, but may also include a standard list that the company uses for all products. Examples of actions include:

- ❑ Continuation of routine monitoring
- ❑ Communication to investigators, patients, IECs/IRBs, DSMBs, regulators
- ❑ Protocol amendment(s)
 - Specific monitoring and investigation

- Alteration of patient population (inclusion and exclusion criteria)
- Change in dose or dose schedule
- ❑ Additional studies
- ❑ Temporary hold on one or more clinical trials in a program
- ❑ Termination of one or more clinical trials in a program
- ❑ Termination of program

d. Role of Epidemiology

There is a broad and long-standing recognition of the importance of epidemiology to the development planning process, not only for defining the natural history and burden of the disease being treated, but for anticipating the important confounding factors and background incidences of concurrent illnesses.⁷ All of these factors must be taken into account in planning the size and demographics of the safety database as well as in evaluating case reports and case series when studies are still blinded.

(1) Patient Population, Natural History of Disease, Concurrent Conditions and Background Rates of Adverse Events

The epidemiology of the disease being treated is an important component of the planning of any clinical development program. The incidence and prevalence will determine the size of the target population. For preventive therapies, identification of populations at higher risk can help to define the study population in a way that can reduce costs by requiring fewer patients to show an effect.

In addition to aiding in the planning of trials to show efficacy, understanding the epidemiology and natural history of the disease is also important for putting potential safety issues into proper context. An observation in the study population of a “higher than expected” incidence of a particular event when compared to the general population may actually be expected when compared to the background rate in the target-disease population. For example, patients with rheumatoid arthritis (RA) have a 2 to 4 fold or greater incidence of lymphoma than the general population independent of therapy.⁸ Knowing this helps to put reports of lymphoma in clinical trials of RA into proper perspective.

⁷ Guess H.A., Stephenson W.P., Sacks S.T., and Gardner J.S.. Beyond pharmacoepidemiology: The larger role of epidemiology in drug development, *Journal of Clinical Epidemiology*, 41: 995-996, 1989.

⁸ Baecklund E., Askling J., Rosenquist R., *et al.* Rheumatoid arthritis and malignant lymphomas, *Current Opinion in Rheumatology*, 16:254-61, 2004.

Understanding the natural history of the disease is important for anticipating certain high risk situations, such as when patients are more likely to have concurrent renal or hepatic insufficiency. While exclusion of patients with these conditions will likely lead to a greater chance for a successful outcome in a clinical trial, it would be important to conduct studies of special populations or high risk patients if they are likely to be treated with the drug once approved. Likewise, if there are specific drugs or classes of drugs that are likely to be used concomitantly in clinical practice, the possibility of a drug interaction should be considered and plans made for separate clinical pharmacology studies where appropriate.

(2) Sources of Data for Background Rates

Knowledge of population background event rates is an essential component of the evaluation of any potential clinical trial safety signal, including the results of aggregate analysis. The approach to obtaining the appropriate background information will vary depending on the adverse event, the patient population and where the study is being conducted. There are numerous sources of data; however, not all are relevant or necessary for every new compound. If the sponsor has relevant prior experience for the same or similar population, a review of their in-house historical data may provide insights into the potential issues for the new product. If the relevant clinical programs were large enough, the pooling of placebo patients can provide background rates for some adverse events that are most relevant for anticipated clinical trial populations. The applicability of the historical clinical trials will depend on the comparability of inclusion or exclusion criteria and possible changes in the availability and use of concomitant therapies.

If the organization has no direct experience, the literature may be a good source of background incidence rates. It is important to consider carefully just how applicable the morbidity and mortality rates in the literature are to the clinical trial population. Conversely, it is important to recognize early the limitations of extrapolating incidence rates from clinical trials to a broader target population.

It may be appropriate to perform analyses on data from external epidemiological databases. There are many sources for such data, which vary in size, completeness, and medical specificity. Several relatively large databases are derived from North American populations, including US State Medicaid databases, such as California, Ohio, and Tennessee, other large US databases from health maintenance organizations and the Veterans' Ad-

ministration, and the database of the Saskatchewan Health Plan in Canada. In Europe, there are also a number of databases, the most well-known being the General Practice Research Database (GPRD) in the UK. Other smaller databases in Europe include PHARMO Record Linkage System in the Netherlands, the MEMO database in Scotland and a recently established database in Spain. Appendix 9 includes a list of available databases from an ongoing compilation by ISPE members.⁹ Details on a number of databases in North America and elsewhere can also be found online at a website maintained by DGI, Inc.¹⁰

Other potential sources of data are disease-specific registries such as bone marrow and liver transplant registries.^{11,12,13,14} HIV disease is an example of a disease for which registries have been useful for following the evolving background adverse event profile as new medications have become available, which effectively change the natural history of the disease. Sweden has nation-wide registries, e.g., for cancer and birth defects, that can be linked to a national death index.¹⁵

The Prescription Event Monitoring (PEM) program in the UK¹⁶ can be of value to investigate certain safety related questions. Although PEM captures product-specific event rates for marketed medicines, these can be used to estimate the expected rates of events for similar populations. Spontaneous reporting system databases such as the publicly available FDA AERS database in the US, the Drug Analysis Prints available from the ADROIT database at the MHRA in the UK, and the WHO ADR database (Uppsala, Sweden) might provide insight into the types of reactions that have been reported for similar drugs. However, they are not at all useful for determining background rates. Absence of denominators, delay in data availability, sparseness of data, and varying degrees of underreporting are some of the factors that limit the usefulness of such information.

⁹ The International Society for Pharmacoepidemiology (ISPE) Database Resource Document is an ongoing project aimed at compiling a list of available databases that might be considered for the conduct of pharmacoepidemiology studies. The databases listed (see Appendix 9) have been supplied by ISPE members. The list is posted for informational purposes only. It is not intended to be comprehensive. Inclusion on the list is not an endorsement by the Society, nor does the Society make any comments about size, validity, or other characteristics or qualities of a specific database (see http://www.pharmacoepi.org/resources/summary_databases.pdf).

¹⁰ See <http://www.dgiinc.org>

¹¹ Center for International Blood and Marrow Transplant Research (CIBMTR); see <http://www.ibmtr.org>

¹² European Liver Transplant Registry; see <http://www.eltr.org>

¹³ Nordic Liver Transplant Registry; see <http://www.scandiatransplant.org/liver01/liver01.htm>

¹⁴ US Transplant – Scientific Registry of Transplant Recipients; see http://www.ustransplant.org/liver_primer.php

¹⁵ See <http://www.sos.se/epc/epid>

¹⁶ See <http://www.dsru.org/pem2002.htm>

(3) Benefit-Risk Considerations

Important contributions that epidemiologists can make include following the literature and evaluating the applicability of newly published studies that may result in changes in the real or perceived benefits and risks of current therapy. For example, postmenopausal hormone therapy was expected to provide protection from both cardiovascular disease and osteoporosis in addition to symptomatic relief. Therefore, infrequent serious adverse reactions were initially considered acceptable because the overall benefit-risk profile was considered very favorable. As subsequent data became available from large randomized clinical trials that were part of the Women's Health Initiative,^{17,18} the perception of benefit-risk changed substantially and in some situations the risks may outweigh the benefits. Future Development Risk Management Plans for products in this class or similar classes of drugs would have to take into account such new information.

e. Specific Issues that Should Always be Considered

When planning for the development of virtually any new medicinal product, there are certain toxicities that should always be explicitly considered. These include:

- (1) **Cardiac electrophysiology:** Drug-induced prolongation of cardiac repolarisation (measured as the QT or QTc (i.e., QT corrected for heart rate) interval on the surface ECG) and subsequent development of life-threatening ventricular arrhythmias of the torsade de pointes type has caused post-marketing withdrawal of several drugs and stopped others in different stages of clinical development. Regulatory authorities pay considerable attention to effects on QT/QTc by drugs in development, as QT prolongation is thought to increase the risk of torsade de pointes and/or sudden death. Guidelines under development within ICH reflect common views and requirements on QT/QTc documentation in preclinical¹⁹ and clinical²⁰ development of new drugs. Market autho-

¹⁷ Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial, *Journal of the American Medical Association*, 288:321-333, 2002.

¹⁸ Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial, *ibid.*, 291:1701-1712, 2004.

¹⁹ ICH Guideline S7B, The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization, Step 3 as of June 2004. See <http://www.ich.org>.

²⁰ ICH E14. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Step 3 as of June 2004. (QT interval prolongation by human pharmaceuticals). See <http://www.ich.org>.

rization will be particularly challenging for drugs that significantly prolong QT/QTc unless they have unique positive effects in life-threatening conditions.

- (2) **Hepatotoxicity:** Hepatotoxicity is considered a risk that should be assessed in all new chemical entities prior to marketing. Similar to cardiac conduction, the development of hepatotoxicity has resulted in the post-marketing withdrawal of several products. Given the frequency and impact of this event and the inability of preclinical data to clearly predict or define the risk, hepatotoxicity should be considered as a potential issue in all developmental pharmacovigilance/clinical development plans. Several attempts are ongoing to define guidelines for better identification of potential hepatic toxicity using preclinical models as well as improved sensitivity and specificity for clinical monitoring. The most recent regulatory guidance on the investigation of potential hepatotoxicity is in an FDA discussion paper.²¹
- (3) **Drug-Drug and Food-Drug Interactions:** Consideration should always be given to the potential for drug-drug interactions, based on what is known about the drug's metabolism, the mechanism of action and the likely concomitant therapies. Depending on the situation, it may be sufficient to analyze adverse events as they relate to concomitant therapy within the planned pivotal clinical trials; or it may be necessary to conduct targeted studies. Multiple issues remain, including the predictability of *in vitro* work, the relevance to patients of interaction studies in healthy volunteers, and potential pharmacodynamic interactions which are not predicted by classic pharmacology studies. Food-drug interactions are also potentially important (e.g., the effect of grapefruit juice on the kinetics of several drugs); available information on experience with products in the same or related chemical and pharmacologic classes should be sought.
- (4) **Immunogenicity:** The assessment of potential immunogenicity remains a significant issue. The development of antibodies may be a rare event which is either not observed or is underestimated based on the relatively short exposure seen in most clinical programs. A plan to assess and monitor potential immunogenicity should be considered, especially in the development of biologics. It is especially important to consider factors such as formulation, stability, storage conditions and

²¹ FDA White Paper. CDER-PhRMA-AASLD Conference 2000 on Drug-Induced Liver Injury: a National and Global Problem, November 2000. See <http://www.fda.gov/cder/livertox>.

changes in the production process that may alter the tertiary structure of a biologic molecule and hence the potential to induce antibodies. Finally, the potential impact of neutralizing or other types of antibodies needs to be considered, as evidenced by the recent finding of pure red cell aplasia with some erythropoietin products.²²

- (5) **Bone marrow toxicity:** Agranulocytosis and aplastic anemia have both been identified as potential adverse reactions of drug treatment. Absence of reliable animal and *in vitro* models make it difficult to find these potential side effects early. Agranulocytosis has a yearly incidence of 5-10 per million in the general population while aplastic anemia is even more rare (annual incidence of 2-5 per million in the general population).²³ Thus, these reactions are not likely to be observed before the drug has been used in a large population, and interpretation of their significance requires knowledge of the population exposed to the product as well as the background incidence in a similar unexposed population.
- (6) **Potential for reactive metabolite formation and hypersensitivity reactions:** Reactive groups and metabolites may be associated with genotoxicity and hypersensitivity/idiosyncratic reactions, such as serious cutaneous adverse reactions, hepatotoxicity or bone marrow toxicity. At the earliest stages of drug development consideration should be given to the identification of chemical structures suspected to be associated with toxicity. The presence of an alerting structure should initiate discussions with a toxicologist to evaluate the significance and relevance of the alert and to prepare a clear rationale for advancement of the compound.

f. Conclusion

The concepts and recommendations in this chapter are intended to provide guidance for managing the complex process of assessing and managing safety information in order to minimize risk to clinical trial subjects during clinical development. They are also intended to ensure the availability and assessment of as much safety information as is reasonably possible

²² Bennett C.L., Luminari S., Nissenson A.R., *et al.* Pure Red-Cell Aplasia and Epoetin Therapy, *New Engl. J. of Med.*, 351: 1403-8, 2004.

²³ Kaufmann D., Kelly K.B., *et al.* *The Drug Etiology of Agranulocytosis and Aplastic Anemia*, Oxford University Press, London 1991.

prior to marketing to optimize the benefits and minimize the risks to future patients. Ideally, the implementation of a procedure that assures a systematic approach to managing safety during development and the use of a Development Risk Management Plan to track progress and action plans along the way will lead to more effective risk identification, risk evaluation and risk minimization. These will go a long way toward protecting volunteers/subjects who agree to participate in clinical trials as well as future patients who will use the drug once it is marketed. Furthermore, it should serve as a basis to define those issues which will require further evaluation in the “real” world or for which specific actions are warranted to minimize risk. The Development Risk Management Plan can thus serve as the basis for developing post-marketing pharmacovigilance and risk minimization plans to be included with new marketing authorization applications.

IV

Collection and Management of Safety Data during Clinical Trials

a. Introduction

Throughout the clinical development of a pharmaceutical product, safety data are collected through the use of instruments such as case report forms (CRFs), serious adverse event reporting forms and laboratory reports. Collection may occur by use of paper, electronic or telephonic media. Data collection methods utilized during the conduct of clinical trials are a vital part of the process of safety monitoring and are of concern to investigators, sponsors, regulators and patients.

Correct data elements must be collected to allow for the proper medical interpretation of individual cases as well as for the analysis of aggregate data.^{1,2} The decision on what safety data to collect and when should be carefully considered based on anticipated needs and concerns for the compound under investigation.^{3,4} In an effort to be all-inclusive, sponsors will frequently collect more data than is actually necessary for analysis.⁵ This may place an undue burden on the investigator and sponsor and divert attention from more important matters during the conduct and monitoring of the study. The aim should be to capture only data that are reasonably expected to be analyzed and assessed. Nevertheless it is prudent to collect more comprehensive safety data during Phase I through III studies in contrast to Phase IV studies, for which the collection of non-serious adverse events and excessive laboratory data, especially for compounds with well established safety profiles, may add little value to the existing knowledge of the product.

Although global Good Clinical Practice standards exist (ICH Guideline E6), detailed standards for the types of data to be collected for safety monitoring are lacking. While ICH Guideline E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) does specify the key data elements for inclusion in expedited reports of serious unexpected adverse drug reactions, and ICH E2B specifies data ele-

¹ Morse, M.A., Califf, R.M., and Sugerman, J. Monitoring and ensuring safety during clinical research, *Journal of the American Medical Association*, 285:1201-1205, 2001.

² Moody, L.E. and McMillan, S. Maintaining data integrity in randomized clinical trials, *Nursing Research*, 51(2):129-33, 2002.

³ Enas, G.G. and Goldstein, D.J. Defining, monitoring and combining safety information in clinical trials, *Statistics in Medicine*, May 15-30, 1995.

⁴ Ioannidis, J.P.A. and Lau, J. Completeness of safety reporting in randomized trials, *Journal of the American Medical Association*, 285: 437-443, 2001.

⁵ Salsburg, D. Deming Principles Applied to Processing Data from Case Report Forms, *Drug Information Journal*, (36): 135-141, 2002.

ments that are to be included in the electronic transmission of expedited individual adverse reaction reports to regulators, these standards were not intended to specify all safety data that might be needed during the conduct of a clinical trial. Study protocols should be the most important tool in defining the methods for study conduct but are not always sufficiently specific and complete regarding safety data surveillance and collection. It is useful to establish a standard template for the safety sections of protocols, which can be amended or supplemented as needed.

A sponsor's study monitors (e.g., Clinical Research Associates or CRAs) have a significant influence on assuring accurate and proper adverse event reporting from study sites. Among their responsibilities, CRAs must assess the completeness and accuracy of safety information, identify omissions, and bring appropriate safety reports to the attention of the pharmacovigilance department in a timely fashion. A useful assessment of their role has been published.⁶

Although this and other chapters focus on new product development and therefore on Phase I-III trials, the role of Phase 4 studies in understanding a product's safety profile should not be underestimated. Phase IV trials are generally distinct from large, post-marketing surveillance (PMS) and observational studies, but may form part of a commitment required by regulators as a condition for approval to market a drug (post-authorization study requirements). Phase IV studies make an important contribution in expanding the clinical trial database. Although safety monitoring during these types of studies may not require the same intensity as for Phase I-III trials, the principles and ideas presented here remain applicable.

Phase IV studies that mimic clinical practice (reflecting routine administration of the drug) and involve large numbers of patients, whether of comparative design or not, may require some routine, general safety monitoring. In contrast, more intense safety monitoring is critical in peri-approval studies (initiated near the completion of registration studies and often called Phase IIIb) where the parameters may be similar to those included in Phase III trials. In some cases, specific focus may be needed for a safety issue that requires exploration. This also applies to post-marketing studies for orphan drugs, where although the primary objective may be further assessment of efficacy, safety monitoring is also a critical element due

⁶ Nylen, R. A. The Impact and Responsibilities of the Clinical Research Associate (CRA) on the Accuracy of Adverse Event Reporting, *Regulatory Affairs Focus*, p. 16-20, April 2000.

to the limited patient exposure prior to approval. Similar and additional⁷ considerations apply to vaccines and to drugs given expedited marketing authorization (e.g., anti-HIV and oncology medicines).

Sponsor requirements for investigator sites differ regarding collection of signs and symptoms when a diagnosis is also specified, what data elements to collect, when collection begins and ends, how promptly safety data must be reported to the sponsor, and how investigators should conduct causality assessments. For an indication of the variability among sponsors surrounding data collection, see items 3 through 8 of the survey results in Appendix 3. Differing safety data terms, definitions and collection methods requested by different sponsors may lead to confusion and inefficiency on the part of investigators. One of the most important issues that is rarely addressed is the manner in which safety experiences are actually elicited during discussions with patients by the investigator and his/her staff during visits or at other times.

Consistency in safety data collection and handling practices can contribute to greater efficiencies in the conduct of clinical trials. This should result in greater confidence in the data available for analysis and allow investigators, sponsors and regulators to focus more time on review of the data, thereby promoting the health and wellbeing of clinical trial patients/subjects as well as future patients who stand to benefit from the therapy.

The remainder of the Chapter discusses various approaches to those issues by addressing Who is responsible for collecting the data, What should be collected, How should the data be gathered, When, and some technical considerations for managing the data once collected.

b. Who?

The collection of data originates with the patient/subject, caregiver or legal representative of a patient in clinical trials. However, it is usually the investigative site (investigator and his/her staff) that is responsible for gathering data from the patient, recording the information properly, and ultimately reporting to the sponsor. Even though patients may be collecting data in diaries or in electronic format, our primary focus is on the collection

⁷ The populations in many vaccine pre-licensing programs are fairly large but still quite small in relation to the intended general population (usually children). They are also traditionally of short monitoring duration. Late sequelae are difficult to detect with reliability and precision. The design of post-authorization studies is therefore critical (e.g., cluster designs where the program starts with a planned geographical distribution so that comparative populations exist in different locations (seasonal and population controls)).

of data at the investigative site. It is the responsibility of the investigator to ensure that patient data are properly collected and reported to the sponsor. In certain Phase I trials a sponsor may also act in the role of the investigator and would assume these responsibilities.

In general the personnel at the site are the patient's primary contact during a trial. All site personnel and the investigator must ensure that safety data are properly collected and forwarded to the sponsor. Although personnel other than the investigator may obtain adverse event information during regular communication, even between visits, it is ultimately the responsibility of the investigator to ensure that information is collected in accordance with the study protocol. Study monitors representing the sponsor will review source documents against case report form entries to check for accuracy and completeness in recording of the data, and to ensure that there is conformity with the protocol. Sponsors have a critical role in clearly defining the data to be collected as well as the process the investigator should use in recording these data. However, if an investigator becomes aware of information that is considered to be important for safety reasons it should be reported to the sponsor (immediately if judged critical), even if the protocol does not specifically state that the information must be collected. To assure the investigator's sensitivity to this point, one of the key responsibilities of the sponsor includes proper training of the investigative site personnel regarding data collection and reporting.

Many studies involve collaboration with contract research organizations (CROs), public and private institutions, other collaborative groups, and co-development partners. In all of these arrangements, data collection is the responsibility of the investigator. Clear agreements must be reached and documented among the collaborating partners as to who is responsible for monitoring the study and retrieving and processing the data. Many of the sponsor responsibilities involving data processing may be delegated to a CRO.⁸

Studies not sponsored by the manufacturer of an approved medicine can, of course, be conducted by independent investigators and their institutions (public or private), who take on the roles and responsibilities of a sponsor in processing and analyzing safety data. However, if a company provides any support for such an independent trial (supplies, research grant, etc.), the company should still obtain at a minimum all reports of

⁸ For example, see US FDA Regulation 21CFR312. 52.

serious suspected adverse reactions from the investigational site(s).⁹ Some companies require reports on all serious *events*. Arrangements must be made between the parties to ensure that the required obligation is fulfilled. Investigators are expected to comply with any local regulations regarding their reporting to authorities of adverse experiences during clinical trials. However, once the relevant reports are received by the company, it should document them in its own database and take them into account during their ongoing safety assessments and when preparing appropriate periodic safety reports (e.g., PSURs).¹⁰

Availability of the final results as a report and/or publication should also be part of an agreement between the investigator and the manufacturer. Animal studies on an approved/marketed product may also be conducted independently of a manufacturer; again, if support is provided (usually supplies of product or active moiety), it is incumbent on the manufacturer to ensure that results are made available. For more details, see Chapter 7, Section d.

c. What?

(1) *General Principles*

Data that should be collected and evaluated for safety will depend on the design of the clinical trial but may include: adverse events (experiences), laboratory values, pharmacokinetic data, results of mental and physical examinations, special study data (e.g., Holter monitors, EEG, ECG, audiology testing, pregnancy testing, etc.), pharmacogenetic data and quality of life data. Patient demographics, study medication doses and duration, a measure of medication compliance, concurrent medical conditions, and concomitant medications are also extremely important in the interpretation of safety data. Additional items such as exercise history may be helpful in understanding changes in values such as CPK and liver enzymes. However, investigators are frequently asked to collect data that are never utilized, wasting the time and resources of both investigators and sponsors. Therefore, sponsors must carefully pre-select the data elements

⁹ There is no standard definition of what constitutes “support” by a company. For example, does it include medical and/or regulatory review of a protocol on request to a company by an independent investigator? Some companies are known to consider any interaction of this sort to constitute support and therefore enter into an agreement with the investigator to receive safety information.

¹⁰ The MHLW (Japan) is encouraging independent investigators to conduct research that manufacturers of approved medicines may not wish to do on new uses (indications, for example); companies would be required to provide drug supplies and to maintain awareness of important safety findings. This proposal is under consideration.

that are necessary for analyzing the safety (and efficacy) of all treatments and clearly state them in the study protocol and/or case report forms. Reports of serious adverse events typically require more detail than non-serious (see section c. (7) below and Appendix 6). In early phases of drug development, it is generally necessary to collect more comprehensive safety data than in post-marketing studies. In addition, certain drug types may require longer routine follow-up as in the case of vaccines, immunotherapies and some biotechnology products.

The collection, monitoring and assessment of data from Phase 1 studies deserve special attention for two reasons: (a) with some exceptions (e.g., oncology medicines, pharmacokinetic studies in subpopulations such as the organ impaired), such studies are conducted in healthy volunteers for whom there is no anticipated health benefit and (b) the results are critical to the future development of the product and must be scrutinized and interpreted with great care. For prophylactic treatments and preventive vaccines, the same considerations apply even to later stage clinical trials.

As explained by Salsburg,¹¹ it is highly unlikely that a case report form will ever contain data fields for all data that might ever be needed for evaluation of all possible safety concerns. He also describes issues surrounding the collection of “excessive” data and the negative impact on data quality. Therefore, case report form fields should be chosen based on the data elements that will be analyzed and can be typically presented in tabular compilations of study results. Safety data that cannot be categorized and succinctly collected in predefined data fields should be recorded in the comment section of the case report form when deemed important in the clinical judgment of the investigator. Because comment sections are not easily coded, they should be used in connection with a standard AE section of the CRF and instructions as to their use given to the investigator during pre-study training.

Prior to study initiation, consideration should be given to how certain data are to be collected: adverse events; diagnoses with or without accompanying signs and symptoms; clinical outcomes; causality assessments; serious and “medically significant” cases; as well as adverse events of special interest (see section c.(4) below and Appendix 1). It is also helpful to decide where in a CRF, if appropriate, non-protocol-related diagnostic and/or

¹¹ Salsburg, D. Deming Principles Applied to Processing Data from Case Report Forms. *Drug Information Journal*, (36): 135-141, 2002.

treatment-emergent procedures should be captured. All of these items require definition and specification.

During clinical development, knowledge of the safety profile of the investigational product is limited. There are no definitive methods for distinguishing most adverse drug reactions (events that are causally attributable to study therapy) from clinical adverse events that occur as background findings in the population and have only a temporal association with study therapy. The CIOMS VI Working Group thus recommends the following:

All adverse events, both serious and non-serious, should be collected for any clinical trial during development, regardless of presumed relationship to the study agent by the investigator or sponsor, in order to allow for subsequent assessment of causality using standardized methods for individual cases and aggregate data. This applies not only to the experimental product but to placebo, no treatment, or active comparator.

In studies initiated during the immediate post-approval period, it is prudent to continue this practice. Once the safety profile of a marketed product is judged to be well understood and established, it may be acceptable to collect less data. While detailed information on serious adverse events should always be collected, for well-established products it may be appropriate to collect non-serious adverse events only if suspected by the investigator to be related to the compound. This would be especially appropriate for large scale, simple post-marketing trials when the population, indication, and doses are consistent with those included in the approved use(s) of the drug.

In addition to the above recommendation, it may be of interest to collect non-serious event reports that led to discontinuation from treatment; this could be important in studies of slightly different populations than studied during development, for example.

The collection of comprehensive laboratory chemistry data during post-approval studies is usually not necessary. As for all studies, the protocol should clearly specify what adverse event and lab data must be collected.

Finally, a commonly overlooked but potentially important aspect of data collection relates to the possible use of herbal and other non-traditional remedies by patients/subjects, who typically do not regard such treatments as drugs or medicines. It is therefore important to inquire specifically about their use since their concomitant use with study treatment

can lead to adverse drug interactions.¹² Recent classification and coding schemes for herbal medicines are available.¹³ In addition, readers may be interested in a recently organized information exchange process designed to strengthen the scientific basis for standards governing the safety, quality and efficacy of herbal medicines under the Western Pacific Regional Forum for Harmonization of Herbal Medicines (FHH).¹⁴

(2) Causality Assessment

Investigators must inform the sponsor of serious adverse events as soon as they become aware of them and, by using clinical judgement, should assess the potential link to the drug treatment. Some hold the opinion that causality determinations on individual case reports are a “waste of time” especially for randomised studies. However, while individual case causality assessment may be difficult for both investigators and sponsors, the investigator’s opinion contributes to the sponsor’s decision on the necessity for expedited reporting to health authorities – a requirement that depends on individual case attribution. Causality judgments based on analysis of multiple cases/aggregate data are almost always more meaningful and typically have a greater impact on the conduct of clinical trials, including changes to informed consent documents, study design, and core safety information. However, while aggregate assessment of data is ultimately a more reliable indicator of drug-event attribution, causality assessment of individual adverse events by the investigator may play a role in the early detection of significant safety problems, and contribute especially to understanding rare events. The investigator is in the best position to judge any unusual changes in the status of the patient that might be related to the administration of the study medication or a study intervention. He/she should know the baseline condition of the patient and therefore should be able anticipate the normal clinical course that the patient is expected to follow. Therefore, the investigator’s opinion on the relatedness of the event to the study treatment or intervention should be solicited when serious adverse events are reported.

¹² See Brazier, N. C. and Levine, M. A. H. Understanding drug-herb interactions, *Drug Information Journal*, 12:427-430, 2003 and Willis, J. Drug interactions – when natural meets ethical, *SCRIP Magazine*, Issue 91, pp. 25-27, June 2000.

¹³ See *Guidelines for Herbal ATC Classification and Herbal ATC Index*, the Uppsala Monitoring Centre, Uppsala, Sweden, 2004. Also, see *WHO Guideline on Safety Monitoring of Herbal Medicines*, *ibid*. Herbal substances are recorded in the WHO-Drug Dictionary. For detailed information, see www.umc-products.com and www.who-umc.org.

¹⁴ The Forum provides an active means for regulatory authorities to share information, coordinate efforts and transfer expertise. See <http://www.fhfm.net>.

Collection of investigators' relatedness assessments for non-serious events adds little value and is not needed for routine regulatory reporting.

It is recommended that investigators not be asked routinely to indicate causality information for non-serious adverse events. However, there may be circumstances when such assessments are useful and important, such as for non-serious adverse events of special interest.

Companies ask investigators to utilize various methods and terminologies for categorizing the “likelihood” that a serious adverse event is caused by the drug. Terms such as likely, unlikely, possible, probable, definite, definitely not, remote likelihood, and cannot-be-ruled-out have been used. Although various companies have used several methods that imply different degrees of causality:

The CIOMS VI Working Group recommends that the investigator be asked to use a simple binary decision for drug causality (related or not related) for serious adverse events.

While there is rarely sufficient information and experience to assign causality to an adverse event definitively as “yes” or “no”, the various gradients of relatedness offer little or no advantage in data analysis or regulatory reporting. Initially, causality assignment is used mainly as a prioritization tool for deciding on whether an individual case must be reported to the regulators. Furthermore, there is very little agreement among different people on the meaning and weight of the terms (probably vs. possibly vs. likely, etc.) even within the same language, but is even more disparate across languages. One possible approach that has been suggested is to ask simply whether there is a “reasonable possibility” or “no reasonable possibility” that the study treatment caused the event; alternatively – Was there a reasonable possibility? Yes or No. Finally, irrespective of any causality assessments, aggregate analysis will be conducted with all the data. The use of “unknown” or “cannot-be-ruled-out” also adds little value in early determination of safety concerns. The use of “cannot-be-ruled-out” to imply drug relatedness would lead to excessive over-reporting and excess noise in the system. It is virtually impossible to completely rule-out the role of a drug in causing an adverse event in single-case reporting.

While not unanimous in the above recommendation, the “binary” decision choice was the method favored by a majority of the CIOMS VI Working Group members.¹⁵

¹⁵ See the Glossary (Appendix 1) for more discussion under Adverse Drug Reaction.

To facilitate the process by which an investigator judges the cause of a serious adverse event, the Working Group advocates adoption of the recommendation by the CIOMS III/V report on core safety information and the DCSI (Development Core Safety Information), namely that on the CRF and on any serious adverse event form there be included a standard list of potential causes from which the investigator must choose the most plausible one in his/her opinion, specifically: medical history; lack of efficacy/worsening of treated condition; study treatment; other treatment, concomitant or previous; withdrawal of study treatment (a withdrawal reaction could be considered drug-related); erroneous administration of treatment; protocol-related procedure; other – specify.¹⁶

The CIOMS VI Working Group recommends inclusion of the CIOMS III/V checklist of potential causes of a serious adverse event on the reporting forms used by the investigator. If an investigator considers that an event is not drug related, the most likely other cause(s) should be indicated.

The CIOMS III/V report also provides criteria that can be helpful in assessing causality for both individual cases and series of cases (aggregate data) with a goal of deciding when the threshold has been reached for adding new adverse drug reactions or other safety data to product information. In the context of clinical trials, these same criteria with some additional considerations is helpful for deciding when it is appropriate to add information to the Investigator's Brochure/Development Core Safety Information (see Appendix 7). Investigators are usually asked to make causality decisions on individual cases and study start-up should include training for making such assessments. Much of the material in Appendix 7 can be helpful in this regard.

(3) Diagnoses vs. Signs and Symptoms

An investigator's expertise is important in aiding the sponsor to interpret adverse events, especially in providing a diagnosis, if applicable. Some sponsors request that an investigator record all signs and symptoms as well as a diagnosis when possible. Others ask for just the diagnosis. If an investigator participates in trials involving different sponsors this may lead to confusion and inconsistencies in how the data are recorded. The collection of non-specific signs and symptoms rather than diagnoses or syndromes often leads to extensive lists of these events in product information,

¹⁶ *Guidelines for Preparing Core Clinical-Safety Information on Drugs*, Second Edition, Including New Proposals for Investigator's Brochures, Report of CIOMS Working Group III/V, CIOMS, Geneva, 1999.

resulting in limited usefulness to prescribers. Therefore, the CIOMS Working Group recommends the following:

The investigator should be encouraged to evaluate the events of trial patients and record on the case report form a diagnosis (when possible and appropriate) rather than each individual sign and symptom. This instruction should be clearly specified in the protocol. However, when an investigator submits a serious adverse event report that includes a diagnosis it is important that the signs and symptoms as well as any other supporting information that led to the diagnosis also be recorded, specifically as part of the narrative description of the case.

The advice to collect and document signs and symptoms for serious AEs would seem to contradict the recommendation given earlier not to collect extraneous or redundant information; it also may be in conflict with the MedDRA® Points to Consider document (par. 2.5.3).¹⁷ However, knowledge of signs and symptoms is especially important for serious adverse event cases that may have to be reported to regulators promptly; frequently there may not be enough information available to provide a confirmed diagnosis. As additional information becomes available, such as results of laboratory work and diagnostic work-ups, the original presumed diagnosis may need to be changed. A description of signs and symptoms may also be important in certain trials such as Phase I studies or in a situation where an investigator is unable to make a confirmed diagnosis. As an aid to making a diagnosis, it might be useful to refer to an existing CIOMS guide that provides diagnostic standards for adverse reactions, that would enhance accuracy and consistency in the use of ADR terms.¹⁸ Training of the investigative site in the proper use of the relevant diagnostic terms is important for consistent data collection.

Prior to study initiation, it is recommended that specific criteria for identifying and defining significant, anticipated adverse events be established and communicated to investigators involved in the detection, assessment and reporting of adverse events.

An example might be significant liver function test elevation, defined as three or more times the upper limit of normal, which is often used as a criterion. Such definitions and criteria should be included in the safety section of the protocol.

¹⁷ See http://www.ich.org/ichMedDRA_PTC.html

¹⁸ *Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use*, Edited by Z. Bankowski, et al., Council of International Organizations of Medical Sciences, Geneva, 1999. This report comes with a CD rom for ease of use. Also, see Venulet, J. and Bankowski, Z. Harmonizing Adverse Drug Reaction Terminology, *Drug Safety*, 19(3):165-172 (1998).

(4) Adverse Events of Special Interest

It is useful to consider a class of adverse events that may not be serious but have special meaning or importance for a particular drug or class of drugs. Although it is ordinarily unnecessary to create specific definitions or criteria for non-serious adverse events, it is important to do so for apparently non-serious events that might be precursors (prodromes) of more serious medical conditions; for example, muscle pain and elevated CPK together may be indicative of potential rhabdomyolysis. Other types of non-serious events may be important in and of themselves, such as those that could affect quality of life in a meaningful way (e.g., impotence, hair loss). Such events examples of what are often referred to as adverse events of special interest, when there is evidence or suspicion of their potential importance. For more detailed discussion, see the Glossary (Appendix 1).

Toxicology studies and other non-clinical research may suggest the potential for serious adverse events in humans. Prior to initiation of clinical trials, the sponsor may identify adverse events of special interest from these data, or from experiences with similar compounds, and require special collection and reporting by the investigator. For example, if a compound in development has been demonstrated to have the propensity to cause tachycardia in pre-clinical studies or if this is a concern with other compounds in the same class, it would be prudent to proceed with caution in any human trials. ECGs should therefore be monitored and tachycardia routinely reported by investigators to sponsors for all subjects/patients until the risk to humans is delineated. While animal studies may or may not be predictive of potential human toxicity, they cannot rule out all potential toxicity.

It is important to define clearly “adverse events of special interest” in the protocol and to specify close monitoring and prompt reporting to the sponsor of these types of events, even if the event is considered non-serious according to the usual regulatory criteria.

(5) Laboratory Chemistry Measurements

The use of clinical lab tests as surrogate markers for toxicity in early clinical studies is critical. Laboratory assays such as haematopoietic (CBC and cell differential), biochemistry panels (e.g., musculo-skeletal, renal, hepatic, cardiovascular and lipid metabolism assays), and urinalysis results should be collected in all early studies. More targeted laboratory investigations involving areas such as endocrine, coagulation, immunologic, and

reproduction systems may be required based on results of early toxicology studies. Certain laboratory parameters may also qualify as adverse events of special interest and require more frequent testing and evaluation.

(6) Morbidity and Mortality as Efficacy Endpoints

In studies involving a disease state associated with significant morbidity or mortality (for example, cancer, sepsis, AIDS), it may be appropriate to collect certain medically anticipated clinical events only as clinical efficacy outcomes rather than adverse events. An example would be death as the result of progression of breast cancer. In studies without such an anticipated clinical endpoint, any event resulting in death would be considered a serious adverse safety event. Collection of clinical outcomes may allay some of the burden for investigators in having to report all disease-related events as serious safety adverse events in studies involving severe illness.¹⁹ The method of collection may differ from that of serious adverse events in that it may be more streamlined (less data) and batched (sent in weekly, for example, rather than immediately). The collection process should be clearly delineated in the protocol. ICH Guideline E2A describes the conditions for managing such situations. Under such a process, it may then be appropriate (although admittedly somewhat problematic) to enter the cases only in the clinical trial database, but not into the separate safety database which most companies maintain for serious clinical trial cases and all spontaneous reports from marketed products (see Sections d.(2) and f. below). On the other hand, if a patient experiences a suspected serious adverse event at the same time as the designated efficacy endpoint event, all the information on both events should be included in both databases.

It is recommended that even when anticipated medically serious clinical events are collected as clinical efficacy outcomes/endpoints, rather than as adverse events, these data must be recorded by the investigator and periodically reported to and reviewed by the sponsor or DSMB, on a schedule specified in the protocol.

The protocol should also specify how promptly and frequent reporting should be. It should also be made clear how often these data will be reviewed, how they will be reviewed (blinded or unblinded), and by whom, including the use of Data and Safety Monitoring Boards, as needed. In the course of reviewing such cases, it may be important to consider whether

¹⁹ Nichas, J. Clinical Trial Safety Surveillance in the New Regulatory and Harmonization Environment: Lessons Learned from the “Fialuridine Crisis”, *Drug Information Journal*, (31): 63-70, 1997.

study therapy could have had the paradoxical role of worsening the clinical outcome (see footnote 19). Prior to trial initiation, agreement should be reached with regulators in all countries where a study is conducted as to how clinical endpoint data will be reported.

(7) Special Situations

Investigators should be sensitized to the concept that even when information is not considered adverse event data, it should be forwarded promptly to the sponsor if it can possibly contribute to the overall knowledge concerning safety of the compound. For example, any deviation from specified doses as defined in the protocol (especially doses that are higher than recommended) should be reported to the sponsor in the same time frame as for serious adverse events even if there are no associated events. Medication errors, including inappropriate route of administration, should also be reported promptly. Companies may wish to use their serious AE forms for convenience, or some other process for collecting the relevant information.

Pregnancies occurring during clinical trials present a unique situation. Any pregnancy that occurs in a female trial participant during a clinical trial should be followed to termination or to term. Under special circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery. There may also be special situations when it will be necessary to monitor the pregnancy of a woman whose male partner is the trial participant (e.g., class effects, evidence from animal reproductive studies). Partner privacy may become an issue in follow-up for these situations. The protocol should describe in detail the process for monitoring and managing pregnancy occurrences.

The collection of genetic data for safety purposes continues to generate much debate^{20 21 22 23}. This topic is beyond the scope of this project but has been considered by another CIOMS Working Group.²⁴

²⁰ Freund C.L., Wilfond, B.S. Emerging ethical issues in pharmacogenomics, *American Journal of Pharmacogenomics*, 2(4): 273-281, 2002.

²¹ Roses, A.D. Pharmacogenomics and the future of drug development and delivery, *Lancet*, 355: 1358-1361, 2000.

²² Sander, C. Genomic medicine and the future of health care. *Science*, 287: 1977-1978, 2000.

²³ Polymeropoulos, M.H.. Application of genetics and genomics in drug development, *Drug Development Research*, 49: 43-45, 2000.

²⁴ *Pharmacogenetics – Towards Improving Treatment with Medicines*. Report of a CIOMS Working Group, CIOMS, Geneva, 2005.

As part of recommendations for good follow-up practices, the CIOMS V Working Group²⁵ provided listings of data elements that should be collected for various types of adverse event cases, depending on the seriousness and expectedness of the case. While the CIOMS V formulation primarily focused on post-marketing cases, the same elements, and more, are important for clinical trial safety monitoring (see Appendix 6). Consideration should be given to the collection of as many of these data elements as possible, as part of the CRF for each patient. When a serious case is reported, these elements should be collected, even if they are not part of the CRF.

While different companies use different forms for collecting data on serious and special adverse event cases from investigators, there has been some interest in the development of a standard form that might be used by all sponsors when possible. In the CIOMS VI survey, a majority of the respondents (16 of 21) would support the use of a global form (see item 9 in Appendix 3). It is recognized that the format and contents of data collection forms are often dependent on the user's internal standards and established computer systems. However, as an illustration of what a prototype form might look like, the Working Group presents an example in Appendix 8. The Working Group is not proposing that this example become a standard but is providing it for those who may wish to create their own form.

No matter what form is used, it is strongly recommended that the choice of data elements and their definitions conform to those specified under ICH Guideline E2B to facilitate the sponsor's data processing and eventual electronic transmission, as needed.

d. How?

(1) General Considerations

Various methods exist for collecting safety as well as efficacy data. Most clinical trial data are collected on paper case report forms (CRFs) or by electronic means.²⁶ The method should be clearly defined in the protocol. The increasing use of wireless and Internet technologies by many sponsors in an attempt to increase study and data management efficiency

²⁵ *Current Challenges in Pharmacovigilance: Pragmatic Approaches*. Report of CIOMS Working Group V, pp.128-130, CIOMS, Geneva, 2001.

²⁶ Ruberg, S.J., McDonald, M. and Wolfred, M. Integrated electronic solutions, *Applied Clinical Trials*, 11(2): 42-9, 2002.

introduces new issues in the move from paper-based to electronic records.²⁷ Usually patients report their symptoms during examination by the investigator or site staff at protocol-specified visits. During or after the examination, investigators or their assistants record adverse events along with other relevant findings on the CRF. Except for in-patient studies, the existence of acute, medically serious adverse events requiring emergency care will usually first be learned by phone or sometimes through an emergency room physician. Inter-institutional communication is quite important under such circumstances. It is usual practice that for serious adverse events, the investigator be asked to obtain copies of relevant hospital records to supplement the usual CRF and serious AE form information on the patient. For cases involving deaths, coroner's reports and any autopsy findings should be obtained. However, it is important that emphasis be placed on the need for the investigator to complete and submit the company's special serious AE form; the often voluminous supplemental records that may be obtained can be uninterpretable.

Before further addressing the mechanism of how safety data should be collected, it is important to consider the basis of all patient data collection: the interaction and dialogue between patient and investigator site personnel. The measurement of objective parameters, such as lab tests, electrocardiograms, etc., is reasonably straightforward and generally does not have a strong subjective component. In addition, site professionals should be observant for signs and symptoms suggestive of adverse effects (rash, etc.). However, there are many ways in which investigators and their staff can and do solicit information and opinions from trial participants and they are not all equivalent or consistent in their ability to elicit complete, meaningful and unbiased data. For example, at each visit open-ended questions might be asked, such as "Has the medication affected you in any way?" (which might imply a suspicion that it could), or "Have you experienced any ill effects from your treatment?" (a leading question which could influence the patient to associate any untoward event with the treatment). In some situations, the patients may be asked to keep a log of their experiences between visits. In such a log, or even during face-to-face questioning, the patient may be presented with a list of possible adverse experiences ("Have you had any headaches, nausea,...?"). Other possibilities for soliciting this type of information include the use of electronic, menu-driven interviewing techniques.

²⁷ Clinical Trials and the Internet, *R&D Directions*, November/December 2001, p. 34-48.

This area has not received much attention, but the CIOMS Working Group believes that it can be very important and recommends the following:

The process used to solicit information from patients during clinical trials should be consistent from site to site, and if possible from program to program, and should be clearly outlined within study protocols, in the informed consent information, and during investigator training. No matter what method or approach is used, it should be used consistently throughout the trial, including at baseline (pre-treatment information).

It is probably best to frame questions to the patients in general terms rather than to invoke the possibility that study treatment may be responsible for ill effects. For example: “How have you felt since I saw you last? Is there anything new that you wish to discuss?”

Although it is not advisable to read a specific list of possible ADRs when soliciting the patient’s recent experience, patients should be alerted to known signs and symptoms indicative of medically important suspected or established ADRs in order to alert the investigator as early as possible.

An example of the latter situation is muscle pain and/or tenderness in trials of HMG CoA enzyme reductase inhibitors (i.e., statins) which could possibly be associated with rhabdomyolysis. Patients can be advised during the informed consent process or perhaps with a handout to be particularly attentive to such important signs and symptoms and to mention them to the investigator at the earliest opportunity. However, this type of “warning” to patients should not be used routinely but only under special circumstances.

One particular difficulty in this area relates to the gathering of subjective data from patients who are unable to provide it, such as neonates and infants, patients with Alzheimer disease, patients in a coma, and others for whom a parent, home caregiver or other proxy represents and speaks for the trial participant. To our knowledge, there are no international guidelines on how such situations should be managed.²⁸ However, as with more normal circumstances, for studies involving such patients the process for obtaining data should be described in the protocol and informed consent information.

²⁸ For one region’s example, see Adults with Incapacity Act 2000 (Scotland; see <http://www.scotland.gov.uk/Topics/Justice/Civil/16360/4927#mod39793>) and UK Department of Health’s Draft Guidance on Consent by a Legal Representative on Behalf of a Person Not Able to Consent Under the Medicines for Human Use (Clinical Trials) Regulations 2003. For more discussion, see Chapter 14 of *Medical Ethics Today*, 2nd edition, British Medical Journal Press, 2004.

Many companies prepare study manuals to supplement protocols, in which high levels of detail on processes and procedures are described; this would be another place in which this subject can be covered.

(2) *Serious and Other Important Adverse Events*

Typically, sponsors require that investigators immediately notify them when a serious adverse event occurs. This may be reported verbally by telephone, by faxing a reporting form that is distinct from the CRF, or by electronic means. As mentioned above, in an effort to simplify the process and provide consistency and less confusion to investigators in reporting serious adverse events to sponsors, a standardized form that could be completed by investigators might be considered (Appendix 8).

Laboratory, biopsy, ECG, EEG, audiology testing and other special study data may be generated from local or central laboratories or clinics. The investigator should arrange to receive immediate notification of any alarming results. These should then immediately be brought to the attention of the sponsor as well. Processes describing collection and notifications should be specified in the protocol. Obviously, where appropriate, reference standards for laboratory values should be obtained by the investigator and sponsor for proper interpretation of the data.

Most sponsors maintain two databases that contain safety data. One contains serious adverse event cases that may require expedited regulatory reporting as well as cases from ongoing surveillance activities on marketed products (e.g., spontaneous reports). It would also be advisable to include non-serious adverse events of special interest. This database (the “safety database”) is used to accumulate safety data on the compound as it progresses through development and during marketing. The other contains all of the safety, efficacy, and other data from the clinical trial, including serious and all non-serious adverse events. This clinical trial database, unlike the usually separate safety database, is typically closed and “locked” for analysis once the study is complete. It is important for the sponsor to have clear policies and procedures for processing of these data and for ensuring that the data within the two databases are consistent and any differences reconciled when necessary.²⁹ Attention must also be paid to the possibility that information in the safety database may be updated after a study is

²⁹ Some companies maintain a minimum set of data elements that must be reconciled between the two databases, such as: project/protocol number, investigator number, patient initials and/or number, gender, birthdate, verbatim AE terms, onset date of AE, severity of event (if used, e.g., mild, moderate, or severe), criteria for serious if case is serious, and investigator’s causality assessment.

completed and the clinical trial database has been frozen. Whether any changes are needed to the final study report or in the analysis of the data (which may already have been completed) will require judgment and depend on the importance of the information in categorizing the safety profile (and possibly the benefit-risk relationship) of the product.

e. When?

A period of observation must be defined in the protocol for each study. Typically, the time that the informed consent is signed by the patient is designated as the start of safety data collection (see survey results for item 4 in Appendix 3). This provides a clear starting point and helps to avoid any selection bias. If a patient will not formally enter a trial until several days or longer after the informed consent is signed, the day of randomization to treatment may be a more appropriate time to begin collecting safety information. Adverse events occurring prior to randomization would be considered as medical history or pre-existing conditions. It is important to collect such information in order to place into perspective “study treatment-emergent” findings; for example, the occurrence of nausea after informed consent signing, but prior to administration of study treatment, would be useful information.

In some studies it may be necessary to collect baseline safety data during pre-drug therapy. If a washout period is included as part of the protocol, with or without the use of placebo, safety data should be collected. This will allow for assessment of any worsening of study treatment-emergent conditions. It is also possible that an invasive procedure will be used as part of screening prior to study inclusion (e.g., tissue biopsy) that carries the risk of adverse events; such data should be collected and be part of the overall safety experience for the trial population. The start of collection of safety data should be clearly indicated in the protocol. Once data are recorded, they should be forwarded to the sponsor in accordance with the protocol’s requirements so that they are available for safety monitoring.

The protocol should specify the observation period for the patient following the last dose of study medication and/or the last protocol-specified visit. Survey results show that this observation period varies widely from company to company (see item 5 in Appendix 3). The protocol should clearly specify how and when collection of safety data should occur during a post-study observation period. It may be accomplished by additional visits or via telephone, for example.

It is recommended that in general, safety data event-collection should continue after the last dose of the drug for at least an additional five half-lives.

This time will vary depending on the type of compound studied and its specific characteristics. While this general guideline may apply to most compounds, due to the diversity of products in development and patient-specific circumstances it is difficult to create a rule that would be appropriate in all cases. For example, compounds such as cytotoxic agents may have delayed toxicity that needs to be monitored over longer time periods. On the other hand, for compounds with extremely long biological half-lives (e.g., several years, as with bis-phosphonates), post-study monitoring can be considerably shorter than the half-life. Organ impairment may prolong the drug half-life. The biological effects of some drugs may continue beyond five half-lives. Again, the time period for collection as well as a description of what is to be collected must be defined in the protocol and factored into the time-lines anticipated for the clinical program.

If a patient is withdrawn from treatment due to safety reasons or if a patient has an ongoing serious event or adverse event of special interest at the end of the study, the patient should be followed until the event disappears, the patient's condition has stabilized, or until a pre-defined outcome is reached.

Any patient who voluntarily withdraws from a study should be carefully questioned for the possible occurrence of an adverse event.

Whenever possible, a patient should be followed through the last scheduled study visit even if the patient is withdrawn from treatment, in order to allow for appropriate intent-to-treat analysis. (See Chapter 6 for more discussion).

The sponsor should be informed if the investigator becomes aware of any unusual safety information or any safety information that appears to be drug related involving a patient who had participated in a study, even after an individual patient completes the study. An investigator should always be diligent in looking for possible latent safety effects that may not appear until after a medication is discontinued. Sponsors should encourage this practice. An example would be the discovery of a suspected hepatotoxic effect three months after a patient had completed a two-year study (with no other plausible cause).

f. Safety Data Management Considerations

Collecting the best data in the world is of no use unless they are properly documented and made available in a consistent and accurate way for examination, analysis, presentation, reporting and sharing with appropriate stakeholders, within and outside the sponsor's organization. A certain level of expertise as well as judgment are needed to ensure that adverse events and other data (e.g., laboratory findings) are properly named, classified, and coded when creating a database. This section provides some guidance and recommendations to that effect.

Generally, in order to assure standardized signal detection and evaluation processes, data quality and completeness are paramount.

The CIOMS VI Working Group recommends the following principles for this important objective:

- ❑ *individual case safety reports from studies should be as fully documented as possible*
- ❑ *there should be diligent follow-up of each case, as needed*
- ❑ *the reporter's verbatim AE terms must be retained within all relevant databases*
- ❑ *if the reporter's AE terms are not considered to be clinically accurate or consistent with standard medical terminology used for coding, attempts should be made to clarify the description of the event with the investigator. If there continues to be disagreement, the sponsor can code the AE terms according to its judgment on the case, but should identify them as distinct from the investigator's terms. Reasons for the difference(s) should be documented.*
- ❑ *personnel with knowledge and understanding of both clinical medicine and the dictionary used should review all codified terms to ensure consistent and accurate codification of reported ("verbatim") terms.*
- ❑ *primary analyses of AE data should be based on the investigator's assigned terms or diagnoses, carefully and properly coded by the sponsor; additional analyses using the sponsor's assignments if any are different can be conducted, but explanations for any differences between the two analyses must be given.*

The rest of this section elaborates on these principles.

(1) Clinical Description of Adverse Events

There are no universally accepted criteria and definitions for many widely used terms commonly used in drug research such as abnormal LFTs, hepatitis, hepatocellular damage, hepatic necrosis, and various clinical syndromes. Care should be taken to ensure that adverse events are not misclassified with inappropriate or even erroneous clinical terms. This situation is often exacerbated when the event affects a body system that is outside the investigator's clinical specialty. For instance, in one antibiotic development program, five cases were reported as "LFT abnormalities" or "hepatitis" without any abnormalities in the relevant laboratory values. Other examples include reporting of "increased LFTs" to describe a patient with jaundice, "acute liver failure" without jaundice or encephalopathy, "leucopenia" to describe a case of agranulocytosis, "aplastic anaemia" without reduction in all haematopoietic lineages, etc. When available, relevant laboratory data, in addition to signs and symptoms, should form part of the clinical evaluation of reported events.

Another common example is skin reactions, most commonly reported simply as "rash", without further description or characterization. The severity of rashes may be either over- or underestimated, such as the reporting of a benign morbilliform rash as erythema multiforme, or a case with mild signs suggesting possible Stevens-Johnson syndrome but reported as just "rash". Inappropriate clinical characterization can potentially obscure the presence of a real safety issue. The CIOMS publication on criteria for diagnosis of many types of adverse events, especially serious events, can assist sponsors in establishing standards in this regard.³⁰

Individual case safety reports (ICSRs) must be categorized and assessed by the sponsor using trained individuals with broad expertise in both clinical medicine and codification. Investigators should be encouraged to obtain specialist consultation for clinically important events that occur outside their own areas of clinical expertise, so that sponsors can obtain all information required for subsequent safety evaluation. Examples include behavioral changes in association with antibiotic treatment, cardiac symptoms in patients treated for depression or schizophrenia, and persistent skin rashes with systemic agents. Sponsors should also consider the use of questionnaires based on diagnostic standards to collect the detailed information needed for the analysis of specific events of major importance, such as liver injury, bone marrow suppression, or cardiac arrhythmias. In certain situations, the sponsor may wish to seek

³⁰ *Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use*, Edited by Z. Bankowski, et al., Council of International Organizations of Medical Sciences, Geneva, 1999. This report comes with a CD rom for ease of use.

external consultation with an independent clinical expert or a group of independent experts, for appropriate categorization and interpretation of adverse events. If a Data and Safety Monitoring Board (DSMB) is used for a study, then depending on its membership, it could fulfill this function in addition to its usual roles and responsibilities of independent safety (and efficacy) monitoring.

The investigator always retains the right not to modify a term with which the sponsor disagrees. As already mentioned, the sponsor should retain the investigator's verbatim term and document thoroughly the reasons for a different opinion. Such disagreements are accommodated, for example, within ICH Guideline E2B, field B.5.3 (Sender's diagnosis/syndrome and/or reclassification of reaction/event), which may be used for documentation purposes. While such significant discrepancies will probably be exceptional, they must be clearly documented for analysis and audit. Nevertheless, there may be merit in analyzing and evaluating "as is" verbatim information from investigators during early stages of development, when the safety profile of the medicinal product is not well-characterized or understood. However, as safety information increases and improves, standardization of terminology and communication with investigators regarding the use of standard terms and definitions should be considered.

Depending on their purpose, adverse event tables can display both the reported (investigator's verbatim) term³¹ and the sponsor's terms. However, as discussed in Chapter 5, primary safety analyses (especially those used to develop the DCSI and CCSI) should be based on investigator-assigned terms.

Most AE reports consist of one or more signs and symptoms with no particular diagnosis possible or relevant (e.g., headache, nausea), especially during the early stages of clinical drug development. The challenge is to know when a symptom/sign complex might represent a diagnosis of a potentially important medical condition. Such information has value in terms of signal detection and evaluation. As described in section c.(3) above, investigators should be encouraged to record a diagnosis or syndrome as the adverse event whenever possible. Even if they do not, when reported signs, symptoms, investigation results, and/or treatment strongly suggest a known clinical syndrome (e.g., chest pain, elevated CK-MB, and acute treatment with a thrombolytic agent), a probable diagnosis, in this case myocardial infarction, may be assigned for

³¹ The original term(s) reported by an investigator may be in a language different from that used by the sponsor in its day-to-day operations and in coding. "Verbatim" in this context is meant to refer to a properly translated version of the original term(s) into the working language of the sponsor.

analysis by the sponsor, even if not reported as such by the investigator; this option is provided for in an ICH Guideline E2B data specification (field B.5.3). As already recommended, it is essential that **all** AEs be collected, regardless of presumed relationship to the study agent, for subsequent assessment using standardized methods, such as those described in Chapters 5 and 6, in order to determine causality from aggregate data.

Certain events may be anticipated based on the class of drug used for treatment. There may also be other events that require special attention based on knowledge of their background rates for the type of population under study. It is useful to specify such events, along with the criteria for their diagnosis, in the protocol and other instructional material for the study sites. For example, the definitions of drug-induced liver injuries and blood disorders developed by CIOMS can provide a useful standard (see footnote 30).

In addition, it is critical that “adverse events of special interest” be defined for the purposes of consistent analysis, assessment, and evaluation of the safety profile of the medicinal product. These definitions and the criteria for use of particular terms should be described in detail in the clinical protocol and any developmental safety plan for the medicinal product.

To avoid inclusion in the DCSI and ultimately in the CCSI of multiple event terms that provide little or no medically useful information, individual signs and symptoms (e.g., fever, rash, and nausea) should be codified for analysis only when they are reported as isolated terms and are not consistent with a clear, specific diagnosis. An aggregate analysis should attempt to ascertain whether the individually codified symptoms and/or signs occur in isolation or as frequently reported combinations, even if they do not initially comprise a recognized clinical syndrome. This is especially important to avoid inappropriate categorization of relatively non-specific signs or symptoms, e.g., fever, which may have multiple unrelated causes.

Some companies and health authorities maintain a list of event terms that are always regarded as medically serious and important even if the specific case might not satisfy the criteria for serious in a regulatory sense (require expedited reporting, for example). Such “always serious” events are used routinely to trigger special attention and evaluation. Although such lists were originally created for post-marketing purposes, especially for spontaneous reports, they might be useful for pre-approval clinical research purposes.³² We do not endorse any particular list since it may be highly dependent on the treatment

³² For a full discussion of this concept and an extensive table of MedDRA® and WHO-ART terms that were suggested as candidates for such a list, see *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Report of CIOMS Working Group V, pp. 107-108 and Appendix 5, CIOMS, Geneva, 2001.

and the specific population(s) under study, and can never be complete. Even without formalizing such a list, remaining alert to the appearance of certain medically important events is a key concept in protecting trial participants and preventing future harm.

(2) *Coding Procedures*

Sponsors should have in place standard procedures for data codification applicable to all products and projects; all personnel responsible for data entry should be well trained in their use. As developed under ICH Topic M1, there is an internationally agreed medical coding terminology-dictionary, viz., MedDRA[®] (Medical Dictionary for Drug Regulatory Activities), which the Working Group recommends and will refer to throughout this discussion. MedDRA[®] codification principles, “Term Selection: Points to Consider,”³³ should be used as the basis for sponsor procedures. However, the principles covered here are independent of the coding dictionary used.

While a complete description of the signs, symptoms and investigations which led to a diagnosis should be obtained from the investigator, especially for serious events, and while such data should be part of the overall study database, these details should not usually be coded for describing the specific event, as outlined in the MedDRA[®] Points to Consider document. The impact of codification on ultimate data output for clinical evaluation must be considered during data entry, especially when dealing with AE terms that do not have exact matches in the codification terminology used. Non-specific “disorder” terms (e.g., the MedDRA[®] Preferred Terms (PTs) “blood disorder NOS”, “cerebral disorder”) should be avoided as they are not useful for retrieval, clinical analysis, or display; reported events that are so ill-defined as to require the use of such non-specific terms should be clarified with the reporter. When using MedDRA[®], it is generally recommended that terms from the Social Circumstances System Organ Class (SOC) should be used only for medical history and not for coding AEs, even if a reported verbatim term is an exact match for a MedDRA[®] Lowest Level Term in that SOC.³⁴

³³ See http://www.ich.org/ichMedDRA_PTC.html

³⁴ The CIOMS VI Working Group endorses the recommendation in the MedDRA[®] Points to Consider, v. 3.3 (9 June 2004) that the SOC *Social Circumstances* generally not be used for coding ADRs/AEs, even if a reported verbatim term is an exact match for a Lowest Level Term in that SOC, because of the potential impact on retrieval, analysis, and reporting. The *Social Circumstances* SOC describes social factors, and as such is intended for use in coding social history data, and is thus not included in the multi-axiality of the clinical disorder SOC. Using it to codify clinical concepts that are more appropriately reflected by terms in a clinical disorder SOC could therefore adversely affect data retrieval and signaling by mismatching to an inappropriate SOC. For example, the term “Aborted pregnancy” in the SOC *Social Circumstances* would not be grouped or retrieved together with the multiple clinical terms reflecting various types of abortion in the SOC *Pregnancy, puerperium and perinatal conditions*, and hence could lead to inappropriate omission from an analysis of abortions/ miscarriages of events so codified.

Sponsors should avoid “excessive coding” of events reported in serious adverse event cases. Each such report should contain only the minimum number of dictionary terms needed to ensure retrieval in the relevant clinical context(s). Conversely, sponsors should take great care not to “undercode” events, namely, assign codes that might downgrade the severity or importance of an event term or terms.

Inconsistencies in clinical event classification and/or codification are common not only among investigators within the same study and/or project, but also among sponsors using different adverse event coding terminologies/dictionaries, and even among sponsors using the same dictionary (including MedDRA®). The current practice of coding AEs in safety databases in strict adherence to the “verbatim” terms reported by investigators, in the absence of clear and uniformly accepted definitions for many clinically important conditions, may hamper subsequent retrieval and analyses. For example, clinically distinct terms encompassing a single medical condition, e.g., hepatotoxicity, may be spread across several SOCs and levels of the hierarchy.

Another challenge in generating the most accurate and useful information is deciding what level of terminology (e.g., Lower Level or Preferred term from a coding dictionary) should be used in presenting AE data (for example, in summary tables).

The CIOMS VI Working Group suggests that AE data should generally be presented as Preferred Terms (e.g., from MedDRA®), organized within the relevant System Organ Classes (SOCs). However, due to the high granularity of MedDRA®, there may be several Preferred Terms describing different AE/ADR cases that involve the same medical concept within one SOC. Therefore, under some circumstances, it might be useful to include data at more than one level of the hierarchy within a SOC (e.g., High Level Terms (HLT) as well as Preferred Terms).

One approach to overcoming the various shortcomings discussed above has been undertaken by a separate CIOMS Working Group on “Standardized MedDRA® Queries (SMQs).” It has been operating for several years as a collaboration between senior scientists from drug regulatory authorities, pharmaceutical companies, the ICH MedDRA Management Board, the MedDRA Management and Support Organization (MedDRA® MSSO), and the WHO. The Group has developed SMQ guidelines (proper database search strategies) for many defined medical conditions, which are meant to aid in case identification from the various signs, symptoms, diagnoses, syndromes, physical findings, laboratory

and other physiological data within a database. Prior to their release for general use, all SMQs are tested in databases of regulatory authorities and pharmaceutical companies.³⁵ They are subsequently made available by the MedDRA MSSO to the user community and are being maintained and updated as appropriate by that organization. Although SMQs for as many important conditions as possible will be developed, it is unlikely that such groupings will ever be available for all clinical conditions relevant to any specific product.

(3) Dealing with Unblinded Data

Throughout the course of a clinical trial program, unless a waiver has been granted (see section c.(6) above) the blind will be broken based on ICH Guideline E2A for some individual AE cases in order to comply with expedited regulatory reporting requirements, mainly for serious, unexpected ADRs. Companies struggle with a variety of choices with regard to dealing with the newly available information on therapy assignment for these patients, including whether certain personnel should have access to the information. Questions include: Should the information be entered in the clinical trial and/or safety database; if so, is entry independent of the therapy (placebo, comparator, new product)? Should one wait until the trial is over until entering the data? Should access to the information be restricted to selected personnel (e.g., access permitted for all or some personnel in the safety department but not biostatistical or clinical personnel involved in the conduct or analysis of the trial)? If unblinded reports are sent to regulators, DSMBs and trial ethics committees, is it advisable or appropriate to keep the cases blinded for investigators, as some companies have chosen to do?

There is no one correct approach to this problem, and no regulatory guidance. The solution will depend on many factors pertinent to a company, its organizational structure, its philosophy toward such matters, and its technical systems for managing data. However, several members of the CIOMS VI Working Group did express a preference for entering the new information into the safety database without attempting to prevent access by safety or other personnel involved in the conduct of the trial. The

³⁵ See the first SMQ report: *Development and Rational Use of Standardized MedDRA Queries (SMQs). Retrieving Adverse Drug Reactions with MedDRA*, CIOMS, Geneva 2004. It covers torsades de pointes/QT prolongation, rhabdomyolysis/myopathy, and hepatic disorders. For details and to monitor the progress of the CIOMS Working Group's efforts, see www.cioms.ch/What'sNew/WorkingGroups.

rationale for making such information readily available is that it should be taken into account in the course of ongoing monitoring and evaluation of safety. However, guidance on this issue, for which there are varying opinions, is beyond the scope of this Working Group.

(4) Data Processing Issues

The processing and interpretation of clinical trial safety data are rarely straightforward and represent challenging activities for sponsors and investigators. Part of this challenge stems from the fact that a comprehensive review of safety data involves analysis of both individual reports as well as aggregate data. This dual approach allows for both a qualitative and quantitative understanding of the safety profile of a drug. An additional challenge is that some important elements of safety information, such as serious adverse event reports, must be reviewed within specified time frames after the sponsor becomes aware of them, while aggregate data are reviewed on a periodic basis, as well as at the end of a clinical trial or clinical development program. These multiple aspects of safety data review during clinical development demand that the data management processes be both flexible and robust.

There are many activities involved in the management of clinical trial safety data, and a full discussion is beyond the scope of this chapter. Core activities include data entry; edit checks; data queries to resolve discrepancies noted in the edit check process; coding of adverse events using a standard dictionary, such as MedDRA[®]; and, in the case of data from multiple trials, pooling datasets for a comprehensive analysis. Each of these activities must be undertaken with care and precision, to insure that the safety database is accurate and complete. However, once a study or clinical development program is completed, there will be great pressure to close (“lock”) the database, so that data analysis can begin and the final reports can be written. While the analysis of safety data should proceed as quickly as possible, there must also be mechanisms for investigators and sponsors to handle suspected adverse drug reactions (ADRs) that may appear after the study is completed. In addition, there must be a mechanism in place for obtaining follow-up information on ADRs that were ongoing at the time the study ended. Ideally, such issues should be covered in study protocols.

Many sponsors use Contract Research Organizations (CROs) to manage some or all aspects of their clinical trials, including data entry, data management, and data analysis. In these cases, the CRO may hold

the clinical database(s). It is important that the sponsor, as the responsible party, have ready access to the data for prompt review and any required action. Thus, agreements and methods for achieving ready access to data must be in place. The same is true for other contractual relationships, such as in co-development licensing agreements.

Ideally, a systematic, reproducible approach to detect, classify and document adverse events would enable sponsors and investigators to develop clinical as well as statistical understanding of the safety profile. Different groups have approached this goal in different ways.³⁶

New approaches to standardized data management techniques have been in development to facilitate analysis and reporting of safety and other clinical trial data. A recently formed open, non-profit organization which involves the biopharmaceutical industry and regulatory authorities, Clinical Data Interchange Standards Consortium (CDISC), is committed to the development of worldwide industry standards to support the acquisition, exchange, submission and archiving of electronic clinical trial data.³⁷ Specific initiatives by CDISC include the following:

- ❑ a model for regulatory submission of data to support a marketing application for a new product; this CDISC Submission Data Standard (SDS) includes data in the form of standard domains (e.g., demographics, drug exposure, concomitant medications, laboratory data, adverse events), which define the data elements for common safety data and other data collected in clinical trials;³⁸
- ❑ analysis dataset models (ADaM), which are being developed to define standard ways to provide datasets for safety and efficacy review and analysis by statisticians at regulatory agencies.

³⁶ For example, see Tangrea, J. A., Adrianaza, M. E., and McAdams, M. A Method for the Detection and Management of Adverse Events in Clinical Trials, *Drug Information Journal*, 25:63-80, 1991; Gait, J. E., Smith, S. and Brown, S. L. Evaluations of Safety Data from Controlled Clinical Trials: The Clinical Principles Explained, *ibid.*, 34:273-287, 2000; and Hsu, P.-W., Pernet, A. G., Craft, J. C. and Hursey, M. J. A Method for Identifying Adverse Events Related to New Drug Treatment, *ibid.*, 26:109-118, 1992.

³⁷ See www.cdisc.org or write to Dr. R. Kush at rkush@cdisc.org. Membership includes biotech and pharmaceutical companies, CROs, and academic medical centers in the EU, Japan, the US and India. Various CDISC working groups have been established (e.g., in Japan, Europe and India). For an explanation of CDISC and a report on laboratory data standards, see S. Bassion. The Clinical Data Interchange Standards Consortium Laboratory Model: Standardizing Laboratory Data Interchange in Clinical Trials, *Drug Information Journal*, 37:271-281, 2003.

³⁸ Submission Data Standards, Analysis Dataset Standards, Operational Data Model, and Laboratory Data Standards (see www.cdisc.org/standards/index/html).

These and other standard CDISC models enable both clinicians and statisticians to review and analyze a much richer, more comprehensive and more accurate collection of safety data than is currently available from post-marketing pharmacovigilance reports. CDISC also has a formal working relationship with the international standards setting (ISO), not-for-profit organization, Health Level 7 (HL7). Its members – health care providers, vendors, payers, consultants, government groups and others – have an interest in the development and advancement of clinical and administrative standards for health care.³⁹

³⁹ For details, see <http://www.HL7.org/>. A “Regulated Clinical Research and Information Management (RCRIM) Technical Committee” (co-chaired by CDISC, HL7 and FDA) works toward accreditation of the CDISC models described above and is involved in other standards-setting, such as: HL7 messages to support the reporting of post-marketing pharmacovigilance data for safety surveillance; standards for submitting ECG waveform data to regulatory agencies; and standard protocol representation, which includes standardization of clinical trial protocol elements to support safety and efficacy assessments and statistical analyses. These efforts are committed to harmonizing all of these standards and models to support regulated clinical research, in addition to strengthening the link between healthcare and clinical trials.

V

**Identification
and Evaluation of Risk
from Clinical Trial Data**

a. Introduction

The ongoing evaluation of the safety profile of a drug during clinical development is a dynamic process that serves several important purposes, first and foremost of which is the protection of human subjects participating in clinical drug trials. If new risks are identified, it would be important to put risk management strategies in place to better understand and minimize the risk to patients. But it is also important to gain an understanding of the safety profile of the drug as early in its development as possible. Once new risks are identified, a development program can be stopped if the risks are deemed unacceptable, or modified to gain a better understanding of or better manage those risks.

The safety information that emerges at the end of clinical development should be sufficiently rigorous to allow for comprehensive regulatory review and determination of the benefit-risk profile of the drug to support marketing approval. It should also be sufficiently comprehensive so that prescribers and patients can be given adequate information for the safe use of the drug.

To the extent possible, the ongoing review of benefits is also very important. Although benefits may be more difficult to assess early in a development program, especially when studies continue to be blinded, ability to assess the benefit-risk profile of a drug at least in a preliminary fashion, is essential. It is not only important to terminate a program early when new risks are felt to be unacceptable, but also to avoid premature termination of a program that shows promise for potential value even in the face of certain risks. This will be especially true in the development of life-saving therapies, particularly when alternative therapies are not available.

The evaluation of clinical safety during drug development is dependent on medical judgement as well as on an appreciation of descriptive and inferential statistics. This chapter focuses on a clinical approach to the detection and evaluation of emerging risks. Quantitative and statistical concepts are presented in Chapter 6. Some authors have suggested that existing methods of safety data evaluation can be substantially improved by standardizing the approach to early detection of safety signals.^{1,2,3,4}

¹ Morse, M.A., Califf, RM and Sugarman, J. Monitoring and Ensuring Safety During Clinical Research, *J. Am. Med. Assoc.*, 285:1201-1205, 2001.

² Ioannidia, P.A. and Lau, J. Completeness of Safety Reporting in Randomized Trials. *J. Am. Med. Assoc.*, 285: 437-443, 2001.

³ Wallander, M. The Way Towards Adverse Event Monitoring in Clinical Trials, *Drug Safety*. 251-262, 1993.

⁴ Lineberry, C. Approaches to Describing Common Adverse Events in the Integrated Safety Summary, *Drug Information Journal*, 25:493-500, 1991.

To ensure that complete and accurate safety information is collected during a clinical trial, it is imperative that sponsors and investigators pay careful attention to the overall development program, the design of each clinical trial, and the process that is in place for the ongoing safety evaluation during drug development. To minimize variability amongst investigators, it is critical that sponsors and investigators maintain consistency in the identification and recording of adverse events and other safety data across a development program. Different groups have approached this goal in different ways. Details on safety data collection in clinical trials can be found in Chapter 4.

An important principle in the evaluation of safety data from clinical trials is that while the data are designed to be analyzed in a comprehensive fashion at the end of a trial or development program, they also must be evaluated in an ongoing fashion, so that important safety signals can be detected early and that trial participants are protected.

Several published ICH guidelines address the appropriate handling of safety data in clinical trials. ICH E6⁵ provides guidance on safety reporting for investigators (Section 4.11), ongoing safety evaluation for sponsors (Section 5.16), reporting of adverse drug reactions to investigators, IRB(s)/IEC(s), and regulatory authorities (section 5.17), and the assessment of safety in a clinical trial protocol (Section 6.8). Section 12 of ICH guideline E3 (Structure and Content of Clinical Study Reports) and section 4 of ICH M4 (Common Technical Document – Efficacy (Clinical Summary))⁶ contain useful recommendations for appropriate analyses and presentation of safety data from completed clinical trials and integrated summaries of safety. Other useful documents are the US FDA's template on safety and efficacy review of new submissions, and the detailed guide used by their internal safety reviewers.⁷ The current chapter, which should be read in conjunction with these guidelines, aims to complement and elaborate upon their concepts with additional practical advice, including interpretation of the results of the analyses suggested in E3 and M4. This will facilitate safety monitoring during ongoing clinical trials.

⁵ ICH Guideline E6, *Guideline For Good Clinical Practice*, 1 May 1996, <http://www.ich.org/>

⁶ ICH Guideline E3, *Structure and Content of Clinical Study Reports*, 30 November 1995, <http://www.ich.org/> and ICH Guideline M4, *The Common Technical Document*, <http://www.ich.org/>

⁷ See Section 7.0 of FDA's "Clinical Review Template," CDER, Office of the Center Director, effective 9 July 2004 (<http://www.fda.gov/cder/mapp/6010.3.pdf>), and Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (January 2005; see <http://www.fda.gov/cder/guidance/3580fnl.pdf>).

It is important to note that ongoing safety evaluation should occur in clinical trials of all sizes and degrees of complexity, including single-center clinical trials conducted by individual investigators to multi-center trials conducted by a group of investigators and multi-center or multi-national trials conducted by a pharmaceutical company. While the logistical aspects of safety data collection and evaluation may vary from setting to setting, the principle of protecting trial participants through early identification, evaluation and management of safety issues is paramount to all clinical trials.

The CIOMS VI Working Group recommends that clinical trial sponsors develop a process to assess, evaluate and act upon safety information during drug development on a continuous basis in order to ensure the earliest possible identification of safety concerns and to take appropriate risk minimization steps. Such steps can include modification of study protocols to incorporate appropriate strategies to ensure that clinical trial participants are not exposed to undue risk.

b. Expectations and Limitations in the Identification and Evaluation of Safety Information from Clinical Trials

It is important to recognize the limitations of clinical trial safety data as they become available, and to have realistic expectations of what can be learned from such data. It is also important to understand the inherent limitations of clinical trials (see Chapter 1, section d.), while at the same time maximizing usefulness by including safety considerations in their design.

Critical for the interpretation of safety data is the number of subjects exposed to the investigational product and for how long. The more subjects are exposed for long durations, the greater will be the confidence in the safety of the product. However, there is no standard rule for what that number or duration should be. Rather, the number of subjects and the duration of treatment required to establish an acceptable safety profile of a product depend on many factors, such as whether the drug represents a new chemical or therapeutic class, whether it is similar to other available products, whether it has potential advantages over existing therapies, the characteristics of the intended patient population (e.g., rare versus common disease indication), and the intended duration of use (e.g., acute versus chronic

conditions).⁸ While the sample size calculations for individual clinical trials are usually dictated by efficacy considerations, the total number of persons exposed to the investigational agent in a clinical development program and for how long should also be influenced by safety considerations.

ICH Guideline E1 recommends specific minimum numbers of subjects for the safety evaluation of drugs intended for long-term treatment of non-life-threatening diseases.⁹ However it is important to note that there are circumstances in which these standardized subject exposures may not be sufficient for safety data evaluation, e.g., when:

- ❑ specific safety concerns are identified (e.g., from animal studies or chemically related products);
- ❑ the product has pharmacokinetic and/or pharmacodynamic properties known to be associated with adverse reactions, e.g., specific metabolic pathways;
- ❑ there is a concern that a product may add to a significant background rate of morbidity or mortality in the target patient population.

The number of persons exposed to the investigational agent should be carefully considered, based on the above considerations, not only at the time the clinical development program is planned but also during the program itself, as the safety profile of the investigational drug becomes better understood. Despite careful planning for the number of subjects, clinical development programs are not able to identify all risks associated with a product. Some risks occur so infrequently that they will become apparent only after thousands or tens of thousands or more have been exposed to the product – an extent of exposure usually achieved only after the product has been marketed. For example, if the “true” frequency of a particular adverse event is 1/1000, then administering the drug to 3,000 persons will result in a 95% chance of observing at least one instance of the event. If the number of persons exposed is decreased to 1,610, then the chance of observing at least one instance of the event is reduced to 80%. If the “true” frequency of the event is 1/10,000, then studying 10,000 persons will yield only a 63% chance of observing at least one event.¹⁰ Observing an event is not the same as

⁸ FDA’s Guidance for Industry on Pre-marketing Risk Assessment, March 2005, <http://www.fda.gov/cder/guidance/6357fnl.htm>

⁹ ICH Guideline E1, *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*, 27 October 1994, <http://www.ich.org/>

¹⁰ These calculations are a reflection of the “rule of three,” which states that if no event of a particular type is seen in x-individuals, one is 95% certain that the event occurs no more often than 3/x; e.g., if x=500, 95% certainty that it occurs in less than 3 in 500 (0.6%).

concluding that it is an adverse drug reaction. Thus, the ability to detect a rare adverse drug reaction is a recognized limitation of clinical trials, where rare is conventionally defined as equal to or less than 1 in a thousand.

For serious adverse events, a detailed understanding of the individual case is important. For non-serious events, a high level of scrutiny of individual events in early phase trials with small numbers of subjects is also reasonable. But the same level of scrutiny may not be practical or useful in large practice-based, post-approval studies, especially when the safety profile is well-established. In this case, analysis of aggregate data is more meaningful and practical.

For more commonly occurring events, the analysis of aggregate data is both important and appropriate in order to explore the possible relationship with the drug. A special challenge in the evaluation of aggregate safety data is the application of appropriate statistical techniques, which have been developed and used much more for efficacy determinations than for safety. Chapter 6 provides a guide to currently accepted approaches for analyzing and interpreting clinical trial safety data.

One of the goals of analysis and interpretation of safety data is to assess the medical significance of one or more suspected adverse reactions in order to develop appropriate and useful product information both during the development program (through the Investigator's Brochure) and after the product is authorized (in the local data sheets/product information), and to develop risk-management strategies to minimize them. It is therefore important that emphasis be placed on medical and scientific perspectives, ultimately on behalf of public health, rather than perfunctory data collection, processing and regulatory reporting, as important as these activities may be. There is a body of literature on risk assessment for pharmaceutical and other sectors, but only recently have attempts been made to approach the subject for drugs in a detailed and systematic way through new methodologies and regulations. Under a broad mandate covering risk management of drugs under US legislation, the FDA has developed a series of draft guidances for industry on (1) premarketing risk assessment, (2) development and use of risk minimization action plans, and (3) good pharmacovigilance practices and pharmacoepidemiologic assessment.¹¹ The FDA defines risk assessment as consisting of "identifying, and characterizing the nature,

¹¹ U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research, Guidance Documents. <http://www.fda.gov/cder/guidance/index.htm>

frequency, and severity of risks associated with the use of a product.” Similar developments are underway in the EU^{12,13} and Japan.

c. Points to Consider During Analysis and Evaluation of Safety Information

There are several factors that need to be considered that influence the evaluation and interpretation of safety information as well as the benefit-risk assessment; they are important both in the analysis of individual cases and of aggregate data. Some of the most important factors are considered below.

(1) Patient Population Characteristics, Including Natural History of Disease

The demographics of the population (e.g., age, gender, race, geographic regions, socioeconomic factors) should be considered during safety data evaluation, for several reasons. Some adverse events occur more frequently in some groups than in others, even in the absence of treatment with an investigational drug. Older adults in general have a higher incidence of cardiovascular disease than younger persons. Thus, the occurrence of a myocardial infarction in a 75 year-old clinical trial subject may be evaluated and interpreted differently than in a 25 year-old participant. It should also be remembered that certain diseases are more prevalent in specific populations (e.g., sickle cell anemia, Tay Sachs Disease) and suspected adverse reactions of such types during clinical trials should be reviewed with this in mind.

In addition to differences in background rates of certain adverse events, there may be drug-demographic interactions that result in certain adverse reactions occurring more frequently in older patients than in younger patients or more frequently in men than in women. For example, the risk of gastrointestinal bleeding with an NSAID is higher in older patients than in younger patients. In this case, the confounding or interacting effects of a demographic factor can be determined

¹² Establishing a European risk management strategy: Summary Report of the Heads of Agencies Ad Hoc Working Group, January, 2003. www.emea.eu.int

¹³ Handling by the CPMP of safety concerns for pre-and post-authorization applications submitted in accordance with the centralized procedure. April 5, 2004. www.emea.eu.int

only if aggregate data are analyzed since it is the incidence of a known adverse reaction that is in question. It is also known that both safety and efficacy results may be pharmacologically-mediated (how a drug is “handled” by the body) and show ethnic and racial differences.¹⁴

Knowledge of the background incidence and prevalence of medically important conditions in the target population is an important tool in the evaluation of individual cases as well as in the analysis of aggregate data. The information helps to provide a context for case reports and incidence rates of AEs. However, caution should be exercised when comparing the incidence in the patients treated with the investigational drug to the incidence from the literature or from historical controls since clinical trials tend to include a highly selective population. Ideally, a comparison should be made to concurrent controls, which could serve to provide further context for the assessment of the benefit-risk profile of the investigational product. Use of historical clinical trial data, especially if there are sizeable similar trials with placebo controls, may be particularly useful if a concurrent control is not available.

Consideration of the natural history of the disease being treated can also be very important in the evaluation and interpretation of safety data. The distinction between a manifestation of the disease being treated and an adverse drug reaction is a special challenge in the evaluation of safety data. When certain adverse events are known manifestations of the disease it is important to know the expected frequency, severity and pattern of presentation. Their occurrence may not be of concern if the incidence is in line with expectations based on the natural history. On the other hand, it is important not to overlook the possibility of an adverse drug reaction related to worsening of the disease treated, even if the frequency is in line with expectations, if the nature, severity or other presentation are not typical.

(2) Current Therapeutic Standards

In the ongoing evaluation of the evolving benefit-risk profile of a drug in development, it is important to take into account what is known about established therapies for the condition under study. The benefit-risk profile for existing drugs can serve as a benchmark against which to

¹⁴ For discussion and recommendations, see ICH Guideline E5.

weigh the acceptability of the emerging profile for a new product. In addition, drugs taken concomitantly with the study drug may be contributing to the incidence of adverse drug reactions either independently or through a drug-drug interaction.

The standard treatment for a disease may change during a clinical development program, especially if the program lasts several years. If a new therapy reaches the market place during a development program, it will be important to update the benchmark for an acceptable benefit-risk profile. In this regard, it is important to note that standard therapy need not refer exclusively to pharmacotherapy, but can refer to non-pharmacological treatments, such as surgery, diet, exercise, psychotherapy, physical therapy, or other treatment modalities.¹⁵

d. Timing of Safety Evaluation

The timely and thorough management and evaluation of safety information is a shared responsibility among all parties involved in the clinical trial process. Toward that end, it is critical that sponsors (including independent sponsor-investigators) define and implement a system and schedule for reviews of safety information. One can consider three general situations requiring safety data review, which are independent of the size and complexity of a clinical trial:

- (1) *Ad hoc* for serious and special interest AEs; it is imperative that there be a mechanism to review important safety data in a timely fashion.
- (2) Routine, periodic, general review of all data; the frequency of an overall periodic review will vary from trial to trial and from development program to development program and depend on such things as the phase of clinical development, the amount of safety and other data already known about the investigational product, the duration of treatment, the amount of safety information known about drugs in the same or a similar class, the number of patients exposed, the number of sites and investigators in the trial, the level of concern over specific adverse events, the anticipated benefit-risk profile of the drug, and the perceived level of acceptable risk for the product.

¹⁵ www.clinicalevidence.com is an important website source of information in this respect.

- (3) Reviews triggered by specific milestones established for a trial or a program (e.g., numbers of completed patients, end-of-trial, end-of-program, preparation of integrated summary of safety and a marketing application). See Chapter 3, section b.8. for discussion.

A recommendation to establish multidisciplinary teams and to use advisors and advisory boards in the course of safety reviews is discussed in Chapter 3.

In addition to the frequent review of serious adverse events (SAEs) and those of special interest, overall assessment of all AEs, regardless of seriousness, causality, or expectedness, should be performed periodically.¹⁶ Periodic and summary reviews should include both interval and cumulative incidences (in relation to known subject exposure) of all AEs in the study database.. When trying to draw conclusions and take any action from evaluation of comparative safety data, it may be important to distinguish between placebo and active comparators.

Each time a study is completed and unblinded, all safety information, not just clinical AEs but ideally emerging efficacy endpoints, vital signs, and clinical investigation results, should be assessed and evaluated relative to the previous information. As needed, the relevant product information (investigator brochure, Development Core Safety Information (DCSI), Company Core Safety Information (CCSI), local datasheets) should be updated.

e. Safety-Signal Detection and Evaluation

The concept, definition and methods for signal detection have been primarily associated with large, post-marketing databases, usually of spontaneous reports.^{17,18,19} While there is a growing body of published literature on the advantages and limitations of various statistical methods to detect

¹⁶ Gait, J.E., Smith, S. and Brown, S.L. Evaluation of Safety Data From Controlled Clinical Trials: The Clinical Principles Explained, *Drug Information Journal*, 34: 273-287, 2000.

¹⁷ Report of CIOMS Working Group V. *Current Challenges in Pharmacovigilance: Pragmatic Approaches*. Council for International Organizations of Medical Sciences. Geneva 2001.

¹⁸ Brown, E.G. and Douglas, S. Tabulation and Analysis of Pharmacovigilance Data Using the Medical Dictionary for Regulatory Activities, in *Pharmacoepidemiology and Drug Safety*, 9: 479-489, 2000.

¹⁹ Jasmenda H., Wu, M.C., Fung, K.K., *et al*. Postmarketing Drug Safety Surveillance. *Pharm. Dev. Regul.*, 231-244, 2003.

signals from post-marketing safety data, the field is still in its infancy.^{20,21,22}
^{23, 24} As data accumulate, statistical methods for the evaluation of safety signals in clinical trials may be possible (see Chapter 6). It is more likely, however, that signal detection during early development will generally be based on clinical judgment.^{25,26,27}

While it is impossible to define standard criteria for the clinical evaluation of safety, the CIOMS VI Working Group believes there are some fundamental steps that can be taken to improve the process for detecting signals. These include:

- ❑ *prompt medical evaluation of all individual serious cases, regardless of attribution or expectedness, and adverse events of special interest, whether serious or not*
- ❑ *periodic aggregate assessment (blinded, partially-blinded²⁸ or unblinded, depending on the status of the trials, as appropriate) of all available clinical safety data (including clinical AEs, laboratory data, selected physical data such as blood pressure), irrespective of causality or seriousness; any relevant non-clinical data should also be reviewed*
- ❑ *safety evaluation of completed unblinded studies, both individually and combined where appropriate, principally from a clinical perspective, but also including relevant statistical analyses.*

²⁰ Wilson, A., Thabane, T. and Holbrook A. Application of data mining techniques in pharmacovigilance, *Br. J. Clin Pharmacol.*, 57 (2): 127-134, 2003.

²¹ Szarfman A., Machado S.G. and O'Neill, R.T. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database, *Drug Safety*, 25 (6): 381-392, 2002.

²² Van Puijenbroek E.P., Bate A., Leufkens, H.G., *et al.* A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidem. Drug Safety*, 11: 3-10, 2002.

²³ Bate, A., Lindquist, M. and Edwards, I.R. A Bayesian neural network method for adverse drug reaction signal generation, *Eur. J. Clin Pharmacology*; 54: 315-321, 1998.

²⁴ Evans S.J., Waller, P.C. and Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidem. Drug Safety*, 10: 483-486, 2001.

²⁵ Kock, G.G.. Discussion: Statistical Perspective, *Drug Information Journal*, 25: 461-464, 1991.

²⁶ Enas, G.G.. Making Decisions about Safety in Clinical Trials – The Case for Inferential Statistics, *Drug Information Journal*, 25: 439-446, 1991.

²⁷ Huster, W.J. Clinical Trial Adverse Events: The Case for Descriptive Techniques, *Drug Information Journal*, 25: 447-456, 1991.

²⁸ "Partially-blinded" refers to data that are categorized as groups A and B, e.g., without revealing the actual treatment name for each arm.

f. Consistent Causality Assessment – Adverse Events vs Adverse Drug Reactions

The identification of a potential safety issue for a medicinal product requires an ability to readily distinguish adverse drug reactions (ADRs) from adverse events.^{29,30} While there are established definitions of AEs and ADRs, there are no agreed criteria for reliably distinguishing between them, making this key element of risk assessment relatively subjective (see Chapter 4, section c.2.). Although investigator causality assessment is helpful in categorizing reports for regulatory reporting purposes, and for evaluating rare or unusual events, it has very limited utility in the analysis of aggregate information. Algorithms for categorizing causality at the case level have been developed for selected events, e.g., drug-induced liver injury³¹ but have not gained wide acceptance.³²

Previous CIOMS guidelines, current EU regulations, and proposed US regulations recommend that core safety information, including the DCSI for investigational products and the CCSI for approved products, should describe adverse drug reactions, and exclude events that have no well-established relationship to therapy. The purpose of DCSI is to provide the best safety information available at every stage of development. Ideally we should have consistent and reliable systems in place for causality assessments. However, as stated previously in Chapter 4 and reflected in the survey results (Appendix 3), there are no uniformly agreed criteria for determining whether there is a causal association between a medicinal product and a given AE, and therefore whether a given AE should be included in the DCSI and/or CCSI.

The decision to include information in the DCSI depends strongly on the concept of threshold as outlined in the CIOMS III/V report.³³ The concept of threshold is discussed further in Chapter 7, section e., including a proposed modification to the previous CIOMS recommendations.

²⁹ Hsu, P.H. and Stoll, R.W. Causality Assessment of Adverse Events in Clinical Trials: I. How Good is the Investigator Drug Causality Assessment?. *Drug Information Journal*, 27: 377-385, 1993.

³⁰ Hsu, P.H. and Stoll, R.W. Causality Assessment of Adverse Events in Clinical Trials: II. An Algorithm for Drug Causality Assessment, *Drug Information Journal*, 27: 387-394, 1993.

³¹ Danan, G. and Benichou, C. Causality assessment of adverse reactions to drugs – A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries, *Journal of Clinical Epidemiology*, 46 (11): 1323-1330, and Benichou, C. Danan, G. and Flahault, A. Causality assessment of adverse reactions to drugs – II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge, *ibid.*, 46 (11):1331-1336, 1993.

³² Stephens, M.D.B. From Causality Assessment to Product Labeling, *Drug Information Journal*, 31: 849-856, 1997.

³³ *Guidelines for Preparing Core Clinical-Safety Information on Drugs*, Report of CIOMS Working Group III/V, Council for International Organizations of Medical Sciences, Geneva, 1999.

When combination medicinal products are used, either fixed (e.g., an ACE inhibitor and a diuretic) or as part of a multi-drug regimen (e.g., for cancer chemotherapy or HIV treatment), AE causality assessment for individual components will be difficult for both individual cases and with aggregate data, and in the absence of consistent and convincing data with regard to a single agent, AE causality should be assessed for the combination.

The CIOMS VI Working Group suggests that the principal use of causality assessment for individual serious adverse events (SAEs) is more relevant for determining the regulatory reporting status, rather than for clinical analysis. It recommends that determination of causality for ongoing signal detection and inclusion in the DCSI and eventually the CCSI should be based on a combination of clinical judgement and aggregate data analysis based on all reported cases. Investigator causality assessment should be taken into account and may be particularly important when evaluating rare or unusual events for which aggregate analytical methods are not applicable.

g. Important Types of Analyses

While it is important to differentiate between serious and non-serious events for the purposes of regulatory reporting, the practical medical significance of the event(s) is of greater importance. Although it is appropriate to apply greater scrutiny to what appear to be serious adverse events, the true safety profile of a medicinal product throughout development can only be assessed by careful evaluation of all AEs/ADRs. Serious AEs and AEs of special interest (see Chapter 4, section c(4)) should be reviewed and assessed individually and in aggregate on a continuous basis. Non-serious AEs should also be critically appraised at regular intervals, in particular those associated with discontinuation of study treatment.

Though non-serious AEs are generally not routinely reviewed individually, they should be given careful attention in preparing study reports and integrated safety summaries. As already mentioned, contributions to evaluating and understanding the safety experience can depend on information other than AE reports, such as physical examination findings, vital signs, clinical laboratory tests, cardiac electrophysiology, and other study or non-study evaluations.

A similar approach should be considered for AEs associated with treatment discontinuation. Investigators need to pay particular attention to

the collection of all relevant information concerning these events, possibly more than would be usual in actual clinical practice. In addition, all subjects who withdraw from a study should be carefully questioned for the reason, including the possible occurrence of an adverse event. It is the responsibility of the sponsor to critically evaluate these events promptly, obtain as much follow-up information as required and available, and analyze them against the known morbidity profile of the study population and any other relevant information (e.g., comparable events with other members of the drug class). The reasons for discontinuation, the time to study withdrawal, and other factors when examined against the same data for comparator treatments (including placebo) can be very revealing.

h. Review of Individual Cases

The individual case safety report is the basic, fundamental unit of safety analysis. Throughout clinical development, review of individual cases, especially cases of serious adverse events, can shed considerable light on the safety profile of an investigational drug product. During early clinical development, review of both serious and non-serious individual adverse event case reports can potentially shed considerable light on the safety of the drug. Medical review and judgment by an appropriately qualified professional is critical for the evaluation of the individual case. The careful and thoughtful evaluation of one or more serious adverse event reports or reports of adverse events of special interest can be critical in detecting an emerging safety signal. The evaluation of an individual case report requires review of many elements of the report, and additional or follow-up information is often necessary. The sponsor should work with the investigator to insure that any additional information required to understand fully the reported event(s) is made available. Patient-specific information, especially co-morbid conditions, personal and relevant family medical history, concomitant treatments (including non-prescription medications, special diets, surgery, physical therapy, dietary supplements, “natural”, herbal, homeopathic, and other alternative medications and treatments) should be carefully reviewed, primarily to permit identification of possible confounding factors, risk factors for an adverse drug reaction, possible drug-drug and drug-disease interactions, and other potential causes of the event. The evaluation of individual cases should be done in the context of the patient population, the indication for the investigational drug, the natural history of the disease, current available therapies, and other benefit-risk considerations (see section I. below).

Investigators and sponsors should evaluate each case in as much detail as possible to determine what factor or factors were responsible for the event, and then to assess the causal role of the investigational product. The use of specific report forms for particular types of events (e.g., liver injury, bone marrow depression, severe skin events) can facilitate the capture of all the information required for clinical evaluation.³⁴

i. Considerations for Periodic Review and Evaluation of Case Reports in Aggregate

Evaluation of aggregate data for understanding the evolving safety profile, and especially for detecting potential safety signals, requires thorough understanding of the existing safety data for the medicinal product, the clinical study patient population, including relevant sub-populations (e.g., the elderly), and the risk factors for a particular adverse event. Although periodic review of aggregate data of all safety information is essential, special attention must be paid to serious adverse event reports and adverse events of special interest, and should include information known about that drug. For example, in large and/or long-term studies, for events that are being closely monitored (e.g., deep vein thrombosis, myocardial infarction), the incidence of these events should be re-evaluated according to subject exposure to determine whether the observed incidence is consistent with the natural history, risk factors, and underlying morbidity of the study population. In such situations, an external DSMB may be desirable, with appropriate analytical methods and stopping rules in place (see Appendix 5).

Routine detection and evaluation of signals should be based on the periodic review of aggregate data. Serious adverse event (SAE) reports and adverse event reports of special interest should be readily retrievable from the safety and clinical trial databases. For these reports, interval and cumulative frequency tables should be generated at specified intervals. When the treatment assignment is known (i.e., expedited reports unblinded, as recommended in ICH E2A), SAE frequency should be compared by treatment group. When, more commonly, treatment assignments are not known, clinically important SAEs that occur with a notably higher incidence than anticipated in the study population (background rates), a partially-blinded analysis may be considered to determine whether there is any apparently

³⁴ Some examples are provided in “Adverse Drug Reactions – A Practical Guide to Diagnosis and Management”, Ed. C. Bénichou, John Wiley & Sons, 1994.

clinically meaningful difference between groups. It is also important to ensure that the intention to assess between-group differences be pre-specified. Such an analysis should not usually be required, and would rarely require unblinded analyses of individual studies and/or pooled safety data. Consideration should also be given to reasons for discontinuation and to the evaluation of data on marked laboratory abnormalities.

Although the relatively small number of subjects exposed to an investigational product may limit the utility of subgroup analyses, where possible data should be stratified for dose, duration, gender, age, and possibly concomitant medications and concurrent diseases. In addition, when possible and where relevant, stratification based on other potential risk factors should also be considered. These approaches are discussed in ICH E3 and ICH M4. Also, see footnote 8.

j. Pooling of Data

In pooling data, the following points should be considered:

- ❑ It is most appropriate to combine data from studies that are of similar design (e.g., similar in dose, duration, methods of eliciting and determining adverse events, and population).
- ❑ If the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
- ❑ Data from any study with an unusual adverse event pattern should be presented separately.
- ❑ The appropriate extent of analysis depends on the seriousness of the ADR and the strength of evidence for causality. Differences in rates of drug-related, serious events or events leading to discontinuation or dosage change deserve more investigation, whereas rates of other ADRs may not merit elaborate analysis.
- ❑ Examination of subjects that have extreme laboratory value abnormalities (outliers) can be useful in identifying subgroups of individuals who are at particular risk for certain toxicity.

Groups of studies that could be used in pooled safety analyses include the following.

- ❑ All controlled studies or subsets of controlled studies
- ❑ All placebo-controlled studies
- ❑ Studies with any positive control

- ❑ Studies with a particular positive control
- ❑ Studies of particular indications
- ❑ All studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating uncommon events
- ❑ All studies using a particular dose route or regimen, or a particular concomitant therapy
- ❑ Studies by geographic region or ethnicity.

These groupings are considered the best source of information about more common adverse events and may be able to distinguish drug-related events from background events. Rates in control and experimental drug groups should be compared. Cumulative dose, time of dosing and dose duration should also be included. In general, subjects exposed to the medicinal product in human pharmacology studies (Phase I) should not be included in the pooled data, although there may be exceptions (e.g., certain oncology studies).

It is almost always useful to pool the first two categories of studies listed above; the others chosen would vary from drug to drug and should be influenced by inspection of individual study results. Whatever methods are used, it should be recognized that, as for results of single studies, any numerical rate is often only a rough approximation of reality.

Care should be taken not to pool studies in which adverse experiences are elicited from patients in different ways (e.g., checklist vs direct questioning vs purely volunteered; see Chapter 4, section d(1)). In addition, special forms may be used to collect detailed information on serious or special interest cases. Reports on those specific AEs should not be pooled with other types of AE reports within studies, or between studies that do not use such forms.

k. Evaluation of Clinical Laboratory Data

Clinical laboratory tests are used in clinical trials for three main purposes:

- 1) Screening of subjects for inclusion and exclusion
- 2) Protection of subjects by early detection of organ toxicity
- 3) Identification of physiological or potentially toxic effects of the investigational agent.

However, the standard battery of laboratory tests assayed by clinical laboratories was not developed for these purposes, but for diagnosis and monitoring of diseases and their response to therapy in individual patients.

All laboratory tests are not equally meaningful as potential indicators of suspected adverse drug reactions. For example, results that measure an aggregate of multiple constituents that vary independently (e.g., total white cell count, serum total protein) are of limited value as indicators of specific safety problems. Some laboratory tests are meaningless outside the total clinical context of a specific patient, e.g., serum and urine osmolality (specific gravity, serum chloride, non-fasting serum glucose), while others are subject to intra-subject or pre-analytical variability so large as to render most individual or aggregate changes uninterpretable (e.g., triglycerides, GGT, venous blood bicarbonate).

Methods for assessment of laboratory data have been discussed in various publications (see Chapter 6, section e.) and regulatory guidance (e.g., ICH E3) and are beyond the scope of this report. ICH M4E³⁵ presents an overview of how clinical laboratory data should be presented in the efficacy section of the Common Technical Document.

There are three principal types of analyses that provide a brief summary of changes in laboratory values in a clinical trial or in a clinical program: 1) measures of central tendency (e.g., group mean or median value), 2) the range of values, along with the number of subjects without abnormal values or with values beyond a certain limit (e.g., twice the upper limit of normal), and 3) individual clinically important values. To characterize changes in laboratory values over time, these analyses should be performed for each study visit at which lab data were collected. To understand the context for these measurements, the above analyses should also note those laboratory values that were accompanied by adverse events and those that led to discontinuation of study medication.

In general, overall population trends are best identified statistically using large, integrated comparative datasets and are most likely to detect relatively minor changes of limited clinical significance, but can rarely lead to the identification of important safety concerns. Safety signals can be detected by analysis of Individual Clinically Significant Abnormalities (see ICH E3), commonly termed “marked abnormalities”. A marked abnormality is a laboratory value that meets predetermined criteria for degree of deviation from the reference range and magnitude of change from a prior value, typically one obtained immediately prior to exposure to study therapy. When

³⁵ ICH Guideline M4, The Common Technical Document For The Registration Of Pharmaceuticals For Human Use. Efficacy – M4E – Clinical Overview And Clinical Summary, Module 5: Clinical Study Reports (<http://www.ich.org/>).

analyses of clinical laboratory data indicate a possible safety signal, further analyses may be necessary. See Chapter 6 for more discussion.

Clinical laboratory values should not be analyzed for marked abnormalities if they are clinically meaningless in isolation (e.g., serum chloride, urine pH, urine specific gravity), if there are alternative methods of measuring the same constituent (e.g., both hemoglobin and hematocrit as indicators of red cell mass), if they are analytically unstable (e.g., bicarbonate, acid phosphatase), or if they represent aggregates of multiple constituents that vary independently (e.g., total WBCs, total protein). Derived values (e.g., anion gap, A/G ratio, red cell parameters) should generally not be subjected to marked abnormality analysis. The leukocyte differential count should be analyzed using absolute values only (i.e., number of cells/unit volume), and not relative values (percentage of the total), which can be spuriously influenced by changes in other cell types.

In addition to the evaluation of individual laboratory values, there may be important clinical correlates of patterns of abnormality of multiple laboratory measurements. For instance, there is published guidance on drug-induced liver injury based in part, on combinations of different patterns of elevation of ALT, alkaline phosphatase (ALP) and conjugated bilirubin.³⁶ It has also been suggested that hepatocellular injury manifesting as simultaneous elevation of ALT and bilirubin but without elevation of ALP was associated with a mortality rate of 10-15%. This outcome was explained on the basis that hepatocellular injury sufficient to reduce bilirubin excretion must involve a large fraction of liver cell mass.³⁷ This principle, utilized for the evaluation of hepatotoxicity for a new drug application by the FDA,³⁸ has stated that even isolated simultaneous elevations of aminotransferase and bilirubin (even if sub-clinical) have been predictive of serious liver injury in subsequent clinical use (e.g., bromfenac, troglitazone, and trovafloxacin). While the positive and negative predictive value of this approach remain to be validated, it is nevertheless essential to apply multivariate laboratory analyses to the differentiation of cholestatic and hepatocellular drug toxicity, since the former is typically relatively benign,³⁹ while the latter may be severe or fatal.

³⁶ Benichou, C. Criteria of drug-induced liver disorders. Report of an international consensus meeting, *Journal of Hepatology*, 11 (2): 272-276, 1990.

³⁷ Zimmerman, H. *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*, 2nd Ed., Lippincott Williams & Wilkins, 1999.

³⁸ CDER-PhRMA-AASLD Drug Induced Liver Injury Clinical White Paper. November 2000; <http://www.fda.gov/cder/livertox/clinical.pdf>

³⁹ Velayudham, L.S. and Farrell, G.C. Drug-induced cholestasis: Expert Opinion. *Drug Safety*, 2 (3): 287-304, 2003.

I. General Benefit-Risk Considerations

No one set of criteria for risk evaluation can or should be applicable to every investigational agent; rather, the criteria will depend on the type of product and many other factors:

- The intended use of the product
 - ❑ Disease prophylaxis or modification of physiological function (e.g., vaccines, hormonal contraceptives)
 - ❑ Diagnosis (imaging agents, radio-isotopes)
 - ❑ Symptomatic treatment (analgesics)
 - ❑ Cure (antibacterial therapy)
- The nature of the illness
 - ❑ Acute non-life-threatening illness (antibiotics)
 - ❑ Chronic disease (antihypertensives, hypoglycemics)
 - ❑ Acute life-threatening illness (biological response modifiers, thrombolytics)
 - ❑ Chronic life-threatening diseases (cytotoxic or antiretroviral agents).
- Availability of alternative therapies

Once risks are evaluated and assessed as to their importance, it is useful to attempt to place them in the context of acceptability, not only by the trial subjects but by the anticipated target population. There are no standard approaches to evaluating or measuring an “acceptable level of risk”, but the issue must be addressed throughout clinical development. A patient’s willingness to accept a certain level of risk may be different from that of the sponsor or the regulator acting on the patient’s behalf, and therefore, consideration must be given to the disease indication, the safety profile of the drug, the product’s efficacy and other therapeutic options that may be available. Risk perception and acceptance, and benefit-risk weighing by individuals, can be subject to strong cultural and ethnic influences. In spite of the lack of validated metrics or methods for its evaluation, the notion of “acceptable risk” should be discussed with regulators, specialists in the disease indication, and if possible with individual patients or patient/disease advocacy groups.

m. Aggregate Analysis and the DCSI

A consistent, logical rationale should be used for deciding when adverse events observed in the study population should be considered attributable to the medicinal product, and therefore included first in the DCSI

and, if confirmed in the overall study database as an ADR, in the CCSI for an approved product (see Chapter 4, section 2.). The results of each completed study should be compared, when appropriate, with the results of prior studies, to determine whether consistent patterns or trends are observed. As discussed in Chapter 6, inferential statistical approaches to AE data and numerical comparisons between treatment groups may be of limited use and clinical relevance; however, descriptive statistics may provide useful information, especially where there are comparative data across multiple studies or in a relevant control population, such as the pooled placebo groups from similar studies.

Clinical judgment is essential to decide when the threshold for adding information to the DCSI has been reached, based on aggregate data. The weight of evidence will depend on multiple factors, including differences between treatment groups (or compared to no treatment), information on the properties of the medicinal product including animal toxicology and pharmacokinetic data, experience with other products in similar chemical and/or therapeutic classes, and epidemiological information on the relevant population. In order to err on the side of caution, the greater the likelihood that a given AE might have a significantly serious adverse outcome for the subject or patient, the lower should be the inclusion threshold (i.e., fewer and less stringent inclusion criteria need be met).

VI

**Statistical Analysis
of Safety Data
in Clinical Trials**

a. Introduction

The use of statistics in clinical trial design and analysis has largely been focused on the establishment of efficacy using mostly inferential but also descriptive methods. Demonstration of efficacy is usually the main goal for individual trials and development programs, while wishing to show that no unacceptable toxicity occurs. However, the role of a statistician and the use of statistics in assessing safety data are also very important and unfortunately do not receive as much attention. Chapter 5 has outlined the principles for analysis of risk using data generated from clinical trials; use of the most appropriate statistical techniques for analysis and display of the data are essential for placing the absolute and relative safety of a medicinal product in proper perspective. Early in drug development (Phase I and early Phase II trials), much of the assessment of safety depends on individual case assessment. However, as the database increases, aggregate analysis tends to become more important, and that is where statistics play a crucial role. The techniques and approaches to use of statistics for analysing safety data have not been developed as fully as for efficacy and it is not uncommon to find inappropriate or incomplete displays and analysis of adverse event data, even in refereed publications.¹ In regulatory submissions for drugs in development the situation is often better, but consideration should be given to ensuring that publications from trials meet high standards of reporting.² A major new extension to the CONSORT (**C**onsolidated **S**tandards of **R**eporting **T**rials) Group statement recognises that efficacy has been a major focus and seeks to redress the balance.³

This Chapter is not intended to be a manual for statistical analysis of safety data; the subject is much too broad and complex. However, it does highlight key points that need attention when considering analysis, and areas which we believe may not be adequately understood or appreciated. There is at least one book that addresses biostatistical aspects of clinical safety data specifically,⁴ and there are several general papers that

¹ For example, see Ioannidis, J. P. A. and Lau, J. Completeness of safety reporting in randomized trials – an evaluation of seven medical areas. *Journal of the American Medical Association*, 285:437-443, 2001, and Ioannidis, J.P.A. and Contopoulos-Ioannidis, D.G. Reporting of safety data from randomised trials, *Lancet* 352:1752-3, 1998.

² McPherson, K. and Hemminki, E. Synthesising licensing data to assess drug safety. *Brit. Med. J.*, 328:518-20.

³ Ioannidis, J.P., Evans, S.J., Gotzsche, P.C., O'Neill, R.T., Altman, D.G., Schulz, K. and Moher, D. CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann. Internal Med.*, 2004;141:781-8. For the original statement see- <http://www.consort-statement.org/> and for the revised, see <http://www.consort-statement.org/statement/revisedstatement.htm#app>

⁴ Solgliero-Gilbert, G. (Ed.), *Drug Safety Assessment in Clinical Trials*, Marcel Dekker, New York, 1993.

address the topic;⁵ recommended references on specific topics will be given throughout this chapter. Books that concentrate on measures of efficacy can also be helpful since most of the same principles apply to safety data.⁶

Of course, this material is not a substitute for professional statistical involvement; however, it is meant to familiarise those not trained in statistics to understand some basic approaches and techniques. In addition, a glossary of various statistical terms and definitions used in this Chapter is provided in Appendix 1.

Professional statistical help is required for design, analysis and reporting of clinical trials; statistical issues related to safety should be considered at each of those stages.

It is important to keep in mind when conducting statistical analyses and assessing their results, that statistical association (P-values or other measures) alone may or may not be of clinical value. In randomised trials they have great strength in testing causality but they inevitably have uncertainty attached to what can be said. The advantage is that this uncertainty is capable of being quantified. Therefore, the issues also require the participation and insight of clinicians. While decision analysis is an important aspect of modern statistical thinking, its application to monitoring the safety of medicines has not been fully developed and even if it were developed further, medical judgement would still need to be applied rather than mechanical reliance on the magnitude of a P-value, for example. Statistical methods are a tool in the process but are by no means the process itself. Examination of both statistical and clinical significance must involve partnership. This chapter concentrates on unwanted, usually adverse effects, but these effects must always be considered in the context of the benefits of a medicine. Attempts have been made to consider the benefit-risk balance in mathematical or statistical terms⁷ but these have not reached maturity or even a consensus on their utility and are not covered here.

⁵ For example, O'Neill, R.T. Statistical analyses of adverse event data from clinical trials. Special emphasis on serious events. *Drug Information Journal*, 21:9-20, 1987; O'Neill, R. T. Assessment of Safety, Chapter 13 in *Biopharmaceutical Statistics for Drug Development*, Karl E. Peace, Ed., Marcel Dekker, New York, 1988; and Gait, J. E., Smith, S. and Brown, S. Evaluation of Safety Data from Controlled Clinical Trials: the Clinical Principles Explained, *Drug Information Journal*, 34: 273-287, 2000.

⁶ Altman, D.G. *Practical Statistics for Medical Research*, Chapman and Hall, London, 1991; Pocock, S.J. *Clinical Trials: A Practical Approach*, Wiley, Chichester, 1983; Piantadosi, S. *Clinical Trials: A Methodologic Perspective*, Wiley, Chichester, 1997. For encyclopedic style works, see Day, S. *Dictionary for Clinical Trials*. Wiley, Chichester, 1999 or Redmond, C. and Colton, T. (Eds). *Biostatistics in Clinical Trials*, Wiley, Chichester, 2001.

⁷ E.g., a recent paper is Holden, W.L., Juhaeri, J. and Dai, W. Benefit-risk analysis: a proposal using quantitative methods, *Pharmacoepidemiol. Drug Safety*, 12:611-6, 2003; and a review- Holden, W.L. Benefit-risk analysis: a brief review and proposed quantitative approaches, *ibid.*, 26:853-62, 2003.

b. Uses of Statistics for Clinical Safety Data

Statistics has a key role in making comparisons and in reflecting uncertainty. Correct use of inferential statistical methods helps to detect real problems and treats apparent effects with appropriate caution, allowing for the possibility that chance has played the major part in creating the findings.

The purpose of a statistical analysis is to present the data in a way that facilitates understanding of the effects of a drug and to make clear whether variation in results is likely to be due to chance or whether substantial effects might be associated with a drug. It is necessary to acknowledge when the data are insufficient to draw conclusions on safety, i.e., ‘absence of evidence is not evidence of absence.’ In such situations, the use of descriptive methods and well-designed graphics will be helpful in this process.

Uncertainty in any summary of a set of data is almost entirely dependent on the numbers of individuals analysed. Therefore, the ability of a study to detect causal effects in the face of variation within and between individuals is dependent on sample size; the smaller or rarer an effect, the larger the sample size required, if any degree of certainty is to be given to the study conclusions. To cite one example, under typical standards of statistical analysis ($\alpha = 5\%$, power 90%),⁸ if the background rate of an event in the population under study is 0.1% (1 in 1,000), then in order to detect with confidence a relative risk of 2.0 (2 in 1,000) in the experimental drug, a study would need about 31,000 patients in each of the placebo and drug groups!

The different stages of clinical trials may require different applications of statistics, but the fundamental principles related to variation and uncertainty apply at every stage. In addition to inferential statistical approaches, as mentioned above, descriptive statistical methods also have an important role in assessing data, particularly with the use of graphical and other displays, and some pointers on good practice are covered here.

Statistical approaches have application at several stages of clinical trials:

Protocol design. The objectives of the intended statistical analyses should be specified along with an analysis plan. This implies a requirement for sufficient numbers of patients to be included in the trial (power and

⁸ Reminder: the α -level is the boundary for rejection of the null-hypothesis (that there are no real differences between the data). At a 0.05 level, the chance of a false-positive finding is 5%; conversely the chance of a true negative is $1 - \alpha$, or 95%. Finding a false-positive result when the null-hypothesis is actually true is referred to as a Type I error.

sample size), something usually predicated on the demonstration of efficacy, with the proviso that unacceptable harm is not seen. It is possible to carry out many different analyses on different safety variables, but it is easy to be misled as to the true degree of uncertainty for the results unless it is clear whether that analysis was pre-planned or not. The requirement for an analysis plan helps resolve this, but care must be taken not to adhere too rigidly to pre-specified analyses lest safety issues be missed. The plan should also describe proposed strategies for dealing with missing data. Special considerations are needed and should be discussed in the protocol if any interim analyses are planned, especially those that necessitate breaking the blinded treatment code. Such analyses require special statistical approaches.⁹

Beware that unless a study is designed and planned to conduct certain analyses, they may not be powered sufficiently to carry them out, or their interpretation may be compromised by carrying out unplanned analyses. There is a very wide range of possible unplanned analyses that if conducted can affect statistical significance tests.

During a trial. As part of safety monitoring during trials, and for any possible interim analyses, data must be assembled and presented clearly to maximise the ability to detect any unexpected and unusual results. This is particularly important if considerations arise for stopping or modifying the trial so that any decisions made are soundly based and their impact on the analysis for the final report is accounted for.

For the final analysis and writing of the trial report and any publication. Comparisons are made mainly between treatment groups (for laboratory data, specific AEs, classes of AEs, numbers of discontinued patients, times to occurrence of AE or withdrawal). Within patient changes, such as baseline to follow-up, usually require a comparison group for their proper interpretation, largely because the effect of treatment cannot readily be distinguished from effects of time and time-dependent phenomena (e.g., time to onset of an AE or discontinuation). Sub-group analyses (e.g., AEs by age and sex) must be treated with great caution; it is their misinterpretation that is a major cause of misunderstanding in medical science.¹⁰

⁹ Jennison, B. W. and Turnbull, B. W. *Group Sequential Methods with Applications to Clinical Trials*, Chapman & Hall/CRC Press, 1999; Whitehead, J. *The Design and Analysis of Sequential Clinical Trials*, Second Edition, Chichester: Wiley, London, 1997. For a Bayesian approach, see Grossman J., Parmar, M.K., Spiegelhalter, D.J. and Freedman, L.S. A unified method for monitoring and analysing controlled trials, *Stats. in. Med.*, 13:1815-26, 1994.

¹⁰ Brookes, S.T., Whitley, E., Peters, T.J., Mulheran, P.A., Egger, M. and Davey Smith, G. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. *Health Technol. Assess.*,5:1-56, 2001.

When combining data across different trials. In order to provide an overview of the safety experience, summaries across trials can be made using the techniques of meta-analysis¹¹ for formal comparisons of treatments. On the other hand, simpler descriptive or graphical summaries of the data from several trials may also be revealing. The pattern of results across different body systems will be examined to search for patterns indicating possible effects that are not seen easily in a single trial.

Although most Phase II and III trials are randomised and usually double-blind, generally the same statistical principles discussed here can apply to non-randomised and non-comparative studies. Most comparative trials are designed to have parallel-treatment groups, although cross-over designs may also be used. Analysis of cross-over studies requires somewhat different approaches, and great care has to be taken in the interpretation of data relating to safety. Adverse reactions may be recognised some time after the administration of the drug (e.g., latent effects), and might incorrectly be attributed to the subsequent treatment in a cross-over treatment period. Even with a wash-out period between treatment legs, the period may not be long enough to eliminate any carryover effects. Thus, although immediate effects can be readily detected and compared in crossover trials, any delayed effects are difficult to attribute to treatment.

Independent of a trial design or Phase, there are many kinds of comparisons that can and should be made within and between treatment groups using the proper statistical tools, depending of course on the kind and amount of data collected. Typical analyses involve such things as: comparisons between treatment groups of specific AEs, classes of AEs (different organ systems, e.g.), and laboratory data; discontinuations from treatment; sub-population results (age, sex, etc.); time-dependent phenomena (time to onset of AE, time to discontinuation, etc.); combining data across trials. Approaches to some of these analyses are covered in detail below. This chapter refers to comparisons between two groups, but the same methods can be extended to multi-arm trials. For studies in which different doses of the same drug are compared, then it is possible to use methods that allow for a trend with dose, but in general the interpretation of comparisons is easiest when the possible comparisons are between two groups.

Recommendations on types of safety analyses as well as on how to display the data can be found in ICH Guidelines E3 (Structure and Content of

¹¹ For example, Lee, M-L. T. and R. Lazarus. Meta-analysis of drug safety data with logistic regression. *Drug Information Journal*, 31:1189-1193, 1997.

Clinical Trial Reports) and M4 (The Common Technical Document or CTD);¹² another useful source is the US FDA's guidance for internal Agency review of safety data in a New Drug Application.¹³ A guide to the coverage of statistical issues for safety data as discussed in ICH Guidelines E3 and E9 (Guidance on Statistical Principles for Clinical Trials) is given at the end of this Chapter (section j.).¹⁴

c. Principle of Intention to Treat

The principle known as “intention to treat” (ITT; also called intent-to-treat) is probably familiar to most readers in connection with analyses of efficacy data from randomised trials, but it may be less familiar in its application to safety data. Intention to treat means that the various study groups are compared using the allocation of treatment to which they were randomised, *whether they received the randomised treatment or not, or whether they continued to take the treatment or were withdrawn early from the trial*. Recommendations have been made that at least one ITT safety analysis should be conducted.¹⁵ This reinforces the point made in Chapter 4 that the collection of data should continue whenever possible to obtain study endpoints even in those who are prematurely withdrawn from treatment, although this recommendation applies especially to analyses of efficacy. Recent proposals have been made on how to create and use a “full analysis” data set for ITT analyses.¹⁶ The CONSORT group (referred to in footnote 3 above) also recommend that an ITT analysis should be applied to data on adverse events.

The rationale for using an ITT approach is to maintain the comparability of the treatment groups attained by the original randomization.

¹² For the complete documents, go to www.ich.org. Clinical safety issues in M4 are found under the Efficacy heading.

¹³ See FDA's Clinical Review Template (CDER, Office of the Center Director), Section 7.0 Integrated Review of Safety (<http://www.fda.gov/cder/mapp/6010.3.pdf>; effective 9 July 2004) and the more detailed Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (January 2005; see <http://www.fda.gov/cder/guidance/3580fnl.pdf>).

¹⁴ For more discussion on ICH E9, see Phillips, A., Ebbutt, A., France, L. and Morgan, D. The ICH Guideline “Statistical Principles for Clinical Trials”: Issues in applying the guideline in practice, *Drug Information Journal*, 34:337-348, 2000.

¹⁵ Peto R., *et al.*, Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples, *Br. J. Cancer* 35:1-39, 1977.

¹⁶ Stewart, W. H. Basing Intention-to-Treat on Cause and Effect Criteria, *Drug Information Journal*, 38:361-369, 2004.

Since patients drop out for various reasons associated with one outcome or another, excluding dropouts can bias the results. This would be considered especially problematic for efficacy analyses where the results may be biased in favor of the treatment. Hence ITT analyses are considered to be the most conservative approach.

Although considered conservative for efficacy, ITT analyses are not conservative for analyzing adverse event data where the results will be biased, on average, towards finding no differences between the groups (in other words, a tendency for the groups to be more similar to each other than they should be). Other analyses, such as including only those who received a minimal number of doses of the study drug, may be more appropriate for analyzing safety. However, these may also be biased. The problem is that the direction of the bias is unknown since the relationship, if any, between the reasons for stopping treatment and the outcome of interest will generally not be known. They may exaggerate or minimise differences between groups.

Because an ITT analysis tends to minimise differences between groups, not only on efficacy variables but also on adverse effects, then using survival analysis methods (discussed below) and “censoring” some data (i.e., excluding patients in the analysis beyond the time when their outcome is unknown) may be very useful.

It is customary to exclude from analysis of adverse effects those patients who do not take any doses of the study drug. This does not mean that the absolute rate of an adverse event may be estimated more reliably; it simply reflects the fact that leaving such patients in an analysis comparing treatment and control groups can be biased. The reasons for non-adherence to treatment should be examined carefully.

d. Some Key Problems in Safety Analyses

Perhaps it is obvious to state that the best possible generally accepted statistical methods should be used to analyse and present safety data, but as already pointed out the subject has not received as much attention as has treatment of efficacy data. Knowledge of and experience with proper methods may therefore be inadequate.

Some of the more important problems associated with safety analyses that require attention are as follows:

- ❑ **power:** usually the ability to find statistically significant differences between treatment and control groups for important adverse effects, which are usually relatively rare, is low; most trials, or even combinations of trials, are not large enough to detect or analyse such adverse events reliably.
- ❑ **multiplicity:** multiple analyses can be and often are performed on the same data set, such as on multiple time points and multiple variables. Multiplicity affects the statistical analysis, especially the calculation of P-values, because many different comparisons of adverse effects are possible. Efficacy variables are pre-defined and limited to a few effects on the disease being studied. The number of different types of possible adverse effects can run into the hundreds or even thousands and making a separate comparison for each of the different possible effects results in a very large number of analyses. Some pointers on the impact of multiple analyses are given below, but this area generally requires expert statistical help.
- ❑ **medical classification:** the grouping of adverse effects into categories represents a challenge; if too narrow, it results in numbers of event types that are too small for meaningful statistical comparison between groups, but if groupings are too wide (having larger numbers in the groups to avoid the first problem), it could hide the existence of a safety problem. This is so, because a specific effect might be hidden within a large number of adverse events that have nothing to do with the treatment being studied. Another difficulty arises in deciding whether groupings of different event terms for a patient can be formally regarded as a syndrome, for which a specific diagnosis might be possible. This requires medical judgement, and the results of the analysis will need careful interpretation rather than reliance on the result of a statistical test. Real adverse effects are often described by several different terms and the effects may occur in different organs; the problem can be described as multi-dimensional and this makes statistical analysis more complex and difficult to pre-specify. Chapter 4 discusses the use of coding dictionaries to describe medical events; the use of different dictionaries and different levels within those dictionaries leads to statistical problems.
- ❑ **time dependency:** adverse effects should be examined carefully as a function of time on drug; simple calculations of incidences (number of events such as AEs or discontinuations divided by number of

patients treated) can be highly misleading and mask the true risks associated with the treatments.

Currently used approaches to analyses of safety data are sometimes over-simplified, and do not take the major characteristics of adverse reactions into account. For example, some reactions have a rapid onset after administration of a drug, and if they do not occur early, are much less likely to occur later. Anaphylaxis is an obvious example. Some reactions will occur, or become obvious clinically, only after a long duration of treatment or long after treatment is ended. Examples include onycholysis or cancers. The most extreme example is carcinogenesis in the daughters of pregnant women who took diethylstilbestrol. Therefore, different time profiles are an important aspect of ADR classification¹⁷ and allowance is often not made for this in statistical analyses.

e. Useful Approaches to Statistical Analysis of Continuous Measurements: Laboratory Chemistries

Analysis methods need to be as sensitive as possible, while taking into account the problems related to multiplicity described above. Surrogate variables for clinically relevant outcomes should be analysed with the best methods. The laboratory tests that involve monitoring throughout a study (such as liver function tests, LFTs) should be analysed using the continuous data as well as binary data (data composed of only two categories, such as present/absent, alive/dead, etc.). Converting continuous measures to a binary indicator, e.g., a criterion for elevated LFTs that is greater than three times the upper limit of normal, loses information; while it provides a useful indicator in practice, it frequently will not be able to show statistically significant differences between groups because of the rarity of such large changes. It is likely that appropriate analysis of the continuous data (values at multiple time points) will show statistically significant effects even when there are very few extreme values.

It is best to analyse laboratory data using baseline values as a comparison whenever possible¹⁸. The most effective approach is usually to use the

¹⁷ Aronson, J. K. and Ferner, R. E. Joining the DoTS: New approach to classifying adverse drug reactions, *Brit. Med. J.*, 327:1222-5, 2003.

¹⁸ Frison, L. and Pocock, S. J. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design, *Statistics in Medicine*, 11:1685-704, 1992.

baseline value (or the mean where multiple measurements are made) as a covariate. The post-treatment value (or their mean where multiple measurements are made) is then the response that is analysed. It is also possible to analyse the before-to-after treatment change using the baseline as a covariate. This requires Analysis of Covariance (ANCOVA), as described in any statistical textbook.¹⁹ In practice, the post-treatment value that may be studied in the context of looking for adverse effects may be the *maximum (or most adversely extreme)* value. This is particularly true of things like liver-function tests (e.g., AST or ALT enzymes) where the highest value seen in a particular patient is the variable analysed. Analysis of covariance can also be used in this context, but caution in interpretation is required; the analysis of extreme values is more vulnerable to chance variation than might be supposed. Using the continuous measures is not always a substitute for studying the very high values that are associated with clinically relevant events (e.g., ALT>5 times upper limit of normal). These binary (AE occurs or not) measures will not usually have high statistical power for the comparison, but may be important in drawing attention to a potential issue.

Analysis of laboratory measurements used for monitoring of adverse effects should usually be done on binary measures of clinically relevant values or changes, but should also be done comparing mean values using analysis of covariance, since this is likely to have greater sensitivity for detecting real adverse effects.

Graphical displays, such as scatter plots of baseline versus later values for each trial participant, can help show both a shift from average and also draw attention to outlying values, both in terms of absolute levels but also large changes. An example is shown in Figure 1 below. The points can be automatically labelled with a patient ID or the treatment group. This example labels each point as 0 for control and X for experimental treatment group patients. It shows that there is a slight tendency for the higher post-treatment values to occur in the experimental treatment group. It is possible to use simple t-tests to compare baseline and final values within a group, though it will be more efficient to compare these changes between the treated and control groups using ANCOVA with baseline value as a covariate, as noted above. In this example the t-test does give a statistically significant result for the difference in mean values ($P=0.01$) and the ANCOVA gives $P=0.001$ suggesting that it is more powerful. If one were to decide that a clinically significant value were over 6 (see Figure 1), then there are 0/39

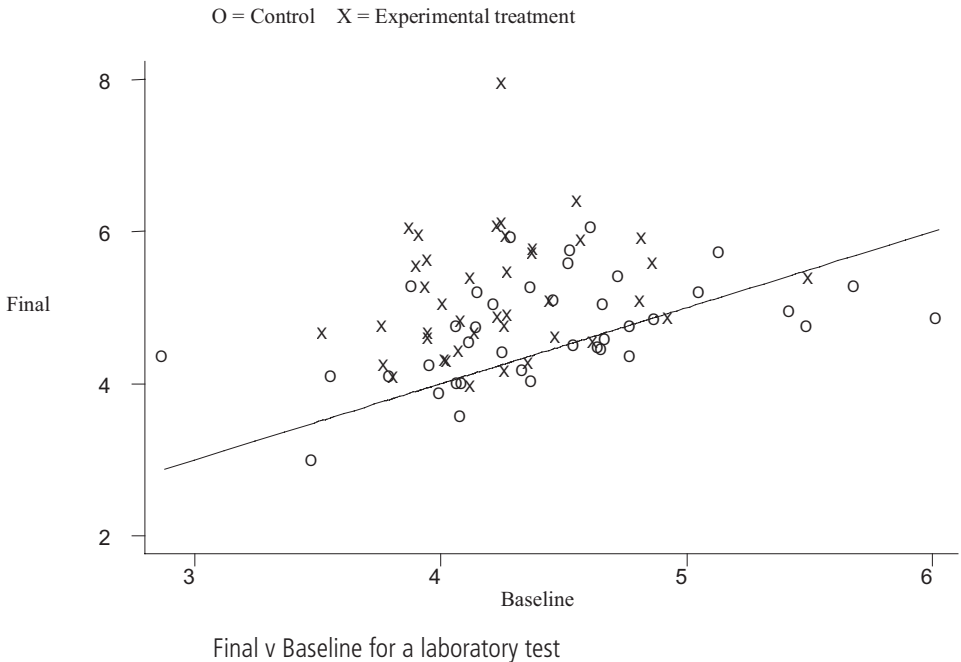
¹⁹ A classic text is: Snedecor, G. and Cochran, W. *Statistical Methods*, 8th ed., Iowa State University Press (1989).

in the control group and 3/41 in the experimental group, a difference which is far from statistically significant ($P=0.24$ using Fisher's exact test). This illustrates that just using a binary cut-off will usually have the least power to detect differences between groups.

Figure 1: Laboratory Value Scatter Plot for Individual Patients

Points are shown for baseline and final values after treatment.

The diagonal line represents equal values for baseline and final measurements.



The ICH E3 guideline notes that analysis should be applied to continuous data rather than just binary categorisations but does not offer suggestions for statistical techniques.

Finding a significant difference between groups does not necessarily prove causality based on a laboratory test result, but the most powerful statistical analysis should be used so that early signs of organ damage are detected. Trends in average values can be a surrogate for rare, clinically important individual changes. If the only analysis conducted is on differences between groups in the proportion of individual patient changes that are clinically relevant, such as 3 or 10 times the upper limit of normal, such an analysis may have too little statistical power and can fail to detect real problems. On the other hand, it is also useful to pay careful attention to

extreme values since it is possible that while the vast majority of patients have no meaningful changes, there could be some with very high values caused by a drug.

Most of the remainder of this Chapter discusses the treatment of binary data, that is whether an adverse event has occurred in an individual or not. Further description of handling continuous lab data can be found in Chuang-Stein, *et al.*²⁰

f. Statistical Treatment of Binary Data

This section will cover several key topics related to how binary data should be analysed: the statistical power needed, the difference between, and use of, “one-sided” vs “two-sided” statistical tests, the problems in conducting multiple analyses (multiplicity), general measures using binary data, the meaning and value of confidence intervals, and the importance of taking into account the effect of time on treatment.

(1) Power Considerations

Statistical power is the ability to detect as statistically significant an effect that is real. If only a few patients are studied then it is very easy to miss real effects. Similarly, if an effect occurs at a very low absolute rate, i.e., the medical event is very rare, even in those treated, then the power to detect it will be low. The power of a particular study will depend on the size of the groups being studied; the baseline or background rate of the adverse effect of interest, which is the rate expected in the comparison group; and the change of interest in rates between groups (for example a doubling or tripling). It also depends on the “P-value” set as being statistically significant, which is usually 0.05. If allowance is made for multiple testing (see below), then this P-value may be much smaller and so the effects will be more difficult to detect as statistically significant and therefore the statistical power will be lower.

Although guidelines are not absolute, the expectation for a typical drug development program is that a minimum of about 1,500 patients will have been treated with a new drug, with about 100 followed for at least a year if treatment is intended for long term use in non-life threatening chronic disease (see ICH Guideline E1). With such limited

²⁰ Chuang-Stein, C., Le, V. and Chen, W. Recent advancements in the analysis and presentation of safety data. *Drug Information Journal*, 35: 377-397, 2001.

numbers, uncommon or rare ADRs (e.g., an incidence of less than 1 in a thousand) will not be detected as having statistically significantly raised rates in the treated group. Therefore, the main use of statistical analysis is to show that uncertainty exists over the true rate of a potential ADR. The introduction to Chapter 5 discusses criteria for numbers of patients included and notes that some rare adverse events may be observed in the complete sets of data prior to authorisation. The problem is that they may easily be ascribed to background or the disease for which the drug is used.

For example, a trial of 1,500 per group will only have 56% power to detect a statistically significant doubling in risk of an ADR from 1 in 100 to 1 in 50 (1% v 2%). In other words in 56% of similar trials it will be concluded that there is a statistically significant difference, but in 44% of trials it will be concluded that the difference is not statistically significant and a real adverse reaction could be dismissed as just background based on the statistical analysis. However, a tripling from 1% to 3% will have good (97%) power. If the control group rate is only 0.1% (1 in 1,000), then the power to detect 5 times that rate is 39% with 1,500 per group, while to detect an increase to 10 times that rate (1%) the power is 87%. This assumes that the P-value used is the conventional 0.05.

It is clear that the problem for statistical assessment of individual trials with small numbers of patients is much greater since power will be much less. For example, the power to detect a difference between a 1% and a 2% rate will be less than 2.5% with 100 per group, while power only approaches a reasonable level (75%) to detect a 10% vs 25% rate with 100 per group. This means that analysis of small trials rarely provides useful results unless the event in question occurs at a very high rate, or if not then the data can be pooled across trials either in a meta-analysis or by using pooled control groups for serious, infrequent events (see below).

(2) One-Sided vs Two-Sided Testing

The use of $P=0.05$ is usually based on the assumption that a difference between treatment groups in either direction of the effect is of equal interest, which is called two-sided (two-tailed) hypothesis testing. In other words, both an increase in rate *and* a decrease in rate with the new drug relative to the control group are of interest. On the other hand, if it is only an increase in the effect that is regarded as relevant,

then a difference in only that direction is of interest and so the P-value should then be 0.025 instead of 0.05; that is called one-sided testing. The one-tailed test with $P=0.025$ is the same test as the two sided test with $P=0.05$. However, the finding that an adverse effect that occurs in the control group is *prevented* by a new drug would always be of great interest. Therefore, a statistical test that allows for either an increase or a decrease in the rate of an adverse effect should virtually always be specified in the protocol. Hence, it is recommended that all statistical testing on safety-related data be done on the basis of two-sided hypothesis tests.

(3) The Consequences of Multiplicity

Protocols are designed to minimise Type I errors (concluding that efficacy exists when it really does not), and the testing of multiple hypotheses within a single study is discouraged. However, the numbers of potential types of adverse events are very large, so that correction for multiple testing in a conventional way will mean that it is impossible to draw any conclusions. It is for this reason that corrections for multiple testing are rarely done using a formal mechanism. There are over 20 “System Organ Classes” (SOC) in each of the major schemes of classification of medical events. A statistical test is usually carried out with a P-value of 0.05 as the cut-off for a finding to be regarded as statistically significant. This P-value applies when a single significance test is done. If two independent tests are done on the same set of data (for example looking at each of two types of AEs in two SOCs) then the probability that one of them is significant is no longer 0.05, but is closer to 0.1 (2×0.05). In order to ensure that the overall probability of finding a significant result remains at 0.05, then each test has to be done with a cut-off of 0.025. This method is called a “Bonferroni correction”.

If AEs are grouped by SOC, and a test is done for each SOC, then 20 tests will be done. It is quite likely that at least one of these tests will be significant if a cut-off of 0.05 is used. This implies that each test will require testing at a level of $0.05/20 = 0.0025$, otherwise the probability of finding a single one significant at 0.05 becomes high (0.64). If the grouping is more specific than at the SOC level, with perhaps 100 different possible groups into which AEs are classified, and a statistical test comparing the rate of AEs between treatment and control is done for each of the 100 groups, then the potential for finding false positive effects (Type I errors) is even higher. Unfortunately, by having a more stringent cut-off for noting statistical significance, there is a penalty.

This penalty is that it becomes harder to reach statistical significance for real effects, which will then have to have very large differences between groups in the rates of AE in order for them to be regarded as statistically significant. So if the statistical cut-off level is reduced by adjustment for multiple comparisons, then inevitably the probability of false negatives rises. False negatives in this context are called Type II errors. This means we have failed to find that a real adverse effect is statistically significantly different between the groups, when in truth there is a real difference. This is described as a situation in which there is low power. The probability of a Type II error is (1- power). Like power, it depends on the background rate of the effect and the magnitude of the difference that is regarded as being of interest.

In practice what usually happens is that no multiple significance testing adjustment is made and the finding of a statistically significant result at $P < 0.05$ is a signal to explore the possibility of a real adverse effect more carefully.

Since we will always be concerned about the lack of power in looking for adverse effects, if adjustment for multiple comparisons is made, then it should use a more sensitive method than Bonferroni, one which will not decrease power as much. Discussion of these advanced approaches is beyond the scope of this Chapter, but useful literature is available.^{21,22,23}

(4) General Measures Using Binary Data

Participants are usually randomly allocated to experimental treatment or control in parallel groups. In crossover trials, participants are randomly allocated to one order of treatment, such as control, then experimental. As pointed out earlier, special methods of analysis are applicable to crossover trials, which will not be covered here.

Assume there are a participants in an experimental treatment group who have an AE of interest, while b do not; the corresponding numbers for the control group are c and d .

²¹ Simes, R.J. An improved Bonferroni procedure for multiple tests of significance. *Biometrika*, 73:751-4, 1986 and Ludbrook, J. Multiple comparison procedures updated. *Clinical and Experimental Pharmacology and Physiology*, 25: 1032-7, 1998.

²² Benjamini, Y. and Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. Royal Stat. Soc. Series B*, 57: 289-300, 1995.

²³ Lin, K.K. and Rahman, M.A. Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs, *J. Biopharm. Stat.*, 8: 1-15, 1998 (also, see discussion pp. 17-22).

Table 1 shows the data in a 2 x 2 layout (a 2x2 contingency table).

Table 1: Occurrence of Adverse Events by Treatment Group

	With AE	Without AE	Total
Experimental	a	b	$a+b$
Control	c	d	$c+d$

The proportion of patients on the experimental drug with that event during the trial = $a/(a+b)$. The control group proportion is $c/(c+d)$. Statistical significance tests can help to decide whether such differences can occur just by chance when there is no true difference. These proportions are referred to as the *risk* of that adverse event. The difference in proportions is then called the *risk difference*, or *absolute difference in risk*. The risks and the difference in risks may be given as percentages but it is better to express them as proportions.

The main statistical test for the comparison of proportions is the relatively familiar chi-square test. This is a statistical test of the hypothesis that there is no difference between the experimental and control groups in the proportions (risks) with the adverse event. This test uses the four numbers in the four cells of the table – a, b, c, d – in a formula that allows for a P-value to be calculated. It makes some assumptions about the data that depend on their being quite large numbers in the table as a whole. An alternative that does not make this assumption is called Fisher’s exact test. These two methods are tests of the *null hypothesis*, that the proportion with that AE is equal in the two groups – i.e., the difference in proportions is zero. A significant result ($P < 0.05$) occurs when the differences between the groups in the proportions with the AE is sufficiently large.

The magnitude of the difference between the experimental and control groups may also be expressed in relative terms. Two of these relative measures are the odds ratio (OR) and relative risk (RR). The odds of the adverse event in the treated group are $a:b$, while the odds in the control group are $c:d$.

$$\text{The odds ratio (OR) is: } (a/b)/(c/d) = ad/bc$$

The *ratio* of the proportions is a *risk ratio* also referred to as a *relative risk* (RR). If there is no difference between groups, the ratio is therefore 1. These measures have become familiar in the post-marketing

arena where analysis of spontaneous reports uses a 2 x 2 table of the type shown above. Unlike clinical trial situations, for which the numbers of patients with adverse effects is accurately known, the only valid calculation for spontaneous reports is a “reporting ratio,” which reflects the number of reports received, but not the real number of patients with the AE. One technique allows a determination of the “Reporting Odds Ratio”²⁴ while another yields a “Proportional Reporting Ratio” (PRR)²⁵ which is similar arithmetically to a relative risk.

The RR for the example given above is $(a/(a+b))/(c/(c+d))$. It can be seen that if a is much smaller than b and also that c is much smaller than d (a rare adverse reaction), then $(a+b \sim b)$ and $(c+d \sim d)$; in such a situation, dealing with rare events, the OR and RR are approximately equal.

To take a specific example from a large trial, the comparison between estrogen alone (E) and placebo in the Women’s Health Initiative (WHI) study,²⁶ generated the data in Table 2 for stroke.

Table 2: Occurrence of Stroke by Treatment Group (WHI Study)

	With stroke	Without stroke	Total
E	158	5152	5310
Placebo	118	5311	5429

The proportions with stroke were:
 $(158/5310) = 0.029765$ with E and
 $(118/5429) = 0.021735$ with placebo.

The difference in proportions is 0.008030, which when rounded is 0.008 or 0.8%.

The odds of having stroke were:
 $(158/5152) = 0.03067$ with E and
 $(118/5311) = 0.02222$ with placebo.

The odds ratio is 1.38, and the relative risk is 1.37.

²⁴ van Puijenbroek, E.P., Bate, A., Leufkens, H.G., Lindquist, M., Orre, R. and Egberts, A.C. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiology and Drug Safety*, 11:3-10, 2002.

²⁵ Evans, S.J., Waller, P.C. and Davis, S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and Drug Safety*, 10:483-6, 2001.

²⁶ Anderson G.L., et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women’s Health Initiative randomized controlled trial. *J. Am. Med. Assoc.*, 291:1701-12, 2004.

The chi-square test compares the observed numbers in each group with the numbers that would be expected if there were no difference in the proportions between the groups, but they had the proportion seen in the trial as a whole. The simple chi-square value from this table of data = 6.9, with an associated P-value = 0.0086. Therefore, the conclusion from these data was that the difference between the groups in the risk of stroke was statistically significant. It is recommended that exact P-values are reported rather than just, for example, $P < 0.01$. Fisher's exact test produces a P-value of 0.009. Usually the chi-square test will have a smaller P-value than Fisher's exact test, but with large numbers, as here, they will be similar. However, the difference can be larger when there are small values in any of the cells in the table. Fisher's exact test should be used whenever the expected numbers in any cell of a 2x2 table are less than 5. An alternative is called "Yate's Correction", which reduces the magnitude of a chi-square test and details can be found in, e.g., the book by Altman mentioned in footnote 6.

Odds are always larger than proportions and the odds ratio for a given set of data is always further from the null value of 1 than is the relative risk.

(5) Confidence Intervals

P-values have their uses, but it is usually better to report *confidence intervals* (CIs). A confidence interval is a measure of the amount of statistical uncertainty around a summary value known as the *point estimate*. This estimate will not necessarily be the *true* value, which may only be known if we have infinite knowledge about the parameter. What is needed is an awareness of whether our estimate is likely to be close to the true value or not. We construct confidence intervals for summaries of data such as proportions or differences in proportions. Similarly, confidence intervals for odds ratios or relative risks (by their nature comparative summaries) may be obtained, as well as the perhaps more familiar CIs for means or differences in means. The confidence intervals for the RR and OR are based on taking their logarithms and so the CIs will be symmetric on a log scale, but asymmetric on the original scale of RR or OR. The null value, implying no difference between compared groups, is zero for both log (OR) and log (RR), corresponding to ORs or RRs that are equal to 1.

Different approaches to statistical inference have different interpretations (particularly the Bayesian approach), but it can be stated generally that a confidence interval reflects statistical uncertainty in a summary value (the *point estimate*).

For the data from the WHI study discussed above, the risk difference (RD) = 0.008, with a 95% confidence interval (CI) = 0.002 to 0.014; the OR = 1.38, with a 95% CI of 1.085 to 1.76; the RR = 1.37, with a 95% CI = 1.08 to 1.73. Each of these intervals excludes the null value for the relevant summary (0 for RD and 1 for OR and RR). In other words, with 95% confidence the data do show a difference between groups. The differences or ratios are statistically significant with a P-value < 0.05. The general principle is that the 95% CI will exclude the null value when the difference is $P < 0.05$, and if it includes the null, then $P \geq 0.05$. There is a danger of relying too much on whether by itself $P < 0.05$ or $P \geq 0.05$; the CI gives more information. This is especially true with non-significant differences between groups, where a large CI will be compatible with the observed data. In a small study or one with rare outcomes, the CI will be very wide and it then shows that even substantial differences cannot be ruled out. This shows that CIs are particularly useful for dealing with adverse event data.

Results of trials should show confidence intervals for a relevant summary of the data rather than just quoting the P-value from a significance test.

Details on how to perform the statistical tests and calculate confidence intervals for odds ratios and risk ratios are given in intermediate level textbooks on medical statistics or epidemiology.²⁷ Currently available statistical software programs are able to calculate confidence intervals for rates or proportions reliably, even with small numbers.

A very simple example of a confidence interval is reflected in the “rule of 3”. This was discussed in Chapter 5 to show the sample size required to detect even a single occurrence of an outcome in a trial. The same principle can be used to construct an approximate 95% confidence interval when zero events (of say a particular potential adverse reaction) are observed. The rule can be restated as “when we saw zero events (of any kind), we could have seen three”. Thus our uncertainty in the observed rate of zero will depend on how many times we looked for that event. If we actually saw zero occurrences in 10 patients, then from a purely statistical perspective the approximate 95% upper confidence level would be 3. If we had looked at 100 individuals and seen zero, then the true rate might easily be 3/100, 3%; similarly if 1,000

²⁷ Rothman, K.J. and Greenland, S. *Modern Epidemiology*, 2nd ed., Lippincott-Raven, Philadelphia, 1998 and Altman, D.G. *Practical Statistics for Medical Research*, Chapman and Hall, London, 1991.

were studied, the upper CI for the true rate would be 0.3%. This “rule” is quite a good approximation when zero events are seen. It cannot routinely be applied when one or more events are seen.

(6) Accounting for Time on or off Treatment

It is very important that the length of time that each patient is “at risk” of having an adverse event be factored into any assessment of risk. The length of time over which a patient is followed in order to determine whether an AE occurred will not always be the same for every participant in a trial. This period may or may not be the same as the duration of treatment, which in some settings such as single dose studies, may well be the same for all patients. The planned time on treatment and any post-treatment follow-up will have been set by the trial protocol as the prescribed observation period. This period for each patient should normally extend to at least 5 half-lives once treatment is stopped. Some patients will not be followed for the planned time, especially in long-term studies. As already recommended, even if treatment is ceased, follow-up should continue so that delayed occurrences of new AEs or changes in an existing AE be recorded, whether they are considered due to a specific treatment or not.

Events that occur beyond the standard observation period can be difficult to include in a formal analysis, since unless all patients are followed for the same length of time post-treatment, it will not be known whether others also experienced the same or different events. Such post-treatment events should be documented, of course, and discussed in a trial report, but it is not usually appropriate to include them in the formal statistical analysis since bias could result. It is essential that the protocol clearly defines the end of the observation period. See Chapter 4 for a discussion on how to handle post-treatment/post-study event reports. Their clinical relevance may in some circumstances be considerable, but formal statistical methods require that all those included in the analysis are, in principle, treated equally. Follow-up beyond the defined end of the study is not likely to be equal for all those who reached the end of the study. However, ignoring such events is not satisfactory either.

Calculating the sum of the total time at risk for all patients by treatment group is useful, and this should be reported, often as person-time (e.g., person-years). The incidence rate is the total number of those having the event divided by the person-years at risk, and the ratio of incidence rates

between treatment and control groups is a *rate ratio*. This assumes that the incidence rate is constant over time but this will often not be true. Rates per person-time are recommended instead of just numbers of patients with an event divided by the total numbers that were in the relevant group. These values can be useful in carrying out a meta-analysis. Other, possibly better methods are discussed below.

Rates per person-time for each treatment group should be reported in addition to numbers of patients with an event divided by the total number of patients in the relevant at-risk group. This is especially important when combining data from studies involving different treatment durations.

An interesting example comes from the Women's Health Initiative (WHI) randomised trial comparing estrogen + progestin (E + P, or HRT) with placebo.²⁸ There was a mean of 5.2 years of follow-up, so that in the HRT group there were 44,075 person-years (p-years) and in the placebo group there were over 41,289 p-years at risk. The rate per 10,000 p-years for coronary heart disease (CHD) was 38 and 30 in the treated and placebo groups, respectively, which are averages over the whole follow-up period of the trial. The *rate ratio* is 1.27 (the same as the risk ratio to two significant figures). A risk has number of individuals as the denominator, whereas a rate has person-time as the denominator. The risk ratio is often referred to as a *relative risk* but both the risk ratio and the rate ratio are described as relative risk measures.²⁹

It should be noted that the assumption made when using person-years as the denominator, is that the risk of having an adverse event is constant at all times during the follow-up period. The risk per unit time is called the hazard rate and using total person-years as the denominator assumes that this rate is constant over time. With some types of adverse reaction this assumption may be reasonable but often this is not the case. For example, most hypersensitivity reactions are relatively rapid in onset and if they do not occur early in treatment then their likelihood of occurring later is very low. At the other extreme, any causal effect on cancer is likely to take at least a year and usually at least three years before it could be detected. This is illustrated by the

²⁸ Rossouw, J.E., *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial., *J. Am. Med. Assoc.*, 288:321-33, 2002.

²⁹ Rothman, K. and Greenland, S. *Modern Epidemiology*, 2nd Ed., Lippincott Raven Press, London, 1998, p. 49.

data shown in Table 3 taken from the WHI report.³⁰ A different assumption is that the *ratio* of the hazard rates in two groups is constant. This may be more realistic and analysis methods that utilise this assumption are given below.

Table 3. Participant-years, Numbers of Cases of Breast Cancer, Rates and Rate Ratios by Follow-up Year and Treatment Group in the WHI Trial

Year	HRT p-years	Placebo p-years	HRT BC*	Placebo BC*	HRT rate**	Placebo Rate**	HRT/placebo rate ratio
1	8435	8050	11	17	13	21	0.62
2	8353	7980	26	30	31	38	0.82
3	8268	7888	28	23	34	29	1.17
4	7926	7562	40	22	50	29	1.72
5	5964	5566	34	12	57	22	2.59
6 +	5129	4243	27	20	53	47	1.13
Total	44075	41289	166	124	38	30	1.27

* BC= Number of cases of breast cancer / ** Rate per 10,000 participant-years

It could be argued that the expected effect of HRT on breast cancer should only start to appear after two to three years, so using the total person-time as the denominator is very misleading. However, as an aside, it is also possible that HRT makes reading of mammograms more difficult even after only a short period of use. It is often found, in the summary of trials submitted for licensing of a new medicine, that the total person-time in the treated group across all the trials, or even the total number of patients treated, is the denominator used in determining the rate of occurrence of adverse events. This is rarely the best way of presenting or summarising the data, and must be treated with great caution. The correct ways of dealing with this issue have been described³¹ but are often ignored.

The correct method is to use a “life-table” or survival analysis, even though here it is not the time to death but an adverse event that is studied. ICH Guideline E3 mentions survival analysis methods for analysing safety data (in section 12.2.3), but it appears that this has often not been followed in practice. It is of greatest importance when there

³⁰ Rossouw, J.E., *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial., *J. Am. Med. Assoc.*, 288:321-33, 2002.

³¹ O’Neill, R.T. Statistical analyses of adverse event data from clinical trials. Special emphasis on serious events. *Drug Information Journal*, 21:9-20, 1987.

are notable numbers of patients who are lost to follow-up or withdraw from the trial for any reason. Using these methods will lead to higher estimates of the rates of an adverse effect than simply calculating the total number of AEs divided by the number of patients treated; however, if drop-out rates are equal between groups it will apply equally to both treatment groups. If the drop-out rate is higher on placebo, for example, then it will lead to a higher rate in the placebo group. The important point is that survival analysis gives a better, less biased estimate than the crude analysis.

From the perspective of illustrating the course of an adverse event, it is very much preferred to present the cumulative hazard and a good example is shown in Figure 2 taken from the report on the Women’s Health Initiative study (see footnote 30).

Figure 2: Example of Kaplan-Meier Estimates of Cumulative Hazard for Stroke (derived from Rossouw, *et al.* See footnote 30)

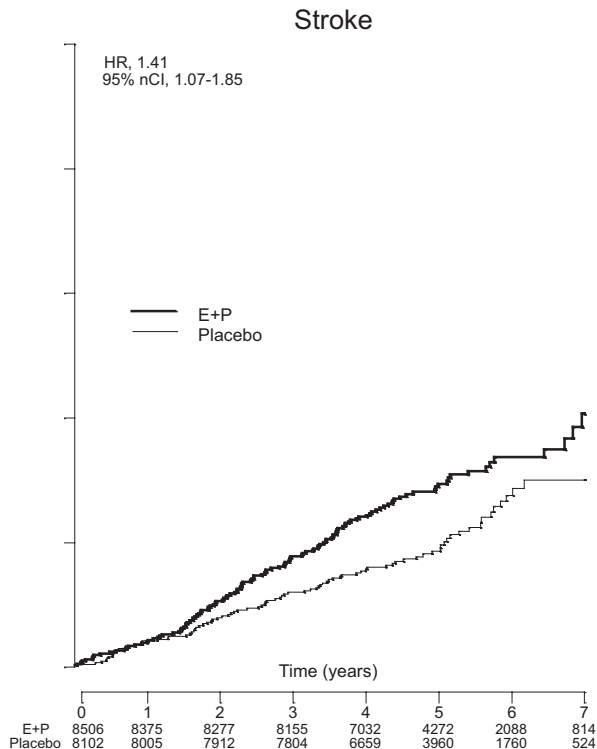


Figure 2 illustrates, for stroke, the cumulative hazard in each of the treatment groups. These curves show the rate at which new strokes are occurring in the two groups, as time from start of the study increases

along the X-axis. The Y-axis relates to the proportions having a stroke. At each time point when an adverse event (stroke) occurs, the risk of occurrence is calculated based on the number of adverse events occurring at that time, divided by the number of participants still at risk of having that event at that time. The numbers in each group still in the trial at that time are also shown below the X-axis. Those who have dropped out of the trial by that time point, for whatever reason, are not counted in the denominator. The method was used for other adverse effects and can also be used to examine benefits; the published figures also showed benefit for two categories of clinical outcome, reduction in colo-rectal cancer and hip fracture.

This and similar “survival” methods may be generally applied to adverse events, though their original use was in looking at death rates. The method is similar to that used for survival curves using a Kaplan-Meier estimate of survival. Kaplan-Meier curves start at 100% (everyone is alive) and move downwards over time; adverse events are best shown as cumulative hazard plots which move upwards over time as shown in Figure 2 above.

The calculation of cumulative survival is simple and is given in most introductory medical statistics books.³² The curves, such as Figure 2, are derived from more complex methods and require computer software for their preparation.

The curves derived from the Kaplan-Meier or cumulative hazard methods can themselves be misleading if too much attention is paid to the data at longer times. This is where the estimates are at their most uncertain, since the numbers “at risk” may be rather small. Good practice truncates these curves so that data based on very few observations are not included. Figure 2, as we have noted above, gives the numbers at risk (which is a good practice in presenting such figures) but it can be seen that the numbers fall off sharply after 4 years of follow-up, so that by year 6 less than 25%, and by year 7 less than 10% of those originally randomised are at risk of having events. There is therefore much greater uncertainty in the position of the curves at the time points beyond 6 years. For most clinical trials in new product development programs, the periods of observation are usually much shorter: for example, days or weeks for acute anti-infective treatment, months for intermediate term therapy, and one or two years for chronic

³² For example, Altman, D.G. *Practical Statistics for Medical Research*, Chapman and Hall, London, 1991, p. 368.

therapy. However, the same cumulative hazard method is appropriate; the numbers at risk may not fall off as quickly or as much compared to very long term observation periods, as in the WHI program.³³

(7) Statistical Tests Using Time Since Start of Treatment

The Kaplan-Meier method does not directly provide significance tests or confidence intervals for comparisons between groups. It is possible to treat the data as comparisons of proportions as discussed above, but these do not take into account differences over time and do not fully utilise the data. The simplest method of comparing the curves is the log rank test.³⁴ Although the result of this test can be expressed as a chi-square value, it is not the same as the simple chi-square test discussed earlier. The log rank test treats the data in a similar way to calculating a Kaplan-Meier estimate. At each time point where an adverse event (a “failure”) occurs, it is assumed that the rate should be the same in the treated as in the control group. An overall rate across both groups is calculated so that an expected number of failures is obtained for each group at that time point. The cumulative difference between the observed number of failures (O) and the expected number (E) for the whole time period under consideration is obtained and $(O - E)^2 / E$ can be compared to a chi-square distribution on one degree of freedom for testing the difference between the curves. This is a test of the null hypothesis that the two curves are identical. It does not assume anything about the hazard rate itself – it does not have to be constant, but it does assume that the ratio of the hazards is always constant and equal to one. There are various subtle modifications of the log rank test that apply different weights to the information at the beginning of follow-up compared with that at the end of follow-up. Further details on survival analysis can be found in Collett (1994)³⁵.

A more complex method for comparing time to event data is a “proportional hazards regression” or “Cox regression”. This, like the log rank test, compares an entire survival curve without making assumptions about the form of the hazard rate at any particular time, but it does assume that the ratio of the hazard rates between two groups

³³ For an extensive discussion of “chronology bias” in general, see Chapter 7 in Feinstein, A. R., *Clinical Biostatistics*, C. V. Mosby, St. Louis, 1977. Also published as *Clinical Biostatistics*. XI. Sources of ‘chronology bias’ in cohort statistics, *Clin. Pharmacol. Ther.*, 12:864, 1971.

³⁴ Peto R., *et al.*, Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples, *Br. J. Cancer*, 35:1-39, 1977.

³⁵ Collett, D., *Modeling Survival Data in Medical Research*, Chapman and Hall, London, 1994.

is constant at all times. This method can be used to adjust for other prognostic factors as well as for making a comparison between a treated and control group. It may be used for data from both randomised trials and observational cohort studies. The result of the Cox model is a hazard ratio, which is analogous to a relative risk averaged over all the time points considered. It also allows for a confidence interval around the hazard ratio to be calculated. The single value for the hazard ratio assumes that it is constant over the time period studied.

In the WHI estrogen-alone study described above (e.g., see Table 2), the estimated hazard ratio for stroke was 1.39 with a 95% confidence interval of 1.10-1.77, derived from a Cox model analysis. This is similar to the point estimate of relative risk calculated above as 1.37 with a CI of 1.08 to 1.73. The Cox model took into account age, prior disease and the treatment group in a simultaneous low-fat diet trial. These adjustments will make less difference to the results in a randomised clinical trial than in an observational study, but even in a randomised trial, important explanatory variables measured at baseline should be included in the analysis.

It is possible to use other statistical models that assume a particular form for the hazard rate, and these are called *parametric* methods. For example, the exponential model assumes a constant hazard rate. It is possible to allow for hazard rates that increase or decrease or are even J-shaped, such as the “Weibull” model. Some of these methods are described by Collett.³⁶ There are also methods available for checking the assumptions of survival analysis and these should be used when examining the difference between groups in rates of occurrence of adverse outcomes. This reflects the general principle that statistical tests make assumptions; these assumptions should be checked for validity in the particular sets of data under study.

When comparing rates using the number of cases with events as the numerator and person-time as the denominator, the basic assumption is that the number of cases follows a Poisson distribution. Analysis of these rates uses *Poisson regression*.³⁷ The results of these analyses can be expressed as incidence rate ratios.

The results from a Cox model analysis are always presented as relative measures of the effect rather than as absolute measures. It is not

³⁶ Collett, D., *Modeling Survival Data in Medical Research*, Chapman and Hall, London, 1994.

³⁷ Clayton, D. and Hills, M., *Statistical Models in Epidemiology*, Oxford University Press, Oxford, 1993.

possible to obtain absolute measures of rates, or relative risks at a specific time point directly from the analysis. With parametric methods it is possible to obtain absolute measures, and this approach may therefore be used more often in the future.

Adverse events that occur with sufficient frequency for formal analysis should be analysed using “survival” type methods, and consideration should always be given to showing graphs of cumulative hazards.

g. Combining Data from Several Trials: The Role of Meta-analytical Techniques

A major problem with most individual clinical trials during drug development and even for Phase IV studies is that they tend to be too small to detect uncommon or rare ADRs. There are obvious benefits to be gained from putting all the available information together to increase statistical power, a process referred to as a meta-analysis (also called a standard “systematic review,” viz., the process of defining the problem, searching for all data, combining, analyzing and presenting the data). In principle, this is more important for analysis of ADRs than for analysis of efficacy. However, most of the problems with individual trials are not solved by combining data. Important problems which remain relate to the classification of ADRs and in ensuring that all the relevant data have been captured. If the trials have excluded those likely to be treated in clinical practice then meta-analysis might give a false sense of reassurance. A major problem with using a meta-analysis is that the data may be derived only from published papers. Those data are prone to “publication bias,”³⁸ namely that you may never know how much relevant unpublished data exist; even if you are aware of such data, access may not be possible. On the other hand, when applying for marketing authorisation for a new drug, both regulators and the company will have access to complete data on the drug and publication bias is not an issue, even if some of the data may have been published.

No absolute criteria can be established for whether data from different trials can be combined so as to yield a valid analysis. However, some points that should be considered are listed here and the “QUOROM” guidelines³⁹ are helpful in setting out some principles.

³⁸ Egger, M., Davey, S.G. and Altman, D.G., Editors, (2001) *Systematic Reviews in Health Care. Meta-analysis in Context. [2nd Edition of Systematic Reviews]*, British Medical Journal Books, London, 2001.

³⁹ Moher, D. Cook, D.J., Eastwood, S., Olkin, I., Rennie, D. and Stroup, D.F. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. **Quality of Reporting of Meta-analyses**, *Lancet*, 354:1896-1900, 1999.

Questions that must be considered for a meta-analysis:

- a) Is the experimental drug the same in all trials?
 - Same dose? Same regimen?
 - Same formulation?
 - Same route of administration?
- b) Is the comparator the same?
 - Placebo or active comparator?
 - Dose of active comparator?
- c) Is the duration of treatment the same?
- d) Are the protocols similar?
 - Are AEs sought in similar ways?
 - Inclusion and exclusion criteria?

A further set of questions relate to the specific patients included.

- e) Is the patient population similar?
 - Age, sex, race, concurrent disease?
 - Disease state, duration and severity?

Even when the answer to some of these questions is “No” it does not mean that a meta-analysis is impossible or inappropriate. It is important to exercise judgement on what is sufficiently similar to shed light especially on rare effects. The main purpose of a meta-analysis in this context is to obtain sufficient data on a rare outcome for which a single trial does not provide a sufficient answer. It may be helpful to use graphical methods in meta-analyses, which can show similarities and differences for common as well as rare effects across different trials in a clear way. They can also be used to illustrate the uncertainty in effects so that apparently dissimilar results may be seen to be simply different by chance.

The greatest strength of a meta-analysis of trials is that the results which are combined are the within-study, between-treatment group differences. It means that the different studies themselves are not assumed to have similar results, but it is assumed that the between-treatment differences are relatively similar across studies. One of the consequences is that it is important that the scale on which the differences are measured is kept consistent across studies. If the (absolute) baseline risk varies across studies, it may be that the (absolute) risk difference differs markedly across studies, but the odds ratio is reasonably consistent. Therefore, pooling the odds ratios across studies may be the best approach. Methods that assume

the between-treatment differences are constant across trials are called *fixed-effect* models; allowance may be made for some heterogeneity in the between-treatment differences, and these are called *random-effects* models. If the variation is very large, then even a random-effects model may not be sensible, and the very idea of combining disparate results should be questioned. The detailed statistical methods are beyond the scope of this chapter but are found in the literature.⁴⁰

A frequently used but weaker, and in some instances flawed, approach to combining data is simply to add up the numbers across all trials of all the adverse events in the experimental group divided by the number of all the patients randomised to treatment. The same is done for the control group and the overall rates compared. In some instances this will give a similar result to that from a proper meta-analysis, but in most cases it will have less precision and may be biased. This is particularly likely when there has been unequal randomisation to experimental and control groups in some of the trials, and such a combination can be very misleading. Over- or under-estimation of between-treatment rates of events can occur. The method should not be used routinely. It also has problems when different durations of treatment and/or follow-up are combined. It is possible to use meta-analysis of individual patient data with survival analysis methods that does allow for different follow-up but this is relatively complex and is not in routine use.⁴¹

A meta-analytic review should be a routine part of the drug development process so that ADRs, and differences in ADR rates between treatment groups, can be detected as readily as possible.⁴² Crude pooling of adverse event numbers across different trials to compare experimental and control groups should be avoided if possible.

⁴⁰ Sutton, A.J., Abrams, K.R., Jones, D.R., Sheldon, T.A. and Song, F. *Methods for Meta-Analysis in Medical Research*, Chichester-Wiley, London, 2000 or the book by Egger, *et al.* (see footnote 38).

⁴¹ Higgins, J.P., Whitehead, A., Turner, R.M., Omar, R.Z. and Thompson, S.G. Meta-analysis of continuous outcome data from individual patients. *Statistics in Medicine*, 20:2219-2241, 2001; Stewart, L.A. and Parmar, M.K. Meta-analysis of the literature or of individual patient data: is there a difference?, *Lancet*, 341:418-422, 1993; and Duchateau, L., Pignon, J.P., Bijnsens, L., Bertin, S., Bourhis, J. and Sylvester, R. Individual patient-versus literature-based meta-analysis of survival data: time to event and event rate at a particular time can make a difference, an example based on head and neck cancer, *Controlled Clinical Trials*, 22:538-547, 2001.

⁴² Lee, M-L. and Lazarus, R. Meta-Analysis of drug safety data with logistic regression, *Drug Information Journal*, 31: 1189-1193, 1997; Temple, R. Meta-analysis and Epidemiologic Studies in Drug Development and Postmarketing Surveillance, *J. Amer. Med. Assoc.*, 281: 841-4, 1999; and Koch, G.G., Schmid, J.E., Begun, J.M. and Maier, W.C. Meta Analysis of Drug Safety Data in Solglierio-Gilbert, G (Ed.), *Drug Safety Assessment in Clinical Trials*, pp. 279-304, Marcel Dekker, New York, 1993.

h. Analysis of Rare Events

When rare events occur in a trial it will be difficult to conclude anything about relative rates of occurrence, or possibly causality, from an analysis based solely on that trial's randomised groups. A conventional statistical test to compare proportions as described above, Fisher's exact test, will find a count of 5 events in one group compared with zero events in the other as not being a statistically significant difference, when the sample size is 25 per group or larger. The chi-square test will give a similar result because it assumes that the overall observed numbers in total give the "expected" numbers for each group. If there are 25 subjects in each of two treatment groups and the observed number of events is 5 and 0, the chi-square test assumes that 2.5 events are expected in each group. In this situation, from a statistical standpoint the difference between 5 observed and 2.5 events expected (or between 0 observed and 2.5 expected) is not seen to be very great. However, if other reasonably reliable evidence indicates that the control group rate actually is expected to be very close to zero, then the count of 5 vs 0 may be very significant medically, even if not statistically. Clearly medical judgment would prevail to see that the trial is stopped even before 5 events of a very serious nature, such as liver failure, occurred in basically healthy patients treated for a headache.

On statistical grounds, as has been noted using the "rule of 3", the upper 95% confidence limit on zero events occurring in 25 patients is $3/25 = 12\%$. If there are data derived from some other, larger source that give a very different bound on the true rate of that event in an approximately similar population, we can use those data. If, for example, we are sure that the rate does not exceed 0.1%, then we can apply statistical methods used in other contexts, notably in spontaneous reporting, to calculate the ratio of observed to expected occurrences and derive a very different P-value. If we are confident that the expected rate is 0.1% (1 in a thousand), the ratio of the observed to the expected is $5/(25 \times 0.001) = 200$. This is very different from an observed/expected ratio based on the conventional statistical test described above, which yields a ratio of 5/2.5. An appropriate statistical test gives a P-value of <0.00001 . Even a single observed event with an expected percentage rate of 0.1% in such circumstances gives a statistically significant result. Hence if external information is available about the rate of an event in a similar population and it is known to be reasonably precise, careful analysis of rare events may then be amenable to statistical analysis rather than being dependent only on subjective judgment.

This type of methodology has generally not been applied routinely in clinical trials but there is an opportunity for it to be used more than it is.

Background rates can be obtained from a number of population-based data sources, as described in Chapter 3. Some of these databases are listed in Appendix 9. Pooling of control groups from historical clinical trials is another potential source of background rates. Optimum use of such data would require that either regulatory authorities or companies with large databases make them available, for example, to determine the expected rates of very serious events like liver failure or cancers. Further research is needed to obtain rates of occurrence of events that are extremely serious and rare. These rates should be published so that interpretation of a single or a few such events can be accomplished more objectively than is currently possible.

When a greater number of a serious but rare events is observed compared to that expected on the basis of background data, this will always be cause for careful scrutiny. However, it is important to keep in mind that the unexpected can and does occasionally occur by chance. Multiple cases can occur close together in time or space (sometimes referred to as a cluster of cases) which may not be caused by the drug. Chance can be an explanation, or there may be some external factor not associated with the trial treatment that is producing multiple cases. This is why a within-trial comparison will always be more reliable for deciding on causality. The use of background data, whether from population-based data or from pooled control groups from many trials, is subject to more uncertainty than the comparison of randomised groups.

Further research is required, through examination of large databases of completed clinical trials, to attempt to obtain rates of occurrence of events that are serious and rare. These rates should be published so that interpretation of a single or a few such events can be accomplished more objectively than is currently possible.

i. Measuring and Expressing Effects in Ways Relevant to Public Health

When an effect of a medicine is genuinely causal, then relative measures like the odds ratio, relative risk, rate ratios, and hazard ratios are often fairly high. At the same time of course, some effects are accepted as causal but do not have very high relative risks (in the sense of being far from 1), such as the effect of a statin seen in the MRC/BHF Heart Protection Study⁴³ on coronary death rate, which was 0.83. These small effects need

⁴³ Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360:7-22, 2002.

to be studied in very large numbers; the Heart Protection Study had over 20,000 patients randomised and followed up. However, they do not give the clinical or public health impact of the results which should always also be expressed on an absolute scale – the risk difference. It is important that both absolute and relative risk information are reported clearly.

A relative risk (RR) of 2 can be a difference between a 10% rate and a 20% rate of occurrence of an AE. It can also be the difference between one in a million and two in a million. The public health impact clearly varies enormously. Benefit-risk balance should always be based on both absolute and relative effects, as when comparing the benefits and risks of a new treatment to no treatment or alternative treatment.

A way of describing absolute effects related to benefits is to consider how many people are treated with a drug in order for a single “event” to be prevented.⁴⁴ The NNT (“number needed to treat” – the number of patients who have to be treated with the drug in order that one of them gets a benefit they would not otherwise have had) has become popular in articles in some medical journals. NNT would appear to be an absolute number, but this is not so. The time period for the treatment and follow-up of the outcome must also be given. “NNT” is implicitly the NNT to obtain benefit. For example, in the Heart Protection Study, the risks of a coronary death over the 5 years of treatment were 5.7% on the statin versus 6.9% on placebo, a difference of 1.2%. This difference suggests that 83 people need to be treated for 5 years to prevent one coronary death (there are other benefits of course). If the difference were constant over time then the NNT for 1 year of treatment would be $5 \times 83 = 415$ people needing to be treated for 1 year to prevent 1 coronary death.

Some authors have used “NNH” as the “number needed to harm;” however, it actually is the number of patients who have to be **treated** with the drug, in order that one of them has an adverse effect (harm) they would not otherwise have had. It is recommended to use “NNT/H”, to make it clear that it is the number needed to be treated (and not, for example, the number harmed). For example, the data from the WHI trial shown in Table 3 above gives a total of 166 women on HRT and 124 on placebo who contracted breast cancer in the 43,909 and 41,165 women, respectively, followed for about 5 years. This is a difference of about 8 per 10,000 over the 5 years. The NNT/H is expressed as 1310 women treated for 5 years who

⁴⁴ Cook, R.J. and Sackett, D.L. The number needed to treat: a clinically useful measure of treatment effect, *Brit. Med. J.*, 310:452-4, 1995 and an erratum, *ibid.*, 310:1056, 1995.

will contract breast cancer they would not otherwise have had. There have been statistical objections to these numbers that are largely related to the issue of time.⁴⁵ These absolute measures of effect are relevant in public health terms, but may need modification in different patient groups and different settings. They are very dependent on the actual absolute value of the rate of the adverse effect in the control group.

Absolute measures of risks (and benefits) associated with treatments should be presented along with the explicit time periods to which the results apply.

j. Comments on ICH Guidelines E3 and E9: Discussion of Statistical Aspects of Clinical Safety Data

ICH Guideline E3 makes a number of suggestions for presentation and analysis of data that pertain to safety of a newly studied medicine. It sets out three levels: 1) extent of exposure, 2) common adverse events and laboratory results that can be compared between treatment groups, and 3) serious adverse events, both those in the conventional ICH/regulatory sense but also other “significant” adverse events that require narrative statements and listings that relate to individual patients.

The comments on analysis are good but limited in the ICH document. Little mention is made of graphical summaries and most attention is paid to providing listings so that all events can be easily examined by regulators. There is mention of dividing events by whether the treating physician thought that they were causally related to the treatment, perhaps on a graded scale (even though the actual treatment allocation might be blinded). Individual case causal assessment is fraught with difficulty, and while it has its place for serious events, the use of such assessments in overall analyses when comparing rates of AEs between treatment groups is limited. It is the randomisation that allows for causal inference when comparing groups between randomised arms, and consideration of the investigator’s causality assessment is not helpful for aggregate analyses.

The E3 guideline does mention life-table approaches to analysis, which is to be recommended strongly, but it does not mention data presentation in

⁴⁵ Hutton, J.L., Number needed to treat: properties and problems. *J.Royal Statist. Soc.A.*, 163:403-19, 2000.

a graphical form. It is important that account be taken of those who are no longer in the study, especially towards the later time period in a trial.

One graphical summary mentioned is that of baseline versus final (or intermediate) scatterplots for laboratory measurements, so that shifts in values, even if they do not lead to clinically significant changes in many individuals, can be detected (see ICH E3, section 12.4.2.2 III). It does not mention that statistical tests, such as simple paired t-tests, can be employed to study these changes; such tests are not often used in practice, but should be. There are no clear guidelines on the problem of multiple significance testing, but as discussed in this chapter they cannot be ignored. Using a P-value of 0.05 means that with many tests 1 in 20 are expected to be “significant” even if there are no true differences between groups being compared, but this does not mean that these differences can be ignored; at the least they require more detailed investigation.

There is emphasis given to “shift” tables and to “treatment emergent signs and symptoms” (TESS). A shift table is essentially a tabular form of a scatter plot with the baseline and follow-up values for a continuous measurement grouped into categories. Such a table shows the numbers of individuals at different times, who have normal or abnormal test results. The numbers who started with “normal” laboratory values that subsequently became higher; the number with normal values at all times; the numbers with high values at the start but normal values later, etc. The post-baseline value included should be either the value at the end of the study, or, especially if there are drop-outs, the maximum value during the study. Tables of this nature are useful but their analysis is usually limited. One test that should definitely not be used as the only one is the chi-square test, since this does not take into account the ordered nature of the categories. “TESS” tables are similar but are done for categorical measures that are not based on an underlying continuous measure or have been converted to a binary variable. Analysis of newly emergent adverse effects can be done using the methods for binary data described in the Chapter.

ICH Guideline E9 has limited coverage of “safety data”. It does emphasise the use of survival analysis methods to examine patterns of occurrence of events over time, but it appears that this technique is not commonly applied, whereas it should be. It also mentions that pooling of data across similar trials can be helpful in studying rare effects, but notes the problems when this is done without the availability and inclusion of a comparator group. Further details on the best methods for combining data across trials are given in section g. in this Chapter.

VII

Regulatory Reporting and Other Communication of Safety Information from Clinical Trials

a. Introduction

Traditionally, safety reporting from clinical trials has focused on individual case reports and has been viewed as a somewhat routine activity mandated by various regulations. Some aspects of the various regulations (e.g., expedited reporting of suspected adverse drug reactions that are both serious and unexpected) are fairly well-defined. CIOMS I Working Group was responsible for the successful introduction of standard criteria, format and timing for the expedited reporting of suspected adverse reactions to marketed drugs.¹ The ICH Guideline E2A focused on extending the harmonization of the regulatory requirements for expedited reporting of suspected adverse reactions from clinical trials in the pre-approval environment.² The more recently adopted ICH Guideline E2D adapted E2A for expedited post-marketing reporting.³ As a result, similar criteria are now more likely to be applied through the life cycle of a medicinal product, from pre-approval to post-approval. CIOMS III/V made recommendations for determination of “expectedness” for clinical trial case reporting based on Development Core Safety Information (DCSI).⁴ These recommendation have been taken up in varying degrees by sponsors of clinical trials, as evidenced by the responses to question 15 of the industry survey (See Appendix 3).

While requirements for expedited reporting to regulatory authorities have been largely harmonized on a global basis, other aspects of the regulations, such as reporting by sponsors to investigators and/or ethics committees, reporting by investigators to ethics committees and DSMBs, when appropriate, and how these reports translate into information for study subjects (via informed consent) are not as clearly defined and vary widely across regions. Companies’ practices also vary widely, as can be seen from the responses to survey questions 19-26 (Appendix 3). In addition, the usefulness of some of the information that is currently shared with investigators and ethics committees on a routine basis has been questioned.

¹ *International Reporting of Adverse Drug Reactions*, Final Report of CIOMS Working Group. Council for International Organizations of Medical Sciences, Geneva, 1990.

² ICH E2A *Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, developed by the Expert Working Group (Efficacy) of the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Step 5 as of October 1994 (<http://www.ich.org>).

³ ICH E2D. *Post-Approval Safety Data Management: Note for Guidance on Definitions and Standards for Expedited Reporting*, Step 5 as of November 2003 (<http://www.ich.org>).

⁴ *Guidelines for Preparing Core Clinical-Safety Information on Drugs. Second Edition, Including New Proposals for Investigator’s Brochures*. Report of CIOMS Working Groups III and V. Council for International Organizations of Medical Sciences, Geneva, 1999.

For purposes of this discussion, we use the term “reporting” to refer to the submission of individual and multiple case reports, line listings or tabulations in compliance with regulations, and the term “communication” to refer to the broader concept of notification of safety information to appropriate stakeholders (investigators, regulators, IEC/IRBs, DSMBs, patients).

In this chapter the CIOMS VI Working Group considers the reporting of cases and the communication of important new safety information by (1) sponsors to regulators, investigators, ethics committees and data and safety monitoring boards and (2) investigators to ethics committees. We consider the following questions: What is (or should be) the intended purpose of regulatory reporting requirements? What do the existing and/or proposed regulations, directives and guidance documents say should be the practice? Do the current regulations and practice adequately address the intended purpose? What alternative approaches might better meet the information needs of regulators, investigators and patients? We also consider whether one set of rules is appropriate for all clinical trials and whether information needs may change during the life cycle of an investigational or marketed product.

The following precepts form the basis for the CIOMS VI Working Group recommendations.

- ❑ Ongoing safety monitoring of the experimental drug is an operational as well as intellectual task requiring scientific, medical, epidemiological and statistical expertise. It is a responsibility allocated to the trial sponsor, overseen by regulatory authorities (fulfilling their obligation to protect public health). In some circumstances, it also warrants utilisation of an independent safety monitoring committee or other outside consultants.
- ❑ The ongoing evaluation of safety information involves judgement and is based on clinical expertise that takes into account all available information on the drug. This expert assessment may result in the identification of a new risk, which needs to be communicated to relevant ethics committees, investigators, regulatory authorities and patients. *Ad hoc* reporting of individual case safety reports is generally not considered an effective way of communicating important new information to investigators and ethics committees.⁵

⁵ We note that the US FDA held a public hearing (21 March 2005) on the various problems associated with reporting of individual case and other clinical trial safety information to IRBs, as the basis for possible changes to current regulations and practices (see <http://www.fda.gov/OHRMS/DOCKETS/98fr/oc04297.pdf>).

- Undue harm can arise when the potential benefits are outweighed by possible risks, based on a balanced assessment of all available safety and efficacy data on the investigational product. Sponsors, regulators, ethics committees and investigators have a joint responsibility to put newly identified risks into such context.

It is important to point out that many of the recommendations included in this Chapter are proposals only. Although the CIOMS VI Working Group as well as its external panel of reviewers agree that these proposals represent a meaningful way forward, none of the recommendations should be interpreted as superseding current regulations. Rather, the recommendations are intended to inform discussions for future regulations, as has been the case with prior CIOMS proposals. Until such time as these proposals may be implemented, sponsors are expected to maintain compliance with all existing regulations.

b. Expedited Reporting from Clinical Trials

(1) Expedited Reporting to Regulatory Authorities

Most of the regulations that describe safety reporting from clinical trials focus on the expedited reporting of individual case safety reports (ICSRs). ICH Guideline E2A which is generally considered the standard for what information to send, stipulates that sponsors should submit suspected adverse drug reactions that are both serious and unexpected to regulators within 7 (if fatal or life-threatening) or 15 calendar days in an appropriate format.⁶

Expedited single case reports from clinical trials are accepted by the majority of regulatory authorities on the CIOMS I or similar form. With the adoption of ICH Guideline E2B⁷ and then E2B(M)⁸ which define standard data elements for electronic individual case safety reports, some regulatory authorities have begun to require the electronic submission of expedited reports in the post-marketing environment. More recently, the EU and Japan have begun requiring electronic submission of expedited reports from clinical trials as well.

⁶ ICH E2A *Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, Step 5 as of October 1994 (<http://www.ich.org>).

⁷ ICH E2B *Guidance on Data Elements for Transmission of Individual Case Safety Reports*, Step 5 as of July 1997 (<http://www.ich.org>).

⁸ E2B (M) *Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*, Step 5 as of November 2000 (<http://www.ich.org>).

Time frames for expedited reporting, i.e., seven (7) and fifteen (15) calendar days, are for the most part consistent across regions. Nevertheless, while authorities generally accept the same format and most have incorporated the 7 and 15 day timeframes into regulation, there continues to be some divergence from the ICH recommended criteria for what constitutes an expedited report from a clinical trial. For example, while most authorities require the expedited reporting of suspected adverse drug reactions that are both serious and unexpected, consistent with ICH Guideline E2A, other authorities require expedited reporting of suspected adverse drug reactions that are serious, regardless of expectedness. Some authorities will ask sponsors to report events of special interest in an expedited fashion regardless of causality or expectedness.

The CIOMS VI Working Group endorses the ICH Guideline E2A and thus recommends the harmonization of criteria for expedited reporting to regulatory authorities, to include suspected adverse drug reactions that are both serious and unexpected. Only under exceptional circumstances and on an ad hoc basis (e.g., when close scrutiny and monitoring of a specific adverse reaction is warranted) should sponsors be expected to report, on an expedited basis, suspected adverse drug reactions that are considered expected. If there is a need to report events without regard to causality, this should generally be on a periodic basis with the periodicity and format, e.g., line listing, agreed in advance with the concerned authority.

(2) Expedited Reporting: Causality

The definition of a suspected adverse reaction, incorporating the concept of relatedness, may be found in ICH E2A.⁹ This definition has been adopted by most regions; however, its meaning has been interpreted inconsistently. The difficulty appears to lie in the use of both the phrase “a reasonable possibility of a causal relationship” and the phrase “a causal relationship cannot be ruled out”. While intended by the authors of ICH E2A to be synonymous, they are subject to interpretation, with the former phrase suggesting a threshold based on clinical judgment but the latter implying something broader and more inclusive, with less room for judgment. Most sponsors currently follow the approach of using clinical judgment to determine if there is a reasonable possibility of a causal association. If sponsors were to report based on whether or not a causal relationship can be definitively

⁹ ICH E2A Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Step 5 as of October 1994 (<http://www.ich.org>).

ruled out, then the number of expedited reports would likely increase dramatically. The impact would be especially significant if some countries continue to require the expedited reporting of serious suspected adverse drug reactions regardless of expectedness. Even with full harmonization, excluding expected cases, the impact on managing the significantly increased number of expedited reports would be great.

CIOMS VI Working Group does not believe that increasing the number of expedited reports, by lowering the threshold for considering an adverse event a suspected adverse reaction, would contribute to the protection of trial subjects or to the overall assessment of safety. To the contrary, individual case reports are generally not an effective means of communicating important new safety information. The CIOMS VI Working Group recommends that regulators adopt the phrase “a reasonable possibility of a causal relationship” and consider dropping the phrase “a causal relationship cannot be ruled out” from the definition of suspected adverse drug reaction.

See Chapter 4, section c.2. and Appendix 1 (Glossary) for more discussion of this issue.

(3) Expedited Reporting: Expectedness

The CIOMS III/V report defines expectedness for clinical trials based on “listedness” in the DCSI for investigational drugs.¹⁰ Since the DCSI, as part of the Investigators Brochure, will apply to all regions where clinical trials are being conducted, its use for determining expectedness facilitates harmonization of reporting. Once a drug is approved, regulations may require the use of the local datasheet (e.g., US Package Insert, EU Summary of Product Characteristics) for determining expectedness in a particular country. The CIOMS III/V and CIOMS V Working Groups also made the recommendation that local datasheets be used for determining expectedness once a drug is marketed, “for reports from all sources, including clinical trials”.^{11,12} However, there are likely to be circumstances where, for the sake of uniform reporting from clinical trials to regulators, ethics committees and investigators, it would be preferable to report based on a

¹⁰ *Guidelines for Preparing Core Clinical-Safety Information on Drugs. Second Edition, Including New Proposals for Investigator’s Brochures. Report of CIOMS Working Groups III and V.* Council for International Organizations of Medical Sciences, Geneva, 1999.

¹¹ *Ibid.*

¹² *Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of the CIOMS Working Group V.* Council for International Organizations of Medical Sciences, Geneva, 2001.

single reference. For example, if there are large Phase IV international trials being conducted in several regions, local datasheets may vary due to varying stages of approval of labelling changes, thus resulting in variability in reportability by country. In such circumstances, the CIOMS VI Working Group recommends use of the CCSI rather than the local label for post-marketing reporting from clinical trials, analagous to the use of the CCSI for determining listedness in the PSUR. Hence the CIOMS VI Working Group makes the following recommendation, which diverges somewhat from the earlier CIOMS recommendation.

In order to maintain global consistency of clinical trial reporting, the Working Group recommends that once a drug is marketed, the CCSI effectively become the reference safety information for the purpose of determining expectedness for regulatory reporting from Phase IV clinical trials. For clinical trials of new indications, new populations or new dosage forms for a marketed drug, every attempt should be made to align the DCSI and the CCSI, but the DCSI should be used if it is different from the CCSI.

Some sponsors determine reportability of a case at the event level (i.e., the case would be reportable if there is a suspected adverse reaction that is both serious and unexpected) and some do so by the case level (i.e., the case has at least one suspected adverse reaction that is serious and at least one suspected adverse reaction that is unexpected). The latter situation results in erroneous reporting when the serious adverse reaction is expected and the unexpected adverse reaction is not serious.

As with spontaneous reports, the CIOMS VI Working Group recommends that the determination of reportability for case reports from clinical trials be determined at the event level. That is, a case would meet the criteria for expedited reporting only if there is a suspected adverse reaction that is both serious and unexpected.

(4) Expedited Reporting: Unblinding

Blinded clinical trials bring specific requirements for unblinding expedited single case reports. This process has been defined in the ICH guidelines and CIOMS recommendations^{13,14,15} and is reiterated here.

¹³ ICH E2A Guideline for Industry: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, Step 5 as of October 1994. <http://www.ich.org>

¹⁴ ICH E6 *Good Clinical Practice: Consolidated Guideline*, Step 5 as of May 1996. <http://www.ich.org>

¹⁵ *Guidelines for Preparing Core Clinical-Safety Information on Drugs. Second Edition, Including New Proposals for Investigator's Brochures*. Report of CIOMS Working Groups III and V. Council for International Organizations of Medical Sciences, Geneva, 1999.

Suspected adverse drug reactions that are both serious and unexpected, and thus subject to expedited reporting, should generally be unblinded. However, there are likely to be special circumstances where an exception to this rule would be appropriate, for example, where the efficacy endpoint is also a serious adverse event (SAE). In this case, the circumstance and the process to be followed should be clearly defined in the protocol and the sponsor should seek agreement from the relevant regulatory authorities. Such exceptions should be clearly described in the protocol and Investigator Brochure.

Exceptions to unblinding are not always clear cut. Therefore it would be important to establish, in advance, clear criteria for the diagnosis and agreement from all concerned authorities for the exception. Even with clear criteria, it may still be necessary to report a case while awaiting further information. For example, if the endpoint of a study is myocardial infarction, the diagnosis may not be confirmed at the time of the report. In that case the blind should be maintained until the endpoint can be ruled out. In circumstances where the endpoints are not clear cut, there should be a mechanism established for making decisions regarding unblinding and it should be described in the protocol. For example, a “committee” of two or three physicians might be established to review each potentially reportable case and decide on whether or not the exception applies. Defining the criteria and establishing a procedure for making decisions should go a long way toward maintaining consistency and conformity to the exception.

Sponsors may elect to establish an independent DSMB with responsibility for the ongoing review and assessment of safety data from one or more clinical trials. (See Appendix 8 on DSMBs.) One possibility is for the sponsor to obtain agreement from relevant authorities that the use of a DSMB might obviate the need to unblind and report individual cases. Instead the DSMB would be responsible for notifying the sponsor of any significant safety issues which would in turn be reported by the sponsor in an expedited fashion to regulators and ethics committees. The exact nature and content of the information would depend on the situation.

Sponsors should discuss with regulators the use of a DSMB in lieu of expedited reporting.

(5) Expedited Reporting: Comparators

Once a case is unblinded the question of whether or not to report comparator or placebo cases arises, especially given that the expectedness

decision upon which the unblinding was based generally relates to the experimental drug. Individual cases which, when unblinded, are found to involve patients on placebo will usually not be reported as expedited reports. With regard to comparators, the CIOMS VI Working Group felt that the sponsor of the clinical trial has the duty to send the report to the company that is the marketing authorization holder (MAH) for the medicinal product or directly to regulators when the other company is not known or when information on the nature of the trial is considered proprietary. When the report is sent to the company that is the marketing authorization holder (MAH) for the drug, the sponsor should inform the MAH of the regulatory reporting status. If the sponsor has chosen to forward the report only to the MAH, the MAH would be expected to report the case to regulatory authorities where applicable. When the sponsor chooses to send the report only to the concerned authority, the most current, up to date reference safety information (e.g., EU SPC) may not be readily available to the sponsor. Even if it is, it may not be in agreement for the suspected ADR in question with the data sheets in all countries where the case may have to be reported. In that case, reporting by the sponsor to the regulator should be made regardless of expectedness. Independent of the method chosen by the sponsor it should be determined in advance and applied consistently throughout a particular clinical trial program.

The CIOMS VI Working Group recommends that unblinded placebo cases should generally not be reported to regulatory authorities on an expedited basis. On the other hand, it is recommended that unblinded comparator cases be reported to regulatory authorities and/or the company owning the comparator on an expedited basis, regardless of expectedness. Likewise, serious suspected adverse reactions for open-label comparators should be sent on an expedited basis to the appropriate regulatory authorities and/or company regardless of expectedness.

It should be noted that this proposal may be in conflict with at least one regulatory guidance, namely that of the EU Clinical Trial Directive. The Directive suggests that comparator reports be expedited to both the regulatory authority and the MAH. The CIOMS VI Working Group felt that there needed to be some flexibility in this regard, perhaps closer to the FDA requirement that stipulates that either the sponsor or the MAH needs to report the case to the regulatory authority. The April 2004 guidance for the EU Directive suggests that expectedness

for the comparator be based on an arbitrarily chosen datasheet to be included in the protocol or the IB. The CIOMS VI Working Group believes that reporting without regard to expectedness is more appropriate than determining expectedness in a somewhat arbitrary manner. An exception is possible when the sponsor can identify a reasonable, broadly applicable representation of the reference safety information for the suspected ADR(s) under consideration.

(6) Expedited Reporting: Spontaneous Reports

Early in the clinical development of a new investigational product when little is known about its safety, a heightened level of awareness and scrutiny of serious adverse events is especially important. Hence the recommendation in the ICH Guideline E2A that unexpected suspected adverse drug reactions from clinical trials which are fatal or life-threatening be reported within 7 calendar days. As the safety profile becomes better understood, and once a drug is approved for marketing anywhere in the world, it should not be necessary to apply the same 7-day time frame for spontaneous reports from the post-marketing environment.

The CIOMS VI Working Group proposes that, as a general rule, 7-day reporting be limited to reports from clinical trials and not include those from the spontaneous reporting environment. This should generally apply to reporting in countries where the drug is not yet approved as well as in countries where the drug is approved.

(Note that this may be in conflict with and does not supersede current regulation.)

(7) Prompt Reporting Other than Case Reports

ICH Guideline E2A and some national and regional regulations define other types of information that would warrant an expedited report by the sponsor to the regulatory authority. Examples include: non-clinical safety information having implications for the potential for serious adverse reactions in human subjects (including but not limited to findings of mutagenicity, carcinogenicity or teratogenicity); an increased frequency (see the CIOMS V report for a discussion of “increased frequency”) or severity of a previously recognized serious adverse reaction; an incidence of a serious adverse event that is significantly higher for the experimental drug than for a comparator; a greater than expected incidence of a serious adverse event compared

to the relevant background rate in the general population; a significant drug interaction observed in a pharmacokinetic study; a protocol procedure-related adverse event unrelated to treatment.

In addition, ICH Guideline E6 states “The sponsor should promptly notify all concerned investigators/institutions and the regulatory authorities of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC’s approval/favourable opinion to continue the trial.”

In the various circumstances described above, where the information that should be expedited is not an individual case report, the current standard is to report within 15 days; however, it may not be clear when the reporting clock starts. The CIOMS V working group suggested such reports might be referred to as prompt notifications rather than expedited reports.¹⁶ In the absence of a well-defined policy, one approach would be to have the clock start when the study co-ordinator (non-clinical or clinical) becomes aware of the potentially important safety finding. However, this is more easily said than done, since it is not always clear when the awareness actually begins. Another approach might be for the sponsor to establish a decision-making committee, define the timeframe within which the committee would meet once there is a possible finding that might constitute a 15-day report, and have the clock start the day the committee decides the information is reportable.

For circumstances other than individual case reports, the CIOMS VI Working Group recommends that sponsors define their internal decision-making process in a standard operating procedure (SOP), including how the clock start date will be determined for prompt notifications.

In addition to the usual criteria for an expedited report, adverse events that are not deemed to be drug-related but are considered to be protocol related should also be reported in an expedited fashion if they are serious.

There is no established format for reporting adverse events considered to be protocol-related. One reasonable approach would be to use the CIOMS I report form and explain the situation in the narrative. An example would be the occurrence of stroke following a significant rise

¹⁶ *Current Challenges in Pharmacovigilance: Pragmatic Approaches*. Report of the CIOMS Working Group V. Council for International Organizations of Medical Sciences, Geneva, 2001.

in blood pressure during the washout phase of a clinical trial for a new treatment for hypertension.

(8) Expedited Reporting: Investigators and IECs/IRBs

While ICH Guideline E2A resulted in the relatively successful harmonization of reporting to regulatory authorities, it did not specifically address the reporting of events to investigators and ethics committees. Rather, it refers the reader to ICH E6 (GCP Guideline) which states, “the sponsor should expedite the reporting to all concerned investigator(s)/institution(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.” Prior to ICH, some countries with a specific regulatory requirement for sending expedited reports to investigators required that individual case safety reports be sent to all investigators conducting trials registered under the same clinical trial authorization (e.g., IND in the US). Subsequent to the adoption of ICH Guideline E6, other countries now require that the same reports that are expedited to the regulatory authorities are also sent to each and every investigator in that country that is conducting a clinical trial with the investigational drug that is the subject of the report.

The CIOMS VI Working Group recommends replacing the current practice of sending large numbers of individual case reports to investigators and ethics committees with a more reasonable approach to communicating important safety information to all who need to know. Such an approach would involve periodic and ad hoc communications to investigators and ethics committees that include an update of important safety information as well as the evolving benefit-risk profile.

The EU Clinical Trial Directive does not include a requirement for sending individual case safety reports to investigators. National authorities within the EU have the option of instead requiring the sponsor to provide the investigator with periodic listings and a concise summary of safety. The periodicity of the listing to investigators is not specified. However, the Directive does introduce the possibility of quarterly line listings to ethics committees in lieu of individual case reports from other regions. Some countries in Europe, e.g., Germany and Austria, have nevertheless incorporated into new national legislation a continued requirement for submitting individual case safety reports to investigators and ethics committees within their countries as well as to the national authority.

When considering expedited reporting to IRBs/IECs, the international rules are even less well-defined and more inconsistent. Even ICH E6 (GCP Guideline) is noncommittal in this regard. While specifying that reports should be expedited to investigators, ICH E6 only specifies that reports be expedited to IECs/IRBs “where required”. Some countries’ regulations, including those of the U.S. FDA, leave it up to the responsible IEC/IRB to define what information it must receive from the investigator. On the other hand, the sponsor is responsible for ensuring that the investigator is following GCP, including compliance with rules defined by the IEC/IRB. Hence most sponsors will instruct the investigator to forward all expedited reports to the respective IRB/IEC, regardless of the country in which the investigator resides.

The new EU Clinical Trial Directive clearly places the responsibility with the sponsor for reporting to the IEC(s).¹⁷ However, the revised final guidance issued April 2004 leaves open the possibility of sending to the IEC only those expedited reports that originate in the IEC’s own country, with a quarterly line listing on cases from other places. In addition, any significant new safety information that would affect adversely the safety of subjects or the conduct of the trial would be reported to ethics committees within 15 days.¹⁸

With the growing number of trials that are multinational and the expanding size of the typical development program, from a couple of hundred subjects to thousands or sometimes tens of thousands of subjects, the volume of reports that an investigator or IEC/IRB may have to process and deal with can be staggering. As sponsors have adopted the CIOMS III/V report recommendations to use a higher threshold than previous practice for considering events expected,¹⁹ the volume of reports to regulators and investigators has increased even further. If regulators institute less strict criteria for considering events to be

¹⁷ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Article 17: Notification of serious adverse reactions. <http://www.emea.eu.int/>

¹⁸ *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use*, issued April 23, 2004 (<http://www.emea.eu.int/>)

¹⁹ CIOMS III/V introduced the concept of threshold for deciding when to add a new adverse reaction to the DCSI, which includes a reasonable degree of suspicion of a causal relationship. Many sponsors were more likely to include events in the IB sooner and thus consider them expected. While the higher threshold (do NOT include events so soon) is considered an improvement from the standpoint of the value of the information in the DCSI, it has resulted in many more expedited reports being sent to regulators, investigators and ethics committees since they remain unlisted/unexpected. For more discussion, see Section e. below.

“possibly drug related” (i.e., if the ICH E2A definition of adverse drug reaction is taken literally and includes anything that cannot be definitively ruled out as causally related; see Appendix 1 for further discussion), the number of “suspected reactions” will increase yet again. As the volume of reports increases so does concern about overwhelming investigators/IECs/IRBs as well as concern over the integrity of the trials by unblinding a significant number of study subjects.

While sponsors have become accustomed to reporting in an expedited fashion to regulatory authorities based on a well-established set of criteria, it is questionable whether it is useful to disseminate the same information to the scores and sometimes hundreds of investigators and in turn to IECs/IRBs. Sponsors and regulatory authorities generally have computerized databases at their disposal for storing, cataloguing, coding and analyzing the information. Investigators and IECs/IRBs generally do not and are often overwhelmed with the amount of paperwork that comes their way. Even if the resources were available for each investigator to manage, maintain and analyze the data, the value of such redundancy is questionable. Likewise, while certain IECs/IRBs will continue to have the need to receive and review individual case reports from their own sites, they are ill-equipped to manage and interpret the many other case reports originating from other sites, often from other parts of the world, and to place them into proper perspective. The responses to survey question 24 (Appendix 3) demonstrate the increasing level of frustration among IECs and IRBs in dealing with the information they currently receive.

Unfortunately, while based on a well-intentioned desire to improve the protection of human subjects, the system has become a resource intensive activity that does not necessarily result in effective communication of useful safety information to those who need to know and act. The CIOMS VI Working Group believes that individual case reporting should not be considered synonymous with communication of important new safety information. When compliance is the goal, sponsors tend to err on the side of conservative assessments of causality and expectedness. In addition, it is well recognised that the investigator assessment of causality is a crude and imprecise tool. As a result, individual case reports do not always (and often do not) include important new safety information. Conversely, important new information that is best derived from an overall analysis of reports in aggregate may not be effectively conveyed through sporadic case reporting.

Although contrary to established regulations, the CIOMS VI Working Group proposes that routine expedited case reporting by sponsors to investigators and IECs/IRBs be eliminated. Instead, sponsors should provide regular updates of the evolving benefit/risk profile and highlight important new safety information. Significant new information, occasionally a single case report, that has implications for the conduct of the trial or warrants an immediate revision to the informed consent would be communicated on an expedited basis. More commonly, important new safety information would be communicated periodically, based on the assessment of accumulating information in aggregate, as delineated in Chapter 5.

See Section c.(3) below for recommendations on update reports to investigators and IECs/IRBs.

c. Periodic Communication of Safety Information from Clinical Trials

(1) Development Safety Update Report (DSUR)

Regulatory requirements for periodic reporting of safety from clinical trials vary widely. Some authorities (e.g., Switzerland, EU and USA) require a periodic report of safety in clinical trials during development. Until the recently implemented EU Clinical Trial Directive, the vast majority of countries had no such requirement. Those that do have a requirement tend to define the format, content and timing of such periodic reports differently. Post-marketing, countries that require PSURs in the ICH E2C format would also receive an update of safety in clinical trials as part of that report.

In the U.S., the FDA IND regulations define an “annual IND report” which includes line listings of the most serious and the most frequent adverse events as well as reasons for discontinuation.²⁰ The new European Clinical Trial Directive, which became effective May 2004, for the first time defines a periodic safety reporting requirement that applies to clinical trials both pre- and post-approval.²¹ In addition to an

²⁰ U.S. Code of Federal Regulations 21CFR312.33: Investigational New Drug Application Annual Reports, Revised as of April 1, 2004. <http://www.accessdata.fda.gov/>

²¹ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Article 17: Notification of serious adverse reactions. <http://www.emea.eu.int/>

annual report to regulators, there is the possibility of quarterly line listings with a brief safety summary to inform investigators and ethics committees.

The CIOMS VI Working Group recommends defining a single Development Safety Update Report (DSUR) for submission to regulators on an annual basis, with a consistent format and content which are yet to be defined. In this regard, the CIOMS VI Working Group endorses the concept published in the EU Clinical Trial Directive Guidance document “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use.” However, it is strongly recommended that the reports be based on an entire development program and not per protocol.

Consideration should be given to establishing a common international birthdate which would be the date of first authorization to begin clinical trials anywhere in the world.²² The CIOMS VI Working Group recommends the use of MedDRA preferred terms for line listings. The DCSI should be attached to the annual DSUR with an explanation of any changes since the last update, with any significant new safety information highlighted.

For products with a well-established safety profile and when most clinical trials are Phase IV in the approved indication(s), it is strongly recommended that the PSUR replace the annual DSUR.

A detailed proposal for the content, format and timing of DSURs was felt to be beyond the scope of CIOMS VI. However, this topic has been adopted by a new drug safety working group, CIOMS VII.

(2) Investigator Brochure and DCSI Updates

One common and very important method for informing investigators of new safety findings is through periodic updates to the Investigators Brochure (IB). ICH Guideline E2A says “In general, the sponsor of a study should amend the Investigator’s Brochure as needed, and in accordance with any local requirements, so as to keep the description of safety information updated.” Some national regulations also refer to keeping investigators informed through periodic updates to the IB, but the periodicity of such updates is generally not specified.

²² The concept of a single DSUR for submission to regulators with an international birthdate has also been proposed by FDA, Docket No. 00N-1484, CDER 199665. Safety Reporting Requirements for Human Drug and Biological Products. <http://www.accessdata.fda.gov/>

The CIOMS III/V report introduced the concept of Development Core Safety Information (DCSI) and made the recommendation that the DCSI should be the part of the IB that defines the company's position on suspected adverse reactions.²³ Some sponsors have established the DCSI as an attachment to the IB. The advantage of making the DCSI an attachment is that it makes it possible to update safety information more frequently than the usual annual update to the IB by updating only the attachment.

The CIOMS VI Working Group endorses the previous recommendations of CIOMS III/V. Sponsors should establish a policy of incorporating DCSI into every IB, either as a special section of the IB or as an attachment to the IB. The DCSI should clearly identify the events for which the company believes there is sufficient evidence to suspect a drug-relationship. These would be the events that would be considered expected ("listed") from the standpoint of pre-approval regulatory reporting criteria.

Consistent with the previous CIOMS III/V Working Group recommendations, the CIOMS VI Working Group recommends that sponsors review the IB and DCSI at least annually and update them as appropriate. If there are no changes to the IB or DCSI, then the investigators and ethics committees should be so informed at a convenient time, such as with a periodic update.

(3) Other Periodic and *Ad Hoc* Communications to Investigators and IECs/IRBs

As noted above, the CIOMS VI Working Group recommends that individual case safety reports not be reported to investigators or to IECs/IRBs on a routine basis. Instead, it is recommended that there be periodic communications to investigators and IECs/IRBs, the timing of which might depend on the stage of development.

For unapproved products, and in lieu of expedited reports, the CIOMS VI Working Group recommends periodic reports to investigators and IECs/IRBs that include a line listing of unblinded clinical trial cases that were expedited to regulatory authorities since the last periodic report, a copy of the current DCSI along with an explanation of any

²³ *Guidelines for Preparing Core Clinical-Safety Information on Drugs. Second Edition, Including New Proposals for Investigator's Brochures.* Report of CIOMS Working Groups III and V. Council for International Organizations of Medical Sciences, Geneva, 1999.

changes, a statement if there are no changes, and a brief summary of the emerging safety profile. Although it is recommended that the default would be quarterly updates, there may be circumstances when a more immediate communication would be appropriate. Likewise, there may be circumstances when less frequent updates should be sufficient.

For approved products, the timeframe for periodic reports to investigators and IECs/IRBs would depend on the extent to which new indications are being developed. For a product undergoing Phase III trials, continuation of the quarterly reports would be advisable. For well-established products, less frequent updates would be appropriate and at some point, there should only be a need to update investigators and IECs/IRBs when there is significant new information to report.

When updates are provided by the sponsor to investigators or IECs/IRBs, whether for unapproved or approved products, line listings should include only unblinded expedited reports from clinical trials. The line listings should include interval data, i.e., only cases expedited since the last update; however, the summary of the emerging safety profile should take into account all of the accumulating data. The use of MedDRA preferred terms is recommended. The line listings generally should not include spontaneous reports; instead, significant issues arising from spontaneous reports can be described in narrative form in the update.

For Phase IV investigators and their associated IECs/IRBs, communication of changes to the CCSI should be sufficient and periodic reports or line listings should no longer be necessary.

In addition to the periodic reports to investigators, there are circumstances when it would be appropriate to communicate important information on a more immediate basis. This will of necessity be based on clinical judgement, the seriousness of the event and the strength of the evidence for causality. Although such safety alerts will most likely be based on an assessment of several reports in aggregate, there may be a single case report that warrants communication to investigators as well as regulators on an expedited basis. For example, a single report of severe hepatotoxicity for which a causal relationship is likely may trigger an expedited communication to investigators if it is the first such report early in development.

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor should issue a prompt notification to all parties, namely regulatory authorities, investigators and IECs/IRBs. A significant safety issue could be defined as one that has a significant impact on the course of the clinical trial or programme (including the potential for suspension of the trial programme or amendments to protocols) or warrants immediate update of informed consent.

(4) Safety Management Process

As described in more detail in Chapters 3 and 5, the CIOMS VI Working Group strongly recommends that sponsors define and implement a system for regular reviews of safety information during development. It is important to identify clear roles, responsibilities and accountability for making sure that safety information is reviewed at pre-defined intervals and that there is a mechanism for triggering an ad hoc review whenever there is a special concern.

The CIOMS VI Working Group recommends that sponsors define a Safety Management Team to review all available safety information on a regular basis so that decisions can be made with cross-functional input. It is further recommended that these reviews take place quarterly pre-approval and be coordinated with the PSUR schedule (six-monthly or annually) post-approval. In addition, ad hoc Safety Management Team meetings may be warranted to address urgent safety issues or significant safety signals.

Safety Management Team meetings should be used to review the overall evolving safety profile during development, to make changes to the DCSI and/or informed consent and to determine if any changes in the conduct of the trials need to be considered. The outcome of these meetings may then provide the basis for the brief summary of safety in the periodic reports to investigators and IECs/IRBs.

d. Other Reporting Considerations

The CIOMS VI Working Group felt that periodic summaries of safety, with the occasional alert report when warranted, should be sufficient for keeping investigators and IECs/IRBs informed of the emerging safety profile of a new drug in development. However, it was also recognized that existing regulations will make the continued submission of individual case reports to investigators and IECs/IRBs a necessity in some regions.

DSMBs are most commonly employed for a single large clinical trial and are not usually charged with providing oversight of an entire clinical program. It would therefore be important to ensure that important new safety information is communicated to the DSMB even if the information did not originate from the DSMB-monitored study.

Often the developer or manufacturer of a product is not the sponsor of a particular clinical trial, but rather has agreed to support an external investigator-sponsor financially or by providing drug supplies. In this situation the investigator as the sponsor is responsible for upholding good clinical research practices and complying with all regulations that apply to the sponsor in the region or regions where the investigator-sponsor is conducting the study. However, it would be important for the developer/manufacturer to ensure ready access to important safety information in order to meet its own obligations for overall assessment, reporting and communication. (See also Chapter 4, section b.)

The CIOMS VI Working Group recommends that a standard provision of any agreement with an outside investigator-sponsor, whether for a clinical or non-clinical study, should be the prompt reporting by the investigator-sponsor to the Company of all serious suspected adverse drug reactions as well as any suspicion of a previously unrecognized hazard to patients. Timely access to the final study report should also be included.

e. Informed Consent

In the conduct of clinical trials, the number one goal must always be to ensure the safety of patients who consent to participate. Suspected adverse drug reactions should be evaluated in a timely manner during the course of clinical trials in order to assess what, if any, actions may be warranted with respect to the continued conduct of the trial. This includes, but is not limited to, assessing the need to communicate important new safety information to participating patients.

The principal means of communication to the patient is via the investigator. The informed consent form (ICF), agreed and approved by the IEC/IRB, should describe the risks and benefits of participating in the trial in a way that the subject or the subject's guardian can understand. The information must be current and balanced.

International Guidelines for Biomedical Research Involving Human Subjects, published by CIOMS in 2002, should be consulted for a

comprehensive compilation of points to consider and rules to follow in developing and communicating informed consent for research subjects.²⁴ The Guidelines cover the process of obtaining as well as renewing informed consent, the importance of ensuring understanding on the part of the subject, and situations where ethics committees might approve a waiver from obtaining informed consent, e.g., in emergency situations, cultural considerations and confidentiality.

A key area for consideration that has not been previously addressed in any real depth relates to the determination of which adverse reactions should be added to the consent form and when. In fact, a common complaint among investigators and ethics committees is their inability to make that determination based on the individual expedited case reports that they currently receive.

In its introduction of the DCSI concept, CIOMS Working Group III/V proposed that a relatively high threshold (compared to the CCSI, for example) be used for adding new, serious AEs; once added, they become “listed” and therefore any subsequent cases no longer require expedited reporting to regulators, investigators and IECs/IRBs. The rationale for this position (i.e., a high threshold for adding to DCSI) was as follows: careful attention to new signals of serious ADRs demands ongoing monitoring and attention; by changing the DCSI on the basis of one case of a given event, for example, there might be a tendency not to pay as much attention to that event if new cases arise. CIOMS Working Group VI believes that the higher threshold approach is no longer deemed appropriate for two reasons: (1) by implementing a systematic process (Chapter 3) during development for pharmacovigilance and risk management, there will be ongoing oversight of all safety issues, and (2) there is heightened sensitivity to ensuring that trial patients are fully informed of any new important information, even if somewhat tenuous (see Chapter 2). Therefore, CIOMS Working Group VI believes that the threshold for adding a new serious AE to the DCSI should be the same as that for the CCSI.

In addition, it is recommended that the same criteria be applied to informed consent information. Applying the CIOMS III/V threshold concept to informing patients ensures consistency of information. A lower threshold for inclusion in the consent form is unlikely to bring clarity of risk and more likely to detract from what is already known.

²⁴ *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Prepared by the Council for International Organizations of medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), CIOMS, Geneva, 2002.

The CIOMS VI Working Group recommends applying the same concept and level of threshold to the DCSI and the informed consent form as has been previously recommended for the CCSI. Thus, communication to investigators and IECs/IRBs of an update to the DCSI may indicate the need to update the informed consent form, the final decision for which rests with the IEC/IRB.

The CIOMS VI Working Group believes that such a policy will be a welcome aid to investigators and ethics committees who are currently in the daunting position of deciding what to add to the informed consent information based on individual case reports. It will also be advantageous to the patient, who will be presented with the most important information and not a long list of reported events of questionable relevance.

Informed consent should be renewed whenever there is new information that could affect subjects' willingness to participate, including new information about risks. CIOMS International Ethical Guidelines suggest that under certain selected circumstances, e.g., for long-term studies, informed consent should be renewed at predefined intervals whether or not there is new information. In most cases, when updating informed consent, it should be sufficient to do so for continuing study participants at the next scheduled visit. However, there may be circumstances where a more immediate communication would be more appropriate. This would be the case, for example, if a new risk has been identified that is life-threatening, even if the benefit-risk relationship is still considered a favourable one. Communication between visits is also advisable for less alarming situations if there is a long time interval between visits.

f. Other Communication Considerations

This chapter covers the reporting and communication of safety information by sponsors of clinical trials to other stakeholders, namely regulators, ethics committees, investigators, DSMBs and subjects. What has not been covered, and yet is an area of increasing attention and scrutiny, is the communication of important safety as well as efficacy results of clinical trials to treating physicians and patients who may not be directly involved with the conduct of the trials but for whom the information may be important for making informed treatment decisions. This subject is discussed at greater length in Chapter 2, section c, including the Working Group's rationale for considering this topic out of scope for CIOMS VI.

g. Conclusion

This chapter introduces several new proposals for the reporting of safety information to regulators, investigators and IECs/IRBs. In addition, suggestions are made regarding the content and timing of informed consent. Although some of the proposals are not in accordance with current regulations in most countries, the CIOMS VI Working Group believes these recommendations have several advantages:

- ❑ Useful and informative safety information would be provided to ethics committees and investigators without barraging them with large numbers of case reports that they may not be equipped to handle or effectively interpret in the context of the overall development program.
- ❑ Sponsors would be encouraged to enhance their systems and procedures for maintaining a proactive stance toward the monitoring of safety during development.
- ❑ Reinforcing the use of a consistent approach for adding information to the DCSI (and hence IB) will result in greater consistency in determining expectedness for reporting to regulatory authorities and for inclusion of ADRs in informed consent forms.

If these proposals are accepted and implemented through regulations, the CIOMS VI Working Group believes that the result will be a much more effective system for managing safety information from clinical trials, and more importantly, for identifying and communicating important new safety information to all who need to be informed and need to take appropriate action in a timely manner.

VIII

Summary of Concepts and Proposals

a. Introduction and Overview

- Patients and trial subjects will have different “acceptable” levels of harm or risk, and in that sense risk and harm are relative concepts to the individual.
- Although general responsibilities for managing drug safety issues are usually covered in GCP regulations or guidances, the details and increasing complexity of the field would benefit from the development of more specific, internationally based Good Pharmacovigilance Practices (GPP).
- Although there are some important differences between pre-marketing and post-marketing safety monitoring and management, there should be a much stronger and closer relationship between them.
- The CIOMS VI Working Group has developed proposals based on scientific principles for harmonizing many aspects of the collection, monitoring, analysis, evaluation/interpretation, and communication to all relevant parties of clinical trial safety information. The general principles proposed apply to Phase I, II, III and IV trials.
- Practical guidance for the design and execution of a rational drug safety surveillance plan during any clinical research program should be directed not only to pharmacovigilance/clinical safety specialists, but to all those involved in the design, planning and execution of the clinical research process for the development of new medicines or diagnostic substances, as well as new uses and preparations of already available products.
- This report is also directed at independent clinical researchers and others not involved in commercially-based medicines development, since the pursuit of enhanced safety standards is principally concerned with the protection of patients.
- In any development program, the ultimate goal is to evaluate and provide a measure of the benefit-risk relationship for the anticipated conditions of use. However, this report only indirectly addresses the benefit side of the relationship and does not deal in a major way with the evolving methodologies for qualitative and quantitative aspects of benefit-risk weighing.

b. Ethical Considerations for Clinical Trial Safety Management

- For anyone designing and conducting a clinical trial, the fundamental principle should be that any study that is not scientifically sound can be considered unethical.
- There is growing importance and sensitivity not only for patient rights generally, but for clinical trials in non-industrialized, developing countries, vulnerable and socially underprivileged patients, transparency (including on payments to investigators and to trial subjects), and the availability of results of all trials, including those with “negative” findings.
- Although gaining informed consent is the cornerstone of all human subject clinical research, there are situations where it may not be possible or appropriate, such as in the use of anonymized tissue samples, in some types of epidemiological research, certain kinds of survey research (to avoid biased results), and in emergency-treatment study protocols (at least initially).
- The CIOMS Working Group VI endorses the concept of transparency of results and outcomes for all clinical research, especially safety data; however, concrete proposals or recommendations on this continuously evolving topic involve many complicated factors which are beyond the scope of the Group at this time.

c. Systematic Approach to Managing Safety During Drug Development

- Although the term “pharmacovigilance” has traditionally been associated with post-marketing activities, the CIOMS VI Working Group recommends that the term be applied to the pre-marketing process for collecting, managing and assessing safety information during development. Likewise, the concepts of risk assessment and risk minimization, together comprising risk management, are terms that are as applicable to the pre-marketing environment as they are to the post-marketing environment.
- It is important for sponsors to ensure that a well-defined and well-structured process is in place that will allow them to readily

identify, evaluate and minimize potential safety risks relative to potential benefits for study subjects in pre-approval trials. Such a process should start before initiating the first Phase I study and continue through post-approval use of the drug or biologic in the general population. It is important to consider and define, in advance, the roles and responsibilities of individuals within the organization who are expected to participate.

- A formal Development Risk Management Plan (DRMP) should be created and modified as needed during a clinical program. In the initial planning stages of a new clinical development program, one goal is to gather the necessary knowledge and information to adequately plan the optimum program from the standpoint of safety. The plan should include early documentation of known, anticipated and potential risks along with plans for addressing them during development and, where appropriate, the DRMP would eventually evolve into a post-marketing risk management plan that will accompany the registration application.
- Sponsors should establish standard operating procedures that define a framework for a process that can be applied consistently across all development programs, but which allows enough flexibility to meet the needs of what will inevitably be a diversity of products and a broad range of safety issues associated with them. In some cases it may be appropriate to supplement standard operating procedures with product-specific procedures.
- A dedicated Safety Management Team (SMT) should be formed for each development program, to review all the available safety information on a regular basis so that decisions on safety can be made in a timely manner. It also recommends that these reviews generally take place at least quarterly pre-approval and be coordinated with pre-approval and, if applicable, post-approval periodic reporting. Quarterly and *ad hoc* safety reviews should consider the overall evolving safety profile of the investigational product, make necessary changes to the IB/DCSI and informed consent, determine if any changes to the conduct of the trials need to be considered, and initiate prompt communications to investigators, ethics committees and regulators when appropriate.
- Roles and responsibilities should be clearly defined for the Safety Management Team as well as for each individual on the team. Each

member of the team must have responsibility and accountability for raising issues, in particular those emanating from their respective disciplines. The team should be empowered to make decisions that will accomplish the goal of minimizing risk while maximizing benefits to subjects in clinical trials, as well as anticipating the use of the product once marketed.

- When licensing partners are involved, a joint safety management process, including clear roles and responsibilities of the respective companies, should be defined in advance with timelines for exchange and joint review of data. Ideally the terms should be part of the initial contract, but at the very least should be incorporated into a follow-on agreement on safety matters.
- Key to the successful implementation of a consistent and systematic approach is the establishment of a mechanism for scheduling meetings, tracking issues and timelines, and assuring completion of action items. The CIOMS VI Working Group recommends establishing a project management function to manage these tasks, document any decisions, and ensure compliance with internal procedures.
- All pertinent data must be readily available to the safety team from the clinical trial and safety databases as well as from other relevant sources, such as the pre-clinical toxicology department (e.g., carcinogenicity and development and reproductive toxicology), *in vitro* mutagenicity studies, and pharmacokinetic and drug-interaction studies.
- It is important to incorporate epidemiology into the development planning process, not only for defining the natural history of the disease being treated, but for anticipating important confounding factors and background rates of occurrence of concurrent illnesses. Understanding these will help to put the evolving safety profile into proper perspective.
- When planning for the development of virtually any new medicinal product, there are certain categories of potential toxicities that should always be considered. These include abnormalities in cardiac conduction, hepatotoxicity, drug-drug interactions, immunogenicity, bone marrow toxicity and reactive metabolite formation.

d. Collection and Management of Safety Data During Clinical Trials

- If an investigator becomes aware of information that is considered to be important for safety reasons it should be reported to the sponsor (immediately if judged critical), even if the protocol does not specifically state that the information must be collected. To assure the investigator's sensitivity to this point, one of the key responsibilities of the sponsor includes proper training of the investigative site regarding data collection and reporting.
- The collection of "excessive" data can have a negative impact on data quality. Therefore, case report form fields should be chosen based on the data elements that will be analyzed and can be typically presented in tabular compilations of study results. Safety data that cannot be categorized and succinctly collected in predefined data fields should be recorded in the comment section of the case report form when deemed important in the clinical judgment of the investigator.
- Safety monitoring during Phase 4 studies, which can make an important contribution in expanding the clinical trial database, may not require the same intensity as for Phase I-III trials, but the same principles and practices remain applicable.
- Although personnel other than the investigator may obtain adverse event information during regular communication, even between visits, it is ultimately the responsibility of the investigator to ensure that information is collected in accordance with the study protocol.
- If a company provides any support for an independent trial it does not sponsor (e.g., supplies, research grant, etc.), the company should still obtain at a minimum all reports of serious suspected adverse reactions from the investigational site(s). Once the relevant reports are received by the company, it should conduct its own causality assessment and decide whether they should be sent to the appropriate regulatory authority (ies), even if it is known that the investigator has already done so on his/her own.
- In early phases of drug development, it is generally necessary to collect more comprehensive safety data than in post-marketing studies. In addition, certain drug types may require longer routine follow-up as in the case of vaccines, immunotherapies and some biotechnology products.

- The collection, monitoring and assessment of data from Phase 1 studies deserve special attention for two reasons: (a) with some exception (e.g., oncology medicines, pharmacokinetic studies in subpopulations such as the organ impaired), such studies are conducted in healthy volunteers for whom there is no anticipated health benefit and (b) the results are critical to the future development of the product and must be scrutinized and interpreted with great care. For prophylactic treatments and preventative vaccines, the same considerations apply even to later stage clinical trials.
- There are no definitive methods for distinguishing most adverse drug reactions (events that are causally attributable to study therapy) from clinical adverse events that occur as background findings in the population and have only a temporal association with study therapy. The CIOMS VI Working Group thus recommends the following:
 - All adverse events, both serious and non-serious, should be collected for any clinical trial during development, regardless of presumed relationship to the study agent by the investigator or sponsor, in order to allow for subsequent assessment of causality using standardized methods for individual cases and aggregate data. This applies not only to the experimental product but to placebo, no treatment, or active comparator.
 - In studies initiated during the immediate post-approval period it is prudent to continue this practice. Once the safety profile of a marketed product is judged to be well understood and established, it may be acceptable to collect less data. While detailed information on serious adverse events should always be collected, it may be appropriate for well established products to collect only those non-serious adverse events suspected by the investigator to be related to the compound. This would be especially appropriate for large scale, simple post-marketing trials when the population, indication, and doses are consistent with those included in the approved use(s) of the drug.
- A commonly overlooked but potentially important aspect of data collection relates to the possible use of herbal and other non-traditional remedies by patients/subjects, who typically do not regard such treatments as drugs or medicines. It is therefore important to inquire specifically about them, since their concomitant use with study treatment can lead to adverse drug interactions.

Recently developed classification and coding schemes for herbal medicines are available.

- Causality judgments based on analysis of multiple cases/aggregate data, rather than on individual cases, are almost always more meaningful and typically have a greater impact on the conduct of clinical trials, including changes to informed consent documents, study design, and core safety information. However, causality assessment of individual adverse events by the investigator may play a role in the early detection of significant safety problems, and are the only source of information on rare events.
- The CIOMS VI Working Group recommends that the investigator be asked to use a simple binary decision for drug causality (related or not related) for serious adverse events. One possible approach that has been suggested is to ask simply whether there is a “reasonable possibility” or “no reasonable possibility” that the study treatment caused the event. Alternatively – Was there a reasonable possibility? Yes or No.
- It is virtually impossible to completely rule-out the role of a drug in causing an adverse event in single-case reporting. Therefore, the use of “unknown” or “cannot-be-ruled-out” adds little value in early determination of safety concerns. The use of “cannot-be-ruled-out” to imply drug relatedness would lead to excessive over-reporting and excess noise in the system.
- The Working Group advocates adoption of the recommendation by the CIOMS III/V report on core safety information and the DCSI (Development Core Safety Information), namely that on the CRF and on any serious adverse event form there be included a standard list of potential causes from which the investigator must choose the most plausible one in his/her opinion, specifically: medical history; lack of efficacy/worsening of treated condition; study treatment; other treatment, concomitant or previous; withdrawal of study treatment (a withdrawal reaction could be considered drug-related); erroneous administration of treatment; protocol-related procedure; other – specify.
- It is recommended that investigators **not** be asked routinely to indicate causality information for non-serious adverse events. However, there may be circumstances when such assessments are useful and important, such as for non-serious adverse events of special interest.

- Investigators should be encouraged to provide a diagnosis (when possible and appropriate) on the CRF rather than each individual sign and symptom. This instruction should be clearly specified in the protocol. However, when an investigator submits a **serious adverse event report** that includes a diagnosis it is important that the signs and symptoms as well as any other supporting information that led to the diagnosis also be recorded, specifically as part of the narrative description of the case.
- Prior to study initiation, it is recommended that specific criteria for identifying and defining significant, anticipated adverse events be established and communicated to investigators involved in the detection, assessment and reporting of adverse events.
- Although it is ordinarily unnecessary to create specific definitions or criteria for non-serious adverse events, it is important to do so for apparently non-serious events that might be precursors (prodromes) of more serious medical conditions; for example, muscle pain and elevated CPK together may be indicative of potential rhabdomyolysis. Such prodromes are an example of what are often referred to as adverse events of special interest, when there is evidence or suspicion of their potential importance.
- It is important to define clearly “adverse events of special interest” in the protocol and to specify close monitoring and prompt reporting to the sponsor of these types of events, even if they are considered non-serious according to the usual regulatory criteria.
- It is recommended that even when anticipated medically serious clinical events are collected as clinical efficacy outcomes/endpoints, rather than as adverse events, these data must be recorded by the investigator and periodically reported to and reviewed by the sponsor or DSMB, on a schedule specified in the protocol.
- The process used to solicit information from patients during clinical trials (i.e., how they are asked questions about their experiences) should be consistent from site to site, and if possible from program to program, and should be clearly outlined within study protocols, in the informed consent information, and during investigator training. No matter what method or approach is used, it should be used consistently throughout the trial, including at baseline (pre-treatment information).

- It is probably best to frame questions to the patients in general terms rather than to invoke the possibility that study treatment may be responsible for ill effects. For example: “How have you felt since I saw you last? Anything new that you wish to discuss?” Although it is not advisable to read a laundry list of possible ADRs when soliciting the patient’s recent experience, patients should be alerted to known signs and symptoms indicative of medically important suspected or established ADRs in order to alert the investigator as early as possible.
- Typically, the time that the informed consent is signed by the patient is designated as the start of safety data collection. This provides a clear starting point and helps to avoid any selection bias. Whenever possible, a patient should be followed through the last scheduled visit even if the patient is withdrawn from treatment, in order to allow for appropriate intention-to-treat analysis.
- As a general rule, it is recommended that safety data event-collection should continue after the last dose of the drug for at least an additional five half-lives of the experimental product. In addition, investigators should be instructed to always be diligent in looking for possible latent safety effects that may not appear until after a medication is discontinued.
- In order to assure standardized signal detection and evaluation processes, data quality and completeness are paramount. The CIOMS VI Working Group recommends the following principles for this important objective:
 - ❑ individual case safety reports from studies should be as fully documented as possible
 - ❑ there should be diligent follow-up of each case, as needed
 - ❑ the reporter’s verbatim AE terms must be retained within all relevant databases
 - ❑ if the reporter’s AE terms are not considered to be clinically accurate or consistent with standard medical terminology used for coding, attempts should be made to clarify the description of the event with the investigator. If there continues to be disagreement, the sponsor can code the AE terms according to its judgment on the case, but should identify them as distinct from the investigator’s terms. Reasons for the difference(s) should be documented.

- ❑ personnel with knowledge and understanding of both clinical medicine and the dictionary used should review all codified terms to ensure consistent and accurate codification of reported (“verbatim”) terms.
 - ❑ primary analyses of AE data should be based on the investigator’s assigned terms or diagnoses; additional analyses using the sponsor’s assignments can be conducted, but explanations for any differences between the two analyses must be given.
- Individual case safety reports (ICSRs) must be categorized and assessed by the sponsor using trained individuals with broad expertise in both clinical medicine and codification. Investigators should be encouraged to obtain specialist consultation for clinically important events that occur outside their own areas of clinical expertise, so that sponsors can obtain all information required for subsequent safety evaluation.
 - Depending on their purpose, adverse event tables can display both the reported (investigator’s verbatim) term and the sponsor’s terms. However, primary safety analyses (especially those used to develop the DCSI and CCSI) should be based on investigator-assigned terms which are consistently defined. Clinically discrepant terms should be appropriately identified to ensure transparency of the process used to derive the final data.
 - Some companies and health authorities maintain a list of event terms that are always regarded as medically serious and important even if the specific case might not satisfy the criteria for serious in a regulatory sense (require expedited reporting, for example). Such “always serious” events are used routinely to trigger special attention and evaluation. Although such lists were originally created for post-marketing purposes, especially for spontaneous reports, they might be useful for pre-approval clinical research purposes. The CIOMS VI Working Group does not endorse any particular list since it may be highly dependent on the treatment and the specific population(s) under study, and can never be complete.
 - Sponsors should avoid “excessive coding” of events reported in serious adverse event cases. Each such report should contain only the minimum number of dictionary terms needed to ensure retrieval in the relevant clinical context(s). Conversely, sponsors should take great care not to “undercode” events, namely, assign codes that might downgrade the severity or importance of an event term or terms.

e. Identification and Evaluation of Risk from Clinical Trial Data

(1) Ongoing Safety Evaluation

- The purpose of ongoing safety evaluation during drug development is to ensure that important safety signals are detected early and to gain a better understanding of the benefit-risk profile of the drug.
- Clinical trial sponsors should develop a system to assess, evaluate and act on safety information during drug development on a continuous basis in order to ensure the earliest possible identification of safety concerns and allow appropriate risk minimization, such as modification of ongoing study protocols, to ensure that clinical trial participants are not exposed to undue risk.
- Safety monitoring, evaluation and analysis should be performed in such a manner as not to compromise the integrity of the individual studies or the overall development program. Study sponsor should be fully aware at every stage of development of the potential risks of the investigational product and the morbidities characteristic of the study population.

(2) Safety Data Management

- Consistent standards and criteria for the diagnosis and recording of adverse events and other safety data must be established.
- Sponsors must ensure that activities involved in the management of clinical trial safety data (e.g., data entry, edit checks, data queries, coding of adverse events using a standard dictionary, etc.), are undertaken with care and precision in order to ensure that the safety database is accurate and complete.
- Attempts should be made to individualize safety evaluation criteria for an investigational drug product based on an assessment of acceptable risk. Since there are no standard approaches to evaluating or measuring an “acceptable level of risk”, the issue must be addressed throughout clinical development. Where possible, the risk associated with a given medicinal product can be compared with the established benefit-risk profile of an existing product used for a similar population and indication, or it can be compared to the risk of the disease itself, if no therapeutic options are available.

(3) Review of Safety Information

- Review of safety data should involve an analysis of both individual reports as well as aggregate data in order to allow for both a qualitative and quantitative understanding of the safety profile of the drug.
- The evaluation of serious adverse events requires a detailed understanding of the individual case. However, for commonly occurring events, the analysis of aggregate data is appropriate in order to explore a possible relationship with the drug.
- All serious adverse event reports must be reviewed within specified time frames, whereas aggregate data should be reviewed on a periodic basis.
- Prompt medical evaluation of all individual serious cases and adverse events of special interest (irrespective of causality), and the periodic aggregate assessment of all available clinical safety data, are critical for improving the process of signal detection in drug development.
- The evaluation of individual cases should be done in the context of the patient population, the indication for the investigational drug, the natural history of the disease, currently available therapies and other benefit-risk considerations.
- The determination of causality of adverse events should be based on a combination of clinical judgement and aggregate data analysis based on **all** reported cases. Investigator causality assessment should be taken into account and may be particularly important when evaluating rare or unusual events for which aggregate analytical methods are not applicable.
- Adverse events of special interest should ideally be identified in the developmental safety plan and protocols for handling by investigators and sponsors as if they were serious, even though they do not necessarily meet the regulatory definition of serious.
- A review of the non-serious adverse events reported in clinical trials should be conducted to look for adverse events of special interest. This could assist in the tracking of those events that may be predicted but could also capture unexpected potential signals.
- Non-serious AEs should be critically appraised at regular intervals, in particular those associated with discontinuation of study treatment. In addition, although non-serious AEs may generally not be

reviewed individually, they must be addressed carefully in study reports and integrated safety summaries.

(4) Frequency of Review of Safety Information

- The frequent review of serious and special interest adverse events, as well as overall assessment of all AEs, regardless of seriousness, causality, or expectedness, should be performed periodically: (1) *ad hoc*, for serious and special interest AEs, (2) routine, periodic, general review of all data, whose frequency will vary from trial to trial and from development program to development program and depend on many factors, and (3) reviews triggered by specific milestones established for a trial or a program (e.g., numbers of completed patients, end-of-trial, end-of-program, preparation of integrated summary of safety, and a marketing application).
- Appropriate analyses should also be conducted periodically for safety-related information other than AEs, including physical examination findings, vital signs, clinical laboratory tests, cardiac electrophysiology, and other evaluations.
- Aggregate safety data should be monitored and evaluated periodically during the course of the overall developmental program, during each study, and at the end of every study to provide an ongoing appraisal of benefit-risk balance.
- Each time a study is completed and unblinded, all safety information, not limited to clinical AEs but ideally including emerging efficacy endpoints, vital signs, and clinical investigation results, should be assessed and evaluated relative to previous knowledge; product information should be updated as needed (investigator brochure, development core safety information, informed consent, company core safety information, local datasheets).

(5) Analysis and Evaluation

- Although the relatively small number of subjects exposed to an investigational product may limit the utility of subgroup analyses, where possible data should be stratified for dose, duration, gender, age, and possibly concomitant medications and concurrent diseases.
- When pooling data, it is most appropriate to combine data from studies that are of similar design (e.g., similar in dose, duration, methods of determining adverse events, and population).

- If the duration of treatment with the investigational agent varies widely among participants in a clinical trial, data on the effect of treatment duration on adverse events may be available. Such an analysis can be important for the detection of adverse reactions that occur only with prolonged treatment compared to adverse reactions that tend to occur early in the course of treatment.
- Groups of studies that are useful in pooled safety analyses include all controlled studies or subsets of controlled studies, placebo-controlled studies, studies with any positive control, studies with a particular positive control, and studies of particular indications.

f. Statistical Approaches for Treating Clinical Safety Data

- The techniques and approaches to use of statistics for analysing safety data have not been developed as fully as for efficacy and it is not uncommon to find inappropriate or incomplete displays and analysis of adverse event data, even in refereed publications.
- Statistical approaches have application at several stages of clinical trials: protocol design, during a trial, for final analysis and writing of the trial report or publication, and when combining data across different trials. Professional statistical help is required and should be obtained at each of those stages.
- Statistical association (P-values or other measures) alone may or may not be of clinical value. In randomised trials they have great strength in testing causality but they inevitably have uncertainty. Examination of both statistical and clinical significance must involve a partnership.
- It is necessary to acknowledge when the data are insufficient to draw conclusions on safety, i.e., ‘absence of evidence is not evidence of absence.’ In such situations, the use of descriptive methods and well-designed graphics will be helpful in this process.
- The ability of a study to detect causal effects in the face of variation within and between individuals is dependent on sample size; the smaller or rarer an effect, the larger the sample size required, if any degree of certainty is to be given to the study conclusions.

- A statistical test that allows for either an increase or a decrease in the rate of an adverse effect should virtually always be specified in the protocol. Hence, it is recommended that all statistical testing on safety-related data be done on the basis of two-sided (two-tailed) hypothesis tests.
- Although most Phase II and III trials are randomised and usually double-blind, generally the same statistical principles discussed here can apply to non-randomised and non-comparative studies.
- Independent of a trial design or Phase, there are many kinds of comparisons that can and should be made within and between treatment groups using the proper statistical tools, depending of course on the kind and amount of data collected. Typical analyses involve such things as: comparisons between treatment groups of specific AEs, classes of AEs (different organ systems, e.g.), and laboratory data; discontinuations from treatment; sub-population results (age, sex, etc.); time-dependent phenomena (time to onset of AE, time to discontinuation, etc.); combining data across trials.
- It is recommended that at least one intention-to-treat (ITT) safety analysis should be conducted. As a consequence, the collection of data should continue whenever possible to obtain study endpoints even in those who are prematurely withdrawn from treatment. ITT analyses are considered to be the most conservative approach.
- Some of the more important problems associated with safety analyses that require attention are:
 - **power:** The power of a particular study will depend on the size of the groups being studied; the baseline or background rate of the adverse effect of interest, which is the rate expected in the comparison group; and the change of interest in rates between groups (for example a doubling or tripling). It also depends on the “P-value” set as being statistically significant, which is usually 0.05. If allowance is made for multiple testing (see below), then this P-value may be much smaller and so the effects will be more difficult to detect as statistically significant and therefore the statistical power will be lower. Most trials, or even combinations of trials, are not large enough to detect or analyse rare adverse events reliably.
 - **multiplicity:** multiple analyses can be and often are performed on the same data set, such as on multiple time points and multiple

variables. Multiplicity affects the statistical analysis, especially the calculation of P-values, because many different comparisons of adverse effects are possible. Clinical trials are designed to minimise Type I errors (concluding that efficacy exists when it really does not), and the testing of multiple hypotheses within a single study is discouraged. However, the numbers of potential types of adverse events are very large, so that correction for multiple testing in a conventional way will mean that it is impossible to draw any conclusions. It is for this reason that corrections for multiple testing are rarely done using a formal mechanism.

- **medical classification:** if the grouping of adverse effects into categories is too narrow, it results in numbers of event types that are too small for meaningful statistical comparison between groups, but if too wide (having larger numbers in the groups to avoid the first problem), it could hide the existence of a safety problem. Another difficulty arises in deciding whether groupings of different event terms for a patient can be formally regarded as a syndrome, for which a specific diagnosis might be possible. This requires medical judgement, and the results of the analysis will need careful interpretation rather than reliance on the result of a statistical test. The use of different coding dictionaries and different levels within those dictionaries can lead to statistical problems.
- **time dependency:** adverse effects should be examined carefully as a function of time on drug; simple calculations of incidences (number of events such as AEs or discontinuations divided by number of patients treated) can be highly misleading and mask the true risks associated with the treatments.
- Currently used approaches to analyses of safety data are sometimes over-simplified, and do not take the major characteristics of adverse reactions into account. For example, some reactions have a rapid onset after administration of a drug, and if they do not occur early, are much less likely to occur later.
- It is best to analyse laboratory data using baseline values as a comparison whenever possible. The most effective approach is usually to use the baseline value (or the mean where multiple measurements are made) as a covariate. The post-treatment value (or their mean where multiple measurements are made) is then the response that is analysed.

- Analysis of laboratory measurements used for monitoring of adverse effects is done on binary measures of clinically relevant values or changes, but should also be done comparing mean values using analysis of covariance (ANCOVA), since this is likely to have greater sensitivity for detecting real adverse effects.
- Graphical displays, such as scatter plots of baseline versus later values for each trial participant, can help show both a shift from average and also draw attention to outlying values, both in terms of absolute levels but also large changes.
- Finding a significant difference between groups does not necessarily prove causality based on a laboratory test result, but the most powerful statistical analysis should be used so that early signs of organ damage are detected. Trends in average values can be a surrogate for rare, clinically important individual changes.
- Results of trials should show confidence intervals for a relevant summary of the data rather than just quoting the P-value from a significance test. A confidence interval is a measure of the amount of statistical uncertainty around a summary value known as the point estimate. This estimate will not necessarily be the true value, which may only be known if we have infinite knowledge about the parameter. What is needed is an awareness of whether our estimate is likely to be close to the true value or not. We construct confidence intervals for summaries of data such as proportions or differences in proportions. CIs are particularly useful for dealing with adverse event data.
- It is very important that the length of time that each patient is “at risk” of having an adverse event be factored into any assessment of risk. The length of time over which a patient is followed in order to determine whether an AE occurred will not always be the same for every participant in a trial. This period may or may not be the same as the duration of treatment, which in some settings, such as single dose studies, may well be the same for all patients.
- Events that occur beyond the standard observation period can be difficult to include in a formal analysis, since unless all patients are followed for the same length of time post-treatment, it will not be known whether others also experienced the same or different events. Such post-treatment events should be documented and discussed in a trial report, but it is not usually appropriate to include them in the formal statistical analysis since bias could result.

- Calculating the sum of the total time at risk for all patients by treatment group is useful, and this should be reported, often as person-time (e.g., person-years). The incidence rate is the total number of those having the event divided by the person-years at risk, and the ratio of incidence rates between treatment and control groups is a *rate ratio*. The risk per unit time is called the hazard rate and using total person-years as the denominator assumes that this rate is constant over time. These calculations assume that the incidence rate is constant over time but this will often not be true.
- Rates per person-time for each treatment group should be reported in addition to numbers of patients with an event divided by the total number of patients in the relevant at-risk group. This is especially important when combining data from studies involving different treatment durations.
- The total person-time in the treated group across all the trials, or even the total number of patients treated, is often the denominator used in determining the rate of occurrence of adverse events. This is rarely the best way of presenting or summarising the data, and must be treated with great caution. The correct method is to use “life-table” or survival analysis, even though here it is not the time to death but an adverse event that is studied. Survival analysis gives a better, less biased estimate than the crude analysis.
- The method is similar to that used for survival curves using a Kaplan-Meier estimate of survival. Kaplan-Meier curves start at 100% (everyone is alive) and move downwards over time; adverse events are best shown as cumulative hazard plots which move upwards over time.
- Adverse events that occur with sufficient frequency for formal analysis should be analysed using “survival” type methods, and consideration should always be given to showing graphs of cumulative hazards.
- The Kaplan-Meier method does not directly provide significance tests or confidence intervals for comparisons between groups. It is possible to treat the data as comparisons of proportions, but these do not take into account differences over time and do not fully utilise the data. The simplest method of comparing the curves is the log rank test.

- A more complex method for comparing time to event data is a “proportional hazards regression” or “Cox regression”. This, like the log rank test, compares an entire survival curve without making assumptions about the form of the hazard rate at any particular time, but it does assume that the ratio of the hazard rates between two groups is constant at all times. This method can be used to adjust for other prognostic factors as well as for making a comparison between a treated and control group. It may be used for data from both randomised trials and observational cohort studies.
- When comparing rates using events as the numerator and person-time as the denominator, the basic assumption is that the number of cases follows a Poisson distribution. Analysis of these rates uses a Poisson regression. The results of these analyses can be expressed as incidence rate ratios.
- A meta-analytic review should be a routine part of the drug development process so that ADRs, and differences in ADR rates between treatment groups, can be detected as readily as possible, especially for uncommon or rare events. Crude pooling of adverse event numbers across different trials to compare treated and control groups should be avoided if possible.
- No absolute criteria can be established for whether data from different trials can be combined so as to yield a valid analysis. However, some points should be considered: Is the experimental drug the same in all trials (dose, regimens, formulation, route of administration)? Is the comparator the same (placebo, active; dose of comparator)? Is duration of treatment the same? Are the protocols similar (inclusion and exclusion criteria; ages, sex, race; duration and severity of disease; concurrent disease)?
- It may be helpful to use graphical methods in meta-analyses, which can show similarities and differences for common as well as rare effects across different trials in a clear way. They can also be used to illustrate the uncertainty in effects so that apparently dissimilar results may be seen to be simply different by chance.
- When a greater number of a serious but rare events is observed compared to that expected on the basis of background data, this will always be cause for careful scrutiny. However, multiple cases can occur close together in time or space (sometimes referred to as a cluster of cases) which may not be caused by the drug. Chance

can be an explanation, or there may be some external factor not associated with the trial treatment that is producing multiple cases. A within-trial comparison will always be more reliable for deciding on causality. The use of background data, whether from population-based data or from pooled control groups from many trials, is subject to more uncertainty than the comparison of randomised groups.

- Further research is required, through examination of large databases of completed clinical trials, to attempt to obtain rates of background occurrence of events that are serious and rare. These rates should be published so that interpretation of a single or a few such events can be accomplished more objectively than is currently possible.

g. Regulatory Reporting and Other Communication of Safety Information from Clinical Trials

It is important to point out that many of these recommendations are only proposals. Although the CIOMS VI Working Group as well as its external panel of reviewers agree that these proposals represent a meaningful way forward, none of the recommendations should be interpreted as superseding current regulations. Rather, the recommendations are intended to inform discussions for future regulations, as has been the case with prior CIOMS proposals. Until such time as these proposals may be implemented, sponsors are expected to maintain compliance with all existing regulations.

- The CIOMS VI Working Group endorses ICH Guideline E2A and thus recommends the harmonization of criteria for expedited reporting to regulatory authorities, to include suspected adverse drug reactions that are both serious and unexpected. Only under exceptional circumstances and on an *ad hoc* basis (e.g., when close scrutiny and monitoring of a specific adverse reaction is warranted) should sponsors be expected to report, on an expedited basis, suspected adverse drug reactions that are considered expected. If there is a need to report events without regard to causality, this should generally be on a periodic basis with the periodicity and format, e.g., line listing, agreed in advance with the concerned authority.

- It is recommended that regulators adopt the phrase “a reasonable possibility of a causal relationship” and consider dropping the phrase “a causal relationship cannot be ruled out” from the ICH E2A definition of suspected adverse drug reaction.
- In order to maintain global consistency of clinical trial reporting, the Working Group recommends that once a drug is marketed, the CCSI effectively become the reference safety information for the purpose of determining expectedness for regulatory reporting from Phase IV clinical trials. For clinical trials of new indications, new populations or new dosage forms for a marketed drug, every attempt should be made to align the DCSI and the CCSI, but the DCSI should be used if it is different from the CCSI.
- As with spontaneous reports, the determination of reportability for case reports from clinical trials should be determined at the event level. That is, a case would meet the criteria for expedited reporting only if there is a suspected adverse reaction that is both serious and unexpected.
- Suspected adverse drug reactions that are both serious and unexpected, and thus subject to expedited reporting, should generally be unblinded. However, there are likely to be special circumstances where an exception to this rule would be appropriate, for example, where the efficacy endpoint is also a serious adverse event (SAE). In this case, the circumstance and the process to be followed should be clearly defined in the protocol and the sponsor should seek agreement from the relevant regulatory authorities. Such exceptions should be clearly described in the protocol and Investigator Brochure.
- Unblinded placebo cases should generally not be reported to regulatory authorities on an expedited basis. On the other hand, it is recommended that unblinded comparator cases be reported to regulatory authorities and/or the company owning the comparator on an expedited basis, regardless of expectedness. Likewise, serious suspected adverse reactions for open-label comparators should be sent on an expedited basis to the appropriate regulatory authorities and/or company regardless of expectedness.
- As a general rule, 7-day reporting should be limited to reports from clinical trials and not include those from the spontaneous reporting environment. This should generally apply to reporting in countries where the drug is not yet approved as well as in countries where the

drug is approved. (Note that this may be in conflict with, and does not supersede, current regulation.)

- For circumstances other than individual case reports, where prompt notification to authorities is warranted (e.g., non-clinical safety information having implications for the potential for serious adverse reactions in human subjects; an increased frequency of a previously recognized serious adverse reaction; an incidence of a serious adverse event that is significantly higher for the experimental drug than for a comparator; a greater than expected incidence of a serious adverse event compared to the relevant background rate in the general population; a significant drug interaction observed in a pharmacokinetic study), sponsors should define their internal decision-making process in a standard operating procedure (SOP), including how the clock start date will be determined for prompt notifications.
- In addition to the usual criteria for an expedited report, adverse events that are not deemed to be drug-related but are considered to be protocol related should also be reported in an expedited fashion if they are serious.
- Although contrary to established regulations, the CIOMS VI Working Group proposes that routine expedited case reporting by sponsors to investigators and IECs/IRBs be eliminated. Instead, sponsors should provide regular updates of the evolving benefit/risk profile and highlight important new safety information. Significant new information, occasionally a single case report, that has implications for the conduct of the trial or warrants an immediate revision to the informed consent would be communicated on an expedited basis. More commonly, important new safety information would be communicated periodically, based on the assessment of accumulating, aggregate information.
- It is proposed that there be a single Development Safety Update Report (DSUR) for submission to regulators on an annual basis, with a consistent format and content which are yet to be defined. It is strongly recommended that DSURs be based on an entire development program and not per protocol. Consideration should be given to establishing a common international birthdate which would be the date of first authorization to begin clinical trials anywhere in the world. The DCSI should be attached to the annual DSUR with an

explanation of any changes since the last update, with any significant new safety information highlighted.

- For products with a well-established safety profile and for which most clinical trials are Phase IV studies in the approved indication(s), it is recommended that the PSUR replace the annual DSUR.
- Sponsors should establish a policy of incorporating Development Core Safety Information (DCSI) into every IB, either as a special section of the IB or as an attachment to the IB. The DCSI should clearly identify the events for which the company believes there is sufficient evidence to suspect a drug-relationship. These would be the events that would be considered expected (“listed”) from the standpoint of pre-approval regulatory reporting criteria.
- Sponsors should review the IB and DCSI at least annually and update them as appropriate. If there are no changes to the IB or DCSI, then the investigators and ethics committees should be so informed at a convenient opportunity.
- For unapproved products, instead of sending individual expedited clinical trial case reports to investigators and IECs/IRBs, as mentioned above, the CIOMS VI Working Group recommends periodic reports to investigators and IECs/IRBs. It is recommended that such reports include a line listing of unblinded clinical trial cases that were expedited to regulatory authorities since the last periodic report, a copy of the current DCSI along with an explanation of any changes, a statement if there are no changes, and a brief summary of the emerging safety profile. Although it is recommended that the default would be quarterly updates, there may be circumstances when a more immediate or less frequent communication would be appropriate.
- For approved products, the timeframe for periodic reports to investigators and IECs/IRBs would depend on the extent to which new indications are being developed. For a product undergoing Phase III trials, continuation of the quarterly reports would be advisable. For well-established products, less frequent updates would be appropriate and at some point, there should only be a need to update investigators and IECs/IRBs when there is significant new information to report. For Phase IV investigators and their associated IECs/IRBs, communications of changes to the CCSI should be sufficient.

- When updates are provided by the sponsor to investigators or IECs/IRBs, whether for unapproved or approved products, line listings should include only unblinded expedited reports from clinical trials. The line listings should include interval data, i.e., only cases expedited since the last update; however, the summary of the emerging safety profile should take into account all of the accumulating data. The use of MedDRA preferred terms is recommended. The line listings generally should not include spontaneous reports; instead, significant issues arising from spontaneous reports can be described in narrative form in the update.
- If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor should issue a prompt notification to all parties, namely regulatory authorities, investigators, IECs/IRBs, and if relevant DSMBs. A significant safety issue could be defined as one that has a significant impact on the course of the clinical trial or programme (including the potential for suspension of the trial programme or amendments to protocols) or warrants immediate update of informed consent.
- Sponsors should define a Safety Management Team to review all available safety information on a regular basis so that decisions can be made with cross-functional input. It is further recommended that these reviews take place quarterly pre-approval and be coordinated with the PSUR schedule (six-monthly or annually) post-approval. In addition, *ad hoc* Safety Management Team meetings may be warranted to address urgent safety issues or significant safety signals.
- Safety Management Team meetings should be used to review the overall evolving safety profile during development, to make changes to the DCSI and/or informed consent and to determine if any changes in the conduct of the trials need to be considered. The outcome of these meetings may then provide the basis for the brief summary of safety in the periodic reports to investigators/IECs/IRBs.
- DSMB's are most commonly employed for a single large clinical trial and are not usually charged with providing oversight of an entire clinical program. It would therefore be important to ensure that important new safety information is communicated to a DSMB even if the information did not originate from the DSMB-monitored study.

- Often the developer or manufacturer of a product is not the sponsor of a particular clinical trial, but rather has agreed to support an external clinical or non-clinical investigator-sponsor financially or by providing drug supplies. A standard provision of any agreement with an outside investigator-sponsor should be the prompt reporting to the Company of all serious suspected adverse drug reactions, or significant findings from, say, an animal study, as well as any suspicion of a previously unrecognized hazard to patients. Timely access to the final study report should also be included.
- The same previously recommended concept and level of threshold for changes to the CCSI (CIOMS III/V report) should be applied to the DCSI and informed consent information. Thus, communication to investigators and IECs/IRBs of an update to the DCSI may indicate the need to update the informed consent form, the final decision for which rests with the IEC/IRB.
- Informed consent should be renewed whenever there is new information that could affect the subjects' willingness to participate, including new information about risks. In most cases, when updating informed consent, it should be sufficient to do so for continuing study participants at the next scheduled visit. However, there may be circumstances where a more immediate communication would be more appropriate (e.g., when a new risk has been identified that is life-threatening or when there is a prolonged time interval between visits).

Glossary and Abbreviations

This glossary contains key terms used in this report. As the reader will appreciate, most of these terms have been in common use for some time, but in spite of initiatives under ICH, WHO and CIOMS, internationally agreed and uniformly adopted definitions do not necessarily exist for many of them. In some cases, the differences between different definitions – such as those within different countries’ regulations – are relatively insignificant, but in others they may be important. It must also be acknowledged that most countries in the world have not participated formally in the ICH process or in CIOMS activities and therefore traditionally rely on WHO for guidance on terminology, especially in the area of pharmacovigilance. However, clinical trials for new drug development are conducted in many such countries and CIOMS Working Group VI is advocating the acceptance and use of the definitions given here. Whenever possible, the definitions for pre- and post-approval conditions should be identical.

It is recognised that many country health authorities are more familiar with, and may have incorporated into regulations, previously published WHO definitions¹ which may differ from some of those given here.

Throughout this Appendix and the full report, unless indicated otherwise, the word “drug” is meant to include all medicines (drugs, vaccines, biotechnology products) for prevention, prophylaxis or treatment of a disease or medical condition, and possibly for use in diagnosis.

In most cases, the definitions are taken from ICH guidelines that have reached Step 4. Other definitions come from CIOMS, WHO, or elsewhere and a few have been created specifically for this work. Some of the terms are accompanied by a commentary to help clarify the definition in the context of safety in clinical trials, or to recommend that the existing, official definition be modified at the next opportunity (e.g., by ICH). Unless indicated otherwise, all definitions are quoted verbatim from their sources.

¹ WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products, WHO Technical Report Series, No. 850, 1995, pp. 97-137 (see <http://www.who.int/medicines/>).

Many of the terms covered in this Glossary are also defined in the European Union Clinical Trial Directive which became legally binding on all 25 Member States in May 2004. Therefore, the corresponding EU definitions are also included for reference, whether or not they differ from the definitions recommended here.²

Although this Glossary covers many terms and definitions related to drug safety and pharmacovigilance, it also addresses many abbreviations, terms and concepts associated with biostatistics and risk, particularly those used in Chapter 6. The origins of statistical terms and definitions are not provided, since they are commonly found in many reference works; the specific terminology presented here was prepared by a senior statistician member of the CIOMS VI Working Group. For more detailed discussion, see Chapter 6.

Readers may be interested in the following general reference sources: “Dictionary for Clinical Trials,” by Simon Day, Wiley Interscience, 1999; “Dictionary of Pharmacoepidemiology,” by B. Begaud, John Wiley and Sons, 2000; “Pharmacovigilance from A to Z,” by Barton L. Cobert and Pierre Biron, Blackwell Science, Malden, MA (USA), 2002; and Medilexicon, the world’s largest online database of medical and pharma-related **abbreviations** – over 70,000 (see Medilexicon.com or <http://eu.xmts.net/34683>).

A special comment is important with regard to abbreviations used in connection with adverse event or reaction reports, especially those that are described as “serious.” There are many abbreviations and acronyms in current use that unfortunately are not completely standardized across the regulatory world and have different meanings. They include the following, some of which are defined below within the Glossary:

ICSR – Individual Case Safety Report (used in ICH Guideline E2B to refer to an electronic report on a single patient)

SADR – Suspected Adverse Drug Reaction (proposed by FDA in its March 2003 proposed Rule on Safety Reporting Requirements for Human Drug and Biological Products)

SAE – Serious adverse event (commonly used in industry)

² For details on interpretation and application of key terms defined in the EU Clinical Trial Directive, see “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use”, April 2004 (<http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/>). Corresponding definitions for other regulatory bodies (e.g. in Japan and the US) are not included primarily because new definitions and interpretations were pending as of the beginning of 2005 when this report was completed.

SSAR – Suspected Serious Adverse Reaction or Serious Suspected Adverse Reaction (commonly used in the EU)

SUSAR – Suspected Unexpected Serious Adverse Reaction (included in the EU Clinical Trials Directive, effective May 2004)

Clearly, the use of the letter S for both “Serious” and “Suspected” can only lead to confusion, especially with the current profusion of different abbreviations. The CIOMS Working Group strongly encourages the harmonization of conflicting terms, abbreviations and definitions, logically through the ICH process.

* * *

Absolute Risk

The number of people in a group who experience an adverse effect divided by the number in that group who could experience that adverse effect.

Acceptable Risk

We do not provide a definition for this concept.

Commentary: Although this term is often used, especially in connection with benefit-risk considerations, it has proven impossible to define (acceptable to whom and under what circumstances, for example?). Readers are advised that they should be aware of this concept but that acceptable risk may mean many different things depending on the context and from whose perspective. If sponsors or regulators wish to invoke the concept in assessing the value or use of a product during development, they should base their judgments on the particular circumstances of the clinical program. See Chapter 5 for more discussion. Attempts have been made to define and measure acceptable risk based on the concept of “utility” (e.g., see Lane, D.A. and Hutchinson, T. The Notion of “Acceptable Risk”: The Role of Utility in Drug Management, J. Chron. Dis., 40:621-625, 1987).

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly when the therapeutic dose(s) may not be established:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

ICH Guideline E6: Good Clinical Practice

In the EU: “Adverse Reaction” – all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Commentary: As shown, the current ICH definition includes the phrase “i.e., the relationship cannot be ruled out.” The CIOMS Working Group believes that it is virtually impossible to rule out with any certainty the role of the drug on the basis of a single case. Therefore, we recommend elimination of that phrase and prefer the ICH E2A elaboration of “reasonable possibility” to mean that there are facts, evidence, or arguments to support a causal association with the drug.

Adverse Event/Adverse Experience

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

ICH Guideline E6: Good Clinical Practice

In the EU: “Adverse Event”: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse Event of Special Interest

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be needed (e.g., regulators).

This definition is proposed by the CIOMS VI Working Group.

Commentary: An adverse event of special interest is a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious (e.g., hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events should be described in protocols or protocol amendments, and instructions provided for investigators as to how and when they should be reported to the sponsor.

Analysis of Covariance (ANCOVA)

A statistical method for making comparisons between groups, while taking into account different variables measured at the start of a trial. It is a form of multiple regression.

Bayesian

A theorem in probability named after Reverend Thomas Bayes (1702-1761). It is used to refer to a philosophy of statistics that treats probability statements as having degrees of belief, in contrast to classical or Frequentist statistics that regards probability strictly as being based on frequencies of occurrence of events.

Binary Analysis

An analysis involving only two categories (e.g., baseline vs final values, in contrast to analysis of multiple values from continuous measurements, as for a progression of laboratory values). The latter can be turned into a binary analysis by setting a single cut-off point so the data are split into just two possible values (e.g., baseline vs highest post-baseline value).

Bonferroni Correction

A correction to allow for the probability of many events that are independent, named after Carlo Emilio Bonferroni (1892-1960). In statistical significance testing, it allows, for example, 10 different significance tests to be made on a data set (e.g., 10 different laboratory parameters) but still have an overall significance for one of the 10 tests at a probability of $P=0.05$, by carrying out each of the 10 tests by using a more stringent probability level of $P=0.005$ (thus, $0.05/10$).

Case Report Form

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
ICH Guideline E6: Good Clinical Practice

Censored, or Censoring of Data

The act of eliminating data from analyses. Observations on certain patients, particularly the time until an event occurs, may be missing or incomplete. That is, the person has been followed for a known length of time but the event of interest for analysis has not yet occurred. Such observations are called “censored” observations, and the process is called “censoring”.

Chi-square

This can refer to a statistical significance test or to the theoretical distribution to which a chi-square test refers (i.e., chi-square distribution). The test is usually a comparison of proportions. In its simplest form, with a 2 x 2 contingency table, it is described as a one degree of freedom test. For example, a statistical comparison of the proportions of adverse reactions in two groups of patients is made using a chi-square test. The test results in a chi-square value from which a P value is obtained. This gives the probability of finding a difference in proportions as large as or larger than the difference observed, even when there is no true difference in those proportions. The data can have more than two treatments, and also more than two categories of response. Chi-square tests of data from larger size tables have higher numbers of degrees of freedom.

Company Core Safety Information (CCSI)

All relevant safety information contained in the company core data sheet prepared by the MAH [Marketing Authorization Holder] and that the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

ICH Guideline E2C: Periodic Safety Update Report for Marketed Drugs

Commentary: The CIOMS VI Working Group believes that for drugs on the market in some places while under investigation in others, con-

sideration should be given to using the CCSI as the basis for expedited reporting on cases arising in post-marketing (Phase 4) clinical trials. See Chapter 7, section b.(3).

Confidence Interval (CI)

An interval which shows the range of uncertainty in a measured summary value, such as a relative risk (RR). It is typically expressed as a 95% CI but it can be 99% or other value. If a 95% CI is from 0.26 to 0.96, it implies that the treated group shows evidence of a reduction in the event rate, but that the data are compatible with a large reduction (RR = 0.26) and also a small reduction (RR = 0.96). Strictly speaking, a 95% CI implies that 95% of such intervals, will, in the long run, contain the true value of the summary (in this example, the RR). The boundaries are the lower (0.26) and the upper (0.96) confidence interval. If the boundary includes the null value, such as an RR of 1, it means the difference is not statistically significant (e.g., a CI of 0.5 to 1.8).

Contingency Table

A table of data arranged in categories in rows and columns. The simplest is a two-by-two (2 x 2) table with 4 cells, but it could have any number of rows and columns.

Contract Research Organization (CRO)

A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

ICH Guideline E6: Good Clinical Practice

Correlation

A measure of the relationship between two (or more) variables. A correlation coefficient, which measures the strength of a linear relationship, can range from -1 (perfect negative linear relationship) through zero (no linear relationship) to +1, a perfect positive relationship.

Covariance

The statistical measure of the way that two variables vary in relation to each other. It is used in calculations of correlation and regression coefficients.

Covariate

This is a variable that is examined as to how it relates to another variable. It usually refers to an explanatory (influential) variable, while the variable of interest is the response or outcome variable.

Cox Model

A form of multivariable regression used in survival analysis, named after Sir David Cox who suggested the method in 1972. It can examine the effect of several explanatory variables on the time to occurrence of some outcome event such as an adverse reaction. It makes some assumptions about the effect of these explanatory variables on the outcome.

Development Core Safety Information (DCSI)

An independent section of an Investigator's Brochure (IB) identical in structure to the Company Core Safety Information (CCSI) that contains a summary of all relevant safety information that is described in more detail within the main body of the IB. It is the reference safety document that determines whether an ADR is listed or unlisted.

Based on: Guidelines for Preparing Core Clinical Safety Information on Drugs. Second Edition. *Report of CIOMS Working Groups III and V, CIOMS, Geneva, 1999*

Development Pharmacovigilance and Risk Management Plan

A plan to conduct activities relating to the detection, assessment, understanding, reporting and prevention of adverse effects of medicines during clinical trials. This plan should be initiated early and modified as necessary throughout the development process for a new drug or drug-use.

This term and definition are proposed by the CIOMS VI Working Group.

Development Safety Update Report (DSUR)

A periodic summary of safety information for regulators, including any changes in the benefit-risk relationship, for a drug, biologic or vaccine under development, prepared by the sponsor of all its clinical trials.

This term and definition are proposed by the CIOMS VI Working Group.

Commentary. A DSUR should serve as a summary of the safety experience in all clinical trials for a drug in development, including trials for new uses of an already approved drug (e.g., new dosage forms, indica-

tions, populations). In practice, it can serve as the foundation for any changes in the Investigator's Brochure and/or Development Core Safety Information (DCSI). The CIOMS VI Working Group believes that the DSUR can serve as a platform for reconciling and harmonizing the currently different periodic reporting requirements for clinical trials in the US (IND Annual Report) and the EU (Annual Safety Report). For details, see Chapter 7. CIOMS Working Group VII, in progress as of this report, is dedicated to proposing details on the format, content and timing of such reports.

Effectiveness

Effectiveness is a measure of the effect a medicine (or medical technology) is purported, or is represented, to have under conditions for the use prescribed, recommended or labeled.

Benefit-Risk Balance for Marketed Drugs. Report of CIOMS Working Group IV, CIOMS, Geneva, 1998

Commentary: The standard definition usually given in medical dictionaries is similar: the ability of an intervention to produce the desired beneficial effect in actual use.

Efficacy

Efficacy is the ability of a medicine or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.

Benefit-Risk Balance for Marketed Drugs. Report of CIOMS Working Group IV, CIOMS, Geneva, 1998

Commentary: Efficacy refers to how well a particular medicine causes the desired effect under ideal or near ideal conditions, as in a clinical trial setting. A drug is "efficacious" if it demonstrates the intended therapeutic effect under standardized/experimental conditions.

Expected and Unexpected Adverse Drug Reaction

An expected ADR is one for which its nature or severity is consistent with that included in the appropriate reference safety information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Based on: Current Challenges in Pharmacovigilance: Pragmatic Approaches, Report of CIOMS Working Group V, CIOMS, Geneva, 2001, p. 109.

An unexpected ADR is defined as: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

ICH Guideline: E6 Good Clinical Practice

[Note: ICH does not define "expected" ADR.]

In the EU: "Unexpected Adverse Reaction" – an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

Commentary: The concept of "expectedness" refers to events which may or may not have been previously observed and documented. It does not refer to what might have been anticipated (expected in a different sense) from the known pharmacological properties of the medicine. Depending on the context, expected and unexpected can refer to labeled vs unlabeled (for official data sheets/package inserts for marketed products) or listed vs unlisted (for the Investigator's Brochure, Development Core Safety Information (DCSI), or Company Core Safety Information (CCSI)). These other terms are also defined within this Glossary.

Fairweather Rules

Rules used by the FDA to analyze carcinogenicity studies. See Fairweather, W.R., *et al.*, Biostatistical Methodology in Carcinogenicity Studies. *Drug Information Journal*, 32: 402-421 (1998).

False Positive

Usually used in connection with diagnostic testing, when a test result is positive in someone who does not have the disease. It is also applied to statistical test results where a significant test result occurs but the null hypothesis (no real difference) is in fact true. The probability of this happening can be set in advance by the analyst.

False Negative

Usually used in connection with diagnostic testing, when a test result is negative in someone who actually does have the disease. It is also applied to statistical test results where a non-significant test result is found, whereas the null hypothesis (that there is no difference) is in fact false. The prob-

ability of this happening depends on the magnitude of the true difference. This magnitude can be assumed and the sample size in a study adjusted in order to ensure that the probability of a false negative is low. In studies of adverse reactions it will often be high because the usual low incidence of ADRs makes finding significant differences difficult.

Fisher's Exact Test

An alternative to a chi-square test that is used when numbers in some cells are small. It gives a P value as its result.

Independent Data-Monitoring Committee (IDMC), Data and Safety Monitoring Board (DSMB), Monitoring Committee, Data Monitoring Committee

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

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Commentary: Data monitoring committees/boards are referred to by several names and they may have different roles and responsibilities depending on the particular circumstances. For convenience and consistency, the CIOMS Working Group favors the term Data and Safety Monitoring Board (DSMB). DSMBs are responsible for monitoring and reviewing both safety and efficacy data, not just "critical study endpoints." For detailed discussion on DSMBs, see Appendix 5 in this report and the references cited in Chapter 2, Section b.

Independent Ethics Committee (IEC) (Also, see Institutional Review Board)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

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In the EU: “Ethics Committee” – an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

Inference, Inferential

Statistical inference is the process of inferring conclusions about data based on the uncertainty in summary data, as opposed to descriptive statistics. This process is inferential.

Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

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In the EU: “Informed Consent” – decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

Commentary: As specified in the Declaration of Helsinki (see Appendix 4, paragraph 22), a physician should obtain a subject’s freely-given consent preferably in writing. If the consent cannot be obtained in writing, “non-written consent must be formally documented and

witnessed.” *Informed consent as applied to children and incapacitated participants requires special consideration; see the EU Clinical Trial Directive (Article 2J, 2001/20/EC), the Declaration of Helsinki (Appendix 4), and the International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS, Geneva, 2002.*

Institutional Review Board (IRB) **(See also Independent Ethics Committee – IEC)**

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

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Commentary: IEC (EC) and IRB are generally used synonymously. However, depending on country or region, the term IRB may be used instead of IEC (or EC), especially if the term is specified in regulations or may be legally binding (e.g., IRB in the U.S.). There also may be slight differences between Ethics Committees and Institutional Review Boards. For detailed discussion, see Chapter 2 of this CIOMS report.

Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

ICH Guideline E6: Good Clinical Practice

In the EU: “Investigational medicinal product” – a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Commentary: For purposes of this CIOMS report, for drugs in development the term “investigational product” refers to the experimental (un-approved) product.

Kaplan-Meier

Named after two statisticians who developed a graphical and tabular method of analysing survival-type data, which is relevant to ADR data.

Labelled or Unlabeled (Also, see Expected and Unexpected)

For a product with an approved marketing application, any reaction which is not mentioned in the official product information is unlabeled. If it is included it is termed labeled.

Current Challenges in Pharmacovigilance: Report of CIOMS Working Group V, CIOMS, Geneva, 2001.

Listed or Unlisted (Also, see Expected and Unexpected)

Any reaction which is not included in the Company Core Safety Information within a company's core data sheet for a marketed product is unlisted. If it is included it is termed listed.

Current Challenges in Pharmacovigilance: Report of CIOMS Working Group V, CIOMS, Geneva, 2001.

Commentary: The terms listed and unlisted were purposely adopted in ICH Guideline E2C (Periodic Safety Update Reports for Marketed Drugs) for use with internal company safety information documents, so as to distinguish them from the terms labeled and unlabeled, which should only be used in association with official "labeling," i.e., the SPC, Package Insert, and generally the regulator-approved data sheets for marketed products. The usage of listed/unlisted has been extended to the Development Core Safety Information (DCSI) as recommended in Guidelines for Preparing Core Clinical-Safety Information on Drugs, Second Edition, CIOMS Working Group III/V, CIOMS, Geneva, 1999.

Meta-analysis

The process of summarising data from more than one study to obtain a single answer. There are various different statistical techniques to accomplish this, each of which makes slightly different assumptions.

Multiplicity

The statistical problem caused by making multiple comparisons with a single set of data. Significance tests are affected by how many such tests are made.

Null Hypothesis

A statistical hypothesis that usually implies no difference between groups. For rates of adverse reactions this may imply a relative risk of 1.

Number Needed to Harm (NNH)

The number of individuals needed to be treated for some specified period of time in order that one person out of those treated would have one harmful event (again, during some specified time period). See NNT for calculation.

Number Needed to Treat (NNT)

The number of individuals needed to be treated for some specified period in order that one person out of those treated should have the desired benefit/outcome, such as the prevention of a medical event under treatment (MI, e.g.). NNT is the reciprocal of the difference in rates of the measured benefit, between a treated and a control group. For example, if the rate of death is 1% in the experimental group as opposed to 2% in a control group over one year of treatment, the difference is 1%. Thus, 100 people would need to be treated for 1 year to prevent 1 death ($1/100 = 1\%$).

Odds Ratio (OR)

The odds of an event (such as death) in one group compared to the odds in a reference group. Odds are used in betting but have useful mathematical properties in analysis of binary data. For example, if there are 10 individuals studied and 2 experience an event, the probability is $2/10 = 0.2$. The odds are 2:8 (2 have the event compared with 8 who do not). Therefore, the odds = 0.25. If these odds are compared with another group in whom the odds are different, say 0.125, then the odds ratio is 2 ($0.25/0.125$). With rare events the OR approximates the relative risk.

One-sided vs Two-sided Testing

One-sided testing (also called one-tailed testing) refers to an analysis that allows for/examines an effect in one direction only (e.g., an increase over a comparator). Two-sided testing accounts for changes in either direction. In most instances, as with comparisons of risk between different products, two-sided testing is preferred. For more details, see section f.(2) of Chapter 6.

Parametric

A form of statistical analysis that makes assumptions about the type of distribution of the data. E.g., a t-test assumes a normal distribution of the data, and is referred to as a parametric test.

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

The Importance of Pharmacovigilance – Safety Monitoring of Medicinal Products, World Health Organization 2002 (ISBN 92 4 1590157), and ICH Guideline E2E, Pharmacovigilance Planning (Step 4, November 2004).

Commentary: There is some uncertainty concerning the phrase “any other drug related problem.” At least in the present context, the CIOMS Working Group understands the phrase to refer to issues that could affect the safety and safe use of medicines, such as medication errors and potential product quality issues (e.g., glass particles in ampoules). The CIOMS Working Group endorses the use of the term pharmacovigilance for clinical safety activities during drug development as well as for marketed products.

PHASES OF CLINICAL STUDIES (I – IV)

Phase I (Human Pharmacology)

Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials.

Phase II (Therapeutic Exploratory)

Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients.

Phase III (Therapeutic Confirmatory)

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit.

Phase IV (Therapeutic Use)

Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug’s safety, efficacy and dose definition. Studies in

Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimising the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies, and studies designed to support use under the approved indication, e.g., mortality/morbidity studies, epidemiological studies.

For all the above definitions – ICH Guideline E8: General Considerations for Clinical Trials

Commentary: As delineated above, ICH Guideline E8 has proposed that studies be categorized according to their objectives (human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use), as distinct from the traditional concept based strictly on temporal phases of drug development. For example, human pharmacology studies (traditionally referred to as Phase I) can be and often are conducted throughout a product's lifetime (even though they are referred to as "Initial studies ..." in the definition above). In some settings, other terms are used to categorize study types; for example, Phase IIA studies are sometimes referred to as "proof of concept studies," Phase IIB can refer to studies that establish proper dosing, and Phase IIIB refers to "peri-approval" studies (Phase 4-like studies initiated prior to drug approval). Depending on the product and nature of the program, there may not be a sharp or distinct division between the various Phases of trials.

Phase IV studies may be required as a condition of regulatory approval. The CIOMS Working Group believes that the ICH definition of Phase IV studies needs modification by deleting the expression "(other than routine surveillance)," which is not accurate, and by emphasizing that such studies should be limited to uses and conditions specified within the approved data sheet (SPC, Package Insert, etc.).

Point Estimate

The best estimate of a summary of data such as a mean or a relative risk. The value of this figure on its own does not indicate how precisely it is estimated.

Poisson Distribution

A distribution of numbers, as in a normal distribution, but which applies to counts of numbers of events rather than to continuous values and is asymmetric. Negative values cannot occur.

Power

In statistical terms, a measure or indication of whether an analysis that is conducted is good at detecting differences. A powerful analysis is one that finds differences to be statistically significant. Power largely depends on how many events are observed, which therefore depends both on how many individuals are studied (the more studied, the greater the power) and on the rarity of the event (the less there are, the less powerful).

Rank

The order of a value in a set of values. Some statistical methods (non-parametric tests) use the order rather than the actual value. In survival analysis the ordering of times is important and a “log rank test” is able to compare times to an event that occurs in different groups.

Regression

A statistical technique that examines relationships between a response variable and one or more explanatory variables. This can be done for continuous measurements but also for binary measures and survival times.

Relative Risk (RR)

A multiplicative factor applied to a reference risk associated with an exposure. It is the risk of an outcome (event) measured in an exposed population (absolute risk) divided by the risk (reference risk) of the same outcome (event) in an unexposed group (the reference population).

Based on: Benefit-Risk Balance for Marketed Drugs. Report of CIOMS Working Group IV, CIOMS, Geneva, 1998 and Dictionary of Pharmacoepidemiology, by B. Begaud, John Wiley & Sons, 2000.

Commentary: The relationship between two risks, generally estimated in different populations, is often referred to as the “risk ratio” as well as relative risk. There is a need to ensure that the two populations that are compared are “comparable” (i.e., same/similar kinds of patients, age, gender, disease state, exposure time, etc.). Example: risk of ADR is 10/100,000 in drug-treated population and 5/1,000,000 in a comparable but untreated population. Relative risk = 20.

Risk

As used in the context of adverse experiences, it is the proportion of individuals who have an event out of all those who could possibly have that

event. Two groups can be compared either by taking their ratio (relative risk) or by subtracting the two risks. The latter is called an absolute risk difference.

Risk Assessment

Risk assessment is subdivided into risk estimation and risk evaluation. It is defined as the integrated analysis of the risks inherent in a product, system or plant and their significance in an appropriate context. *Risk estimation* includes the identification of outcomes, the estimation of the magnitude of the associated consequences of these outcomes and the estimation of the probabilities of these outcomes. *Risk evaluation* is the complex process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the decision. It therefore includes the study of risk perception and the trade-off between perceived risks and perceived benefits. It is defined as the appraisal of the significance of a given quantitative (or where acceptable, qualitative) measure of risk. *Risk analysis, perception and management. The Royal Society UK, 1992*

Risk Management

Risk Management is the making of decisions concerning risks and their subsequent implementation, and flows from risk estimation and risk evaluation. It is defined as the process whereby decisions are made to accept a known or assessed risk and/or the implementation of actions to reduce the consequences or probability of occurrence.

Risk analysis, perception and management. The Royal Society, UK, 1992.

Commentary: In the field of drug safety there is no accepted, universal definition of “risk management,” but in current usage, it refers to the overall process for the technical and communication activities needed to understand and prevent or minimize risk/harm, including the assessment of any programs put in place. The US FDA refers to risk management as the combination of risk assessment and risk minimization (see the Guidance for Industry. Development and Use of Risk Minimization Action Plans, FDA, March 2005 (<http://www.fda.gov/cder/guidance/6358f1l.htm>)).

Scatterplots

Graphical diagrams that show the variation of individual continuous values for two variables in a set of data. Different symbols can be used for the

points themselves to distinguish between different groups. They are often used to show before and after treatment values of the same variable (e.g., the liver enzyme value for each patient plotted as a function of time).

Sensitivity

This can have two meanings in statistical terms. The first is whether an analysis has high power (sensitive) or not. It can also mean sensitivity to the assumptions made for an analysis, i.e., a test of whether the results of the analysis change when assumptions about effects (parameters) are changed.

Serious Adverse Event or Reaction: Standard Criteria

Any untoward medical occurrence that at any dose:

- ❑ results in death,
- ❑ is life-threatening,*
- ❑ requires inpatient hospitalisation or prolongation of existing hospitalisation,
- ❑ results in persistent or significant disability/incapacity, or
- ❑ is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.* Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

* **Note:** the term “life-threatening” refers to an event or reaction in which the patient was at risk of death at the time of the event or reaction; it does not refer to an event or reaction which hypothetically might have caused death if it were more severe.

ICH Guideline E2A: Definitions and Standards for Expedited Reporting

In the EU: “Serious Adverse Event or Serious Adverse Reaction” – any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Commentary: The ICH definition of a serious AE or ADR has been adopted for postmarketing applications in ICH Guideline E2D. The EU definition given above is considered by the CIOMS Working Group as incomplete without the paragraph beginning with “Medical and scientific judgment” in the ICH definition.

Signal

A report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance. *Based on: Benefit-Risk Balance for Marketed Drugs. Report of CIOMS Working Group IV, CIOMS, Geneva, 1998 and Dictionary of Pharmacoepidemiology, by B. Begaud, John Wiley & Sons, 2000.*

Commentary: A signal can arise from non-clinical as well as clinical sources. It should be based on data and not theory, and can refer not only to a new (unexpected) and potentially important event, but also to an unexpected finding for an already known event, such as information on an ADR related to the nature (specificity), intensity, rate of occurrence or other clinically relevant finding that represents a meaningful change from that expected in the subject/patient population under investigation or treatment. A signal is not a confirmed finding, but is generally referred to as an hypothesis-generating situation that must be validated (“signal strengthening”) or disproved.

An older definition of a signal by the WHO Collaborating Centre for International Drug Monitoring (British Medical Journal, 304:465, 22 February 1992) focused on post-marketing conditions and predated the new definitions of adverse event and adverse reaction introduced under ICH: “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.”

Significance, Significant, Significantly

These terms refer to the quantitative interpretation of statistical tests. These tests produce levels of probabilities (P-values) that indicate whether the differences measured are low (significant) or high (non-significant) if there are no true differences. The conventional cut-off for “significant” is usually $P=0.05$ (5%), but reliance only on P values or “significance” can be misleading.

Adverse reactions are often rare so that power is low and statistically significant results may not be seen even in the presence of clinically important effects.

Simes

A method similar to a Bonferroni correction (see above) but with greater power.

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

ICH Guideline: E6 Good Clinical Practice

In the EU: Identical to the above definition.

Survival Analysis

A statistical analytical technique originally developed for studying time until death (survival time) following an intervention (or no intervention), such as in cancer treatment trials. However, it is applicable to studying time to some other type of event such as an adverse reaction or a non-fatal myocardial infarction. Some types of survival analyses use non-parametric tests such as the Log Rank Test, others can be “semi-parametric” such as the Cox model (see above), or parametric (exponential or Weibull (see below)).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

This term and acronym were introduced within one of the guidances to the EU Clinical Trial Directive in connection with expedited reporting: “All suspected adverse reactions related to an IMP (the tested IMP and comparators) which occur in the concerned trial that are both unexpected and serious (SUSARs) are subject to expedited reporting.” [Note: IMP = investigational medicinal product]

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2004 (<http://pharmacos.eudra.org/F2/pharmacos/docs/>).

Systematic Error

An error that is not random/haphazard, but which will occur in the same direction within one or many studies. For example, studying treatments for too short a duration will systematically underestimate long-term effects.

Type I and Type II Errors

A Type I error in statistical testing is a false positive (see above). A Type II error is a false negative (see above), usually arising by studying too few individuals.

Weibull Distribution

A distribution of data that is relevant to parametric survival analyses.

Yate's Correction

A correction applied to data in a 2 x 2 contingency table when carrying out a chi-square test. With modern computer software, however, a Fisher's exact test is generally preferred.

Appendix 2

Membership and Process of CIOMS Working Group VI

CIOMS Working Group VI on the Management of Safety Information from Clinical Trials met in a series of eight formal meetings in Europe and North America from March 2001 until October 2004. Listed below,

Name	Organization*	Part-time / full-time
Mary Couper	WHO (Geneva)	Part-time
Gerald Dal Pan	FDA	Part-time (Second-half)
Gaby Danan	Aventis	Full-time
Brian Davis	MCA/MHRA (UK)	Part-time (First-half)
Stephen J.W. Evans	MCA /London School of Hygiene and Tropical Medicine	Full time
Hylar Friedman	Pfizer	Full-time
Trevor G. Gibbs	GlaxoSmithKline	Full-time
Arnold J. Gordon	Pfizer/Consultant	Full-time
Philip Harrison	MCA/MHRA	Part-time (Second-half)
Mohammed Hassar	Institut Pasteur du Maroc	Full-time
Linda S. Hostelley	Merck & Co., Inc.	Full-time
Martin Huber	Hoffman-La Roche	Part-time
Leonie Hunt	Therapeutic Goods Administration (TGA, Australia)	Full-time
Juhana E. Idänpään-Heikkilä	CIOMS/University of Helsinki	Full-time
Sidney N. Kahn	Bristol-Myers-Squibb/Consultant	Full-time
Marianne Keisu	AstraZeneca	Full-time
Gottfried Kreuz	BfArM (Germany)	Full-time
Tatsuo Kurokawa	Pharmaceuticals and Medical Devices Agency (PMDA) (Japan)	Full-time
Edith La Mache	EMA (London)	Part-time
Hani Mickail	Novartis	Full-time
Siddika Mithani	Health Canada	Full-time
Jeff Powell	Eli Lilly	Full-time
Vicktor Raczkowski	FDA (US)	Part-time (First-half)
Patricia Saidon	ANMAT (Argentina)	Part-time
Wendy Stephenson	Wyeth	Full-time
Hugh Tilson	University of North Carolina	Part-time
Akiyoshi Uchiyama	Yamanouchi/GlaxoSmithKline	Full-time
Bozidar Vrhovac	University of Zagreb (Croatia)	Full-time
Ernst Weidmann	Bayer	Part-time

* Some members had more than one affiliation during the project. Some suggestions were contributed in writing by Barbara Sickmueller (BPI, Germany).

followed by a chronology of their work, are 29 senior scientists from drug regulatory authorities, pharmaceutical companies and academia who participated in the project.

At the first official meeting held at WHO in Geneva, Switzerland, in March 2001, the Group agreed on the outline of the project and the topics to be addressed. Some of the candidate topics had been identified during the CIOMS Working Group V exercise (Current Challenges in Pharmacovigilance: Pragmatic Approaches, Report of CIOMS Working Group V, CIOMS 2001) and additional topics were identified by senior colleagues of pharmaceutical companies and drug regulatory authorities.

CIOMS Working Groups I, II, III, IV and V had addressed pharmacovigilance issues mostly for the post-authorization phase. It was obvious, however, that there were many issues regarding management of the basic safety information on pharmaceutical products collected during developmental research prior to marketing authorization. In fact, a need was foreseen to introduce the concept of a comprehensive safety plan for implementation throughout Phase I through III trials that would evolve into a post-authorization pharmacovigilance plan. Based on its early discussions, Working Group VI decided to place its main focus on good practices surrounding the collection, assessment and reporting/communication of safety data during clinical trials prior to marketing. Special emphasis was placed on the ethical underpinnings of conducting medical research and clinical trials in human subjects.

In 2000-2003, drug regulatory authorities, pharmaceutical companies and clinical investigators were challenged by several new national, regional and international guidelines and regulations, including those dealing with ethical aspects of biomedical research. Implementation of ICH Guideline E6 on GCP was completed, the World Medical Association's Declaration of Helsinki was revised in 2000 (and subsequently clarified in 2002 and 2004), the European Commission published the Clinical Trials Directive in 2001 and its guidances in 2003, and CIOMS published the revised International Ethical Guidelines for Biomedical Research Involving Human Subjects in 2002. Moreover, the Group reviewed new developments in drug safety regulations and concepts and in risk-management put forth by the US FDA and the EU EMEA. Similarly, it was also kept up-to-date on new initiatives in Japan, Australia and South America. All these aspects are reflected or referred to in the final report of the Group.

Individual topic chapters and other sections of the CIOMS VI report were assigned for consideration and drafting to subgroups early in the

project, but many participants served on multiple subgroups. The draft texts and concepts were subsequently reviewed, discussed and debated several times within the entire Working Group which led to revisions and refinements of the texts. A survey of pharmaceutical companies on their safety practices during clinical trials was conducted in early 2003; the results of that survey helped inform the Group's deliberations.

G. Kreutz and W. Stephenson acted as chairs and L. Hostelley served as secretary of the Working Group with occasional assistance of M. Keisu and L. Hunt. After the first meeting in Geneva in March 2001, the subsequent meetings were as follows: November 2001 (Philadelphia, PA), May 2002 (Visby, Sweden), November 2002 (Montreal, Canada), May 2003 (Cologne, Germany), October 2003 (Washington, DC), May 2004 (Lucerne, Switzerland) and September-October 2004 (New York, NY). During 2003 and 2004, the appointed editorial group for the report (A. J. Gordon, M. Keisu, S. Mithani, Victor Raczowski followed by Gerald Dal Pan, and W. Stephenson) held teleconferences and meetings to coordinate and design the overall report.

Outside experts were invited to critique a late draft of the report; they included pharmacovigilance and related specialists from the pharmaceutical industry, academia, and health authorities (see Acknowledgements at the beginning of this report). Their valuable input was incorporated into the final document.

A. J. Gordon accepted the role of chief editor and compiled and edited the draft consolidated reports and prepared the final manuscript for publication by CIOMS.

Appendix 3

CIOMS VI Working Group Survey on Pharmaceutical Company Safety-Management Practices During Clinical Trials

Introduction

In order to ascertain prevailing practices in the industry for many of the areas under consideration in this publication, a survey was conducted via the Internet during February and March 2003. The topics covered in the survey included broad organization and policy issues as well as case processing and data management. The results of this survey were helpful to the CIOMS Working Group in formulating its proposals. The Working Group gratefully acknowledges the help of the companies that responded to the survey. None of the companies is identified in the results.

Results

[Note: Any answers appearing in italics were provided by the respondents and were not choices in the original questionnaire.]

Of 5 Japanese, 19 European, and 35 US companies sent the questionnaire, there were 21 responses: Japanese = 4, European = 9, U.S. = 8 (based on headquarters location of the parent company at the time the questionnaire was disseminated).

Abbott	Merck (US)
Astra Zeneca	Merck AG (Germany)
Aventis	Novartis
Berlex	Pharmacia
Boehringer Ingelheim	Pfizer
Daiichi	Procter & Gamble
Eisai	Sanofi-Synthelabo
Eli Lilly	Schering Plough
GSK	Shionogi & Co.
Hoffman LaRoche	Yamanouchi
Wyeth	

1. Is responsibility for the overall management of the safety of pre-marketed (investigational) vs. marketed compounds divided between separate areas within your company?

Yes	8
No	13

2. Recently, companies and regulators have been expanding the practice of pharmacovigilance/drug safety to incorporate the concept of “risk management,” which includes detection, assessment, management, and communication of product safety issues both during development and marketing of a drug.

- a. Has your company developed, or is it currently developing, such an all-encompassing approach to drug safety?

Yes	20
No	1

- b. If yes, do you have a distinct group that is responsible for clinical safety risk management?

Yes	7
No	10

- c. If yes to 2.b., what are the responsibilities of this group?
(7 respondents)

Day to day safety issues (review of serious event reports, lab data, etc.)	4
Strategic decisions related to compound development and approval	4
Management of safety crises	4
Development and implementation of specific risk mitigation/management programs	1

- d. If yes to 2.b., what department is primarily responsible?
(7 respondents)

Clinical development	3
Pharmacovigilance/safety	4

3. Some companies rely on standard medical texts or the various CIOMS publications, such as the compendium, “Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use” (CIOMS, Geneva, 1999), for strict definitions of medical events such as conditions/ diagnoses. Such terms are used to code the event in the database only if the reported signs and symptoms are consistent with the predefined criteria for the diagnosis (i.e., all the specified criteria must be met before a term such as “acute hepatic failure” is applied to the case). Thus, both the reported term(s) AND the term(s) assigned by the company to ensure consistent coding will be included in a case report data file and summary prepared by the company.

a. Do you always code and enter into your pharmacovigilance database only the exact term(s) used by the investigator?

Yes	15
No	5

b. Do you use standard definitions (e.g., CIOMS, other recognized-medical sources) as predetermined criteria for assigning a term for a diagnosis or condition, even if the result disagrees with the investigators term(s)?

Yes	4
No	17

c. If yes to 3.b., do you enter into your database both your choice of term(s) and the investigators?

Yes	4
No	0

4. When does your company begin collecting adverse events in a clinical trial? (21 respondents)

Informed consent is signed	14
Subject is randomized	0
Protocol specified interventions begin	0
First administration of the treatment (placebo-washout, placebo, active RX)	2
Protocol specific	4
SAE's at time of consent / AEs with first RX	1

5. How long after a subject receives the last dose of study drug do you purposely (by plan) continue to collect information on all adverse events (non-serious and serious)? (20 respondents)

Protocol specific	16
30 days	8
5 half-lives of the compound	5
14 days	2
Completion of all visits	2
At least 42 days for live attenuated vaccines	1
No company standard	1
2 days	0
7 days	0

6. Does your company require that the investigator record all signs and symptoms for an adverse event on the clinical case report form (CRF) even if a diagnosis is made by the investigator?

Yes	4
No	17

7. Are signs and symptoms that are collected along with a diagnosis on a CRF coded in your company database for the clinical trial?

Yes	13
No	8

8. Are signs and symptoms that are collected along with a diagnosis coded in your company safety (pharmacovigilance) database for serious cases?

Yes	12
No	9

9. Would your company support the use of an industry-standardized global form for collection of serious adverse event data from investigators?

Yes	16
No	5

10. If a serious adverse event case includes more than one event, at what level do you assess drug relatedness? (21 respondents)

Every event (serious or not)	11
Serious adverse event ONLY	8
Diagnosis	4
Case as a whole	1

11. If you conduct causality assessments for each serious event/case, what method(s) do you use for this assessment? (21 respondents)

"Introspection"	12
No specific method	4
Specific algorithm, home grown	2
Naranjo	1
Algorithm using earlier similar cases	1
Temporal relationship + alternative explanations	1
Suspected/non-suspected	1
Two degrees: excluded and cannot be ruled out	1

12. Does your company take the investigator's causality assessment into account in choosing AEs for analysis or inclusion in product safety information (whether the Investigators Brochure, core data sheet, or official product data sheet/SPC/Package Insert)?

Yes	20
No	1

13. a. Does your company currently collect investigator causality assessment for adverse events on the clinical case report form or serious adverse event report form?

Yes	20
No	0

For which adverse events?

All (serious and non-serious)	14
Only serious	4
Only non-serious	0

b. When asking for an investigator’s causality assessment do you allow:

Yes/No	9
Qualitative answer using a scale*	11

* 3 to 6 degrees depending on company, including unclassifiable and from not related to definitely.

c. Are the investigator’s causality assessments (no matter what scale, if any) utilized in data analysis or for regulatory reporting:

For data analysis only	0
For regulatory reporting only	2
Both analysis and reporting	19
Not used at all	0

d. Would your company support a single, global standard that requires the investigator to indicate either “Yes” or “No” as the only choices for the investigator’s opinion for a causal association between an event and a study treatment?

Yes	14
No	7

14. a. Do you add a medical comment (company’s interpretation of the case, including causality and/or appropriateness of the medical terms/diagnosis provided by the investigator) to your record of **every serious** event report?

Yes	14
No	7

b. If no, which reports contain such a comment? (5 respondents)

All unexpected related events	2
All possibly related events	0
All unexpected events (serious and non-serious)	0
<i>Alternative etiologies, missing data</i>	1
<i>Serious, Unexpected, Related</i>	1
<i>None</i>	1

15. a. Has your company adopted the Development Core Safety Information (DCSI) concept proposed by CIOMS III/V?

Yes: 7	No: 14
<ul style="list-style-type: none"> • Is it used to determine expectedness? Yes: 6 No: 1 • Has this increased the number of expedited reports? Yes: 2 No: 2 	<ul style="list-style-type: none"> • Do you have plans to adopt this approach? Yes: 7 No: 6

16. What is (are) the method(s) your organization uses to determine AE attribution (causality assessment) to study agents in aggregate analyses (study reports and integrated summaries of safety) for subsequent inclusion in marketing application submissions and ultimately in prescribing information? (21 respondents)

Comparison versus historical controls	6
Investigator assessment	14
Medical plausibility (company)	16
Comparison vs. Placebo	16
• With test of statistical significance	7
• Without test	8
Comparison vs. Active comparator	15
• With test of statistical significance	6
• Without test	6
Introspection	1
Use of significance test depends of the nature of the event	1
Relative risk and risk over time	1

17. a. Does your company currently include in its clinical development plans for most compounds predefined criteria for identifying potential safety signals and strategies for the evaluation of such potential signals?

Yes	12
No	9

b. If yes to 17.a., do they include prior assessments of population background event rates or plans to conduct such assessments if required?

Yes	9
No	3

18. a. Are all AEs (including laboratory abnormalities), serious and non-serious, across an entire development program regularly aggregated and reviewed?

YES	16
How often?	
Every 6 months	1
Yearly	6
End of each phase of development	10
At submission	8
"Depends"	6
Pre-specified points	8
<i>Every 3 months for serious AEs</i>	1
<i>Quarterly</i>	1
NO	5

- b. For these reviews, if data are included from blinded studies, are these data unblinded for the reviewer? (16 respondents)

	Yes	No	NA
Every 6 months	0	10	2
Yearly	1	10	1
End of development phase	5	6	1
Submission	7	3	2
Depends	4	3	1
Pre-specified points	3	7	0

19. a. What new safety information does your company communicate to investigators? (21 respondents)

Alert mailings (expedited reports to regulators)	19
Investigator brochure updates	20
Periodic updates	3
<i>Ad hoc</i> letters for a particular issue	1
DCSI updates	1
Serious-unexpected cases whose causality is not ruled out (unblinded first; placebo reports not sent)	1

Method	Electronic	Paper	Fax	Phone	Other
Alert mailings	5	16	7	1	3*
IB updates	0	19	0	0	3*
Periodic reports	1	3	1	0	0

* By hand delivery, site visit, or respondent uncertain how they are delivered.

b. Are these communications sent to? (21 respondents)

[Note: A company could provide more than one answer to this question, thus, the numbers add up to more than 21. For example a company may send IB updates to all phase 1-3 investigators and alert mailings only to those under an IND, EU process or other formal regulation.]

All Investigators worldwide studying the compound in Phase 1-3	17
All Investigators worldwide studying the compound in Phase 4	9
Only Investigators conducting studies under an IND, EU process, or other formal regulation	7
Only Investigators taking part in the specific development program (e.g., indication)	1
Only Investigators involved in the study protocol from which the data come	1

c. If periodic reports are sent to investigators (other than IB updates), how frequently does this occur? (10 respondents)

No periodic reports	6
Yearly	1
Monthly	1
Quarterly	0
Every 6 months	0
<i>As needed</i>	1
<i>Protocol specific</i>	1
<i>Specific issue</i>	1
<i>DCSI update</i>	1

d. If single case alert reports are sent to investigators, what format is used? (19 respondents)

CIOMS I form	14
MedWatch form	9
Letter format	10
Japanese form	2

e. If single case alert reports are sent to investigators, when is this done? (21 respondents)

Simultaneously with submission to regulators	12
Within a short time after submission to regulators 1-2 days but <15 days Twice a month (in Japan) Not defined Within 15 days Several days	9

20. What is your company policy for the frequency of updating safety information in the Investigator Brochure (IB)? (21 respondents)

Yearly	19
When significant new information is discovered	12
Every six months	1
Quarterly	1
No standard policy	0
<i>Start of a new Phase</i>	1
<i>DCSI quarterly update or IB yearly</i>	1

21. Does your company utilize the same IB for a given product for all countries?

Yes	17
No	4

22. An issue under consideration is whether study subjects already participating in a trial should always be informed of any new, important safety information that the investigator receives (e.g., a new serious ADR that is added to the investigator brochure.)

a. Does your company have a policy or practice with regard to this issue?

Yes	10
No	11

b. If yes, how is this done? (10 respondents)

Company requests that investigator change the official informed consent and discuss it with subject for re-consent	9
Rely on IRB/ERC for each study site to decide	2
Company requests investigators to inform subjects but no re-consent done	0
<i>Change informed consent if ADR significant</i>	1
<i>If significant issue added to the IB</i>	1
<i>Only when a serious ADR is added to DCSI</i>	1

23. If permitted by regulation, would your company support the concept of periodic reporting to investigators of aggregate analyses of safety information **in place of multiple expedited individual case reports?**

Yes	19
No	2

24. The roles and responsibilities of Institutional Review Boards (IRBs), Ethics Review Committees (ERCs), and Data and Safety Monitoring Boards, and their interaction with site-investigators and study sponsors are under increased attention by health authorities in many countries. Has your company experienced any issues in this area, such as new requirements for any of the following: changing/updating informed consent on the basis of new safety data during a study, providing IRBs/ERCs special/customized data from trials, or any other new requirement with regard to safety data and study progress?

Yes	15*
No	6

* Examples of specific responses:

- Varies by Country
- Requests to update ICs, inquiries regarding specific events
- Changing/updating informed consent
- IRB specific request for updating the patient's information judged not relevant by other IRBs or DSMB

- ❑ Informed consents have been updated with significant new risk information
- ❑ Some IECs making individual requests for particular data, and/or refusing data prepared by the company
- ❑ More questions on individual ADRs
- ❑ We have had several instances of IRBs asking for detailed information for specific case reports that they have received as part of the investigator mailings
- ❑ Submit customized data to IRB
- ❑ Infrequent
- ❑ Changing informed consent, changing IB, providing specific information to IEC
- ❑ Increase level of awareness of volume of SAE reports and greater likelihood or request for overall assessment from company, concerns raised by some regarding perception that may need to add information to ICF whenever new SAE report sent to investigator
- ❑ General unclarity in some areas, i.e., no standardized process across all studies

25. How does your company transmit safety information to IRBs/ERCs while a study is ongoing? (21 respondents)

Sent directly by company	9
Sent to Investigators who are expected to forward it	12
Varies from country to country	10
Varies from study to study	2
Depends on site	1

26. Has any **regulator** requested that your company send periodic summary reports of clinical trial safety data to investigators, IRBs/ERCs or to the regulator (other than IND annual reports in the U.S. and under the rules of the EU Clinical Trial Directive)?

Yes Portugal and Spain MCA for CTX EU countries applying CT directive	5
No	16

World Medical Association Declaration of Helsinki

ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

a. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

b. Basic Principles for all Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed

ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the

physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

c. Additional Principles for Medical Research Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.¹

¹ The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Data and Safety Monitoring Boards (DSMBs)

A Data and Safety Monitoring Board (DSMB), or Data Monitoring Committee (DMC) is an independent committee established by the sponsor and consists of a group of individuals with pertinent expertise that reviews on a regular basis, accumulating data from an ongoing clinical trial. The purpose of such a committee is to protect the safety of trial participants, the credibility of the study and the validity of study results.^{1,2} DSMBs are of value in the following situations:³

- ❑ large, randomized multi-center high morbidity/mortality trials;
- ❑ studies where data could justify early study termination or where the design or expected data accrual is complex;
- ❑ early studies of a high-risk intervention;
- ❑ studies carried out in emergency situations in which informed consent is waived;
- ❑ studies involving vulnerable populations; or,
- ❑ studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information may have raised safety concerns.

The function of a DSMB is primarily to advise trial sponsors or their Steering Committee about the continuation or curtailment of the trial, recommend modifications to the study protocol and/or investigative procedures, and to verify the continuing validity and scientific merit of the trial.^{4,5}

¹ Ellenberg, S.S., Fleming, T.R., DeMets, D.L. *Data Monitoring Committees in Clinical Trials – A Practical Perspective*. Edited by V. Barnett. John Wiley and Sons Ltd., Chichester, England, 2002, pp. 12-15.

² U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER) Center for Devices and Radiological Health (CDRH), November 2001, *Guidance for Clinical Trial Sponsors*, February 2004, <http://www.fda.gov/cber/gdlns/clindatmon.htm>

³ UNICEF, UNDP, World Bank, World Health Organization Special Program for Research and Training in Tropical Diseases (TDR), 31 March 2004, version 0.61, *Operational Guidelines for the Establishment and Functioning of Data & Safety Monitoring Boards* (draft), http://www.acrpnnet.org/chapters/belg/whotdr_guidelines.doc

⁴ Slutsky, A.S. Data Safety and Monitoring Boards. *The New England Journal of Medicine*, 350: 1075-7083, 2004.

⁵ Ellenberg, S.S. Monitoring Data on Data Monitoring. *Clinical Trials*, 1: 6-8, 2004.

Recommendations made by the DSMB are based on a sequential benefit-risk assessment;⁶ consideration is given to whether the potential benefits of the investigational intervention have been established or whether the risks appear greater than previously anticipated.

A DSMB should comprise a defined scientific membership with appropriate expertise for the task at hand, and where possible, should represent the cultural territories involved in the studies.^{7,8} DSMBs should have a clear scientific remit and this should be clearly outlined in appropriate documentation sometimes referred to as a Charter or Terms of Reference.^{9,10} They may also be required to follow standard operating procedures that may address issues such as conflicts of interest, confidentiality, remuneration, member replacements and co-options.¹¹ The Board should ideally have a clear written review and communication policy that relates to the review of blinded, partially-blinded and unblinded data and how this may be disclosed within sessions. Some of these may be open to the sponsor (open sessions) or held entirely in closed sessions.¹² Partially-blinded and unblinded data should not be available to the sponsor or the Steering Committee members unless this should be required to justify appropriate action to modify or terminate a study.¹³ In such cases, only the minimum information to support such recommendations should be released until the data integrity is secured.¹⁴

In certain trials, interventions can exert effects both on morbidity and/or mortality, or may reduce the risk of a major adverse health outcome, e.g., cardiovascular events, recurrence of cancer. DSMBs are used in trials

⁶ Committee for Proprietary Medicinal Products (CPMP) (2004), *Concept Paper on the Development of a Committee for Proprietary Medicinal Products (CPMP), Points to Consider on Data Monitoring Committees*, The European Agency for the Evaluation of Medicinal Products, February 2004, <http://www.emea.eu.int/pdfs/human/ewp/245902en.pdf>

⁷ Ellenberg, S.S., Fleming, T.R. and DeMets, D.L. *Data Monitoring Committees in Clinical Trials – A Practical Perspective*. Edited by V. Barnett. John Wiley and Sons Ltd., Chichester, England, 2002, pp. 45-55.

⁸ Walker, A.E. and McLeer, S.K.. Small Group Processes Relevant to Data Monitoring Committees in Controlled Clinical Trials. *Clinical Trials*, 1 (3): 282-296, 2004.

⁹ Hemmings, R. and Day, S. Regulatory Perspectives on Data Safety Monitoring Boards: Protecting the Integrity of Data. *Drug Safety*. 27 (1): 1-6, 2004.

¹⁰ Ellenberg, S.S., Fleming, T.R., DeMets, and D.L. *Data Monitoring Committees in Clinical Trials – A Practical Perspective*. Edited by V. Barnett. John Wiley and Sons Ltd., Chichester, England, 2002, 175-183.

¹¹ Sydes, M.R., *et al.* Systematic Qualitative Review of the Literature of Data Monitoring Committees for Randomized Controlled Trials. *Clinical Trials*. 1: 60-79, 2004.

¹² O'Neil, R.T. Regulatory Perspectives on Data Monitoring, *Statistics in Medicine*, 21: 2831-2842, 2002.

¹³ Fleming, T.R. , Ellenberg, S. and De Mets, D.L. Monitoring clinical trials: issues and controversies regarding confidentiality, *Statistics in Medicine*, 21: 2843-2851, 2002.

¹⁴ Ellenberg, S.S., Fleming, T.R. and DeMets, D.L. *Data Monitoring Committees in Clinical Trials – A Practical Perspective*, Edited by V. Barnett. John Wiley and Sons Ltd., Chichester, England, 2002, 74-86.

where interim monitoring of the study data is essential to protect clinical trial subjects. Wherever possible, they should always be independent of the sponsor, whether or not trials fulfill a commercial or non-commercial remit. Thus, due to the independent nature of these committees, an objective review of the interim data for any emerging concerns can be assured.

Study oversight by way of a DSMB provides further protection of study participants over and above the pharmacovigilance functions traditionally undertaken by sponsors adhering to international standards. A trial that is large, of long duration, and multi-center raises a greater potential for concerns about safety due to greater overall treatment exposures and because this may be associated with adverse effects not previously identified in shorter duration clinical development programs.

DSMBs are most frequently established for controlled trials that have mortality and major morbidity as primary or secondary outcomes, since monitoring of accumulating data may be critical in such trials. As part of its function, the DSMB should evaluate the accuracy and timeliness of the data, study recruitment and whether it is adequate to answer the questions in the appropriate timeframe. It should also ensure that the reporting of the patient records, adverse events and study endpoints is done in accordance with the protocol.

It is important that DSMBs keep abreast of changes in the external environment (for example, reporting of efficacy and safety data from other relevant large trials). In addition, DSMBs must have access to data that areas up-to-date as possible, especially when recommendations on stopping a trial might have to be made. Sponsors should ensure that the DSMB is kept updated (particularly during the open sessions at meetings) about the evolving benefit and risk profile of the drug under development.

DSMBs should formulate the rules for monitoring the trial before reviewing any study data on treatment effects. Such rules should include statistical boundaries for stopping of the trial. These stopping boundaries should generally be asymmetrical – a less conservative boundary for adverse effects than for beneficial treatment effects. It should be noted, however, that statistical stopping boundaries are not absolute rules, but are guidelines to aid the DSMB in its deliberations.^{15,16} Results from other

¹⁵ Kiri, A. , Tonascia, S. and Meinert, C.L. Treatment effects monitoring committees and early stopping in large clinical trials, *Clinical Trials*, 1: 40-47, 2004.

¹⁶ Wilhelmssen, L. Regulatory Perspectives on Data Monitoring Committees (DSMC), *Statistics in Medicine*, 21: 2823-2829, 2002.

trials as well as other circumstances can offset the exact statistical stopping rules. In certain situations, a negative trend (not just a clear benefit or clear harm), that rules out a clinically important benefit if the study should continue to its scheduled end, may be sufficient for recommendation of early termination, as such a trend may demonstrate that the probability of documenting a benefit of the treatment under study is extremely low. There may be situations in a trial where the primary and secondary endpoints do not consistently favor the same treatment during a trial. The primary endpoint may indicate a benefit and one or several of the secondary endpoints may indicate adverse effects. Caution must be exercised to ensure that trials are not terminated prematurely, and particularly in these circumstances, a balanced view on the safety issues is important.

It is recommended that DSMBs should also consider efficacy data evaluation,¹⁷ and not limit their evaluation to safety data. The lack of efficacy as it relates to safety may pose a risk to clinical trial participants. For example, in certain sub-populations within the clinical trial, evaluation of efficacy data (and the lack of efficacy thereof), would result in the modification of the patient population enrolled, and therefore reduce the risk of enrolling the types of patients where interim evaluation has not shown a favorable benefit-risk relationship. Relative to the above, certain adverse event patterns might be acceptable if the treatment were effective, and might be completely unacceptable if the observed data were suggesting lack of benefit.

Recommendations about early trial termination or continuation must be based on a global consideration of all available data from the trial including information on primary and secondary efficacy measures, adverse effects, and quality of trial conduct, along with relevant information external to the trial.

Safety monitoring in long-term outcome studies can be particularly challenging for DSMBs. For example, in such studies the primary efficacy endpoint can have serious safety implications. If an early interim review of the data suggests participants treated with the investigational product are at a higher risk for the outcome of interest than those in the control arm, the DSMB may consider recommending early termination on safety grounds. Such assessments have potential implications for falsely concluding that there is an adverse effect. Statistical considerations for early stop-

¹⁷ Ellenberg, S.S., Fleming, T.R. and DeMets, D.L. *Data Monitoring Committees in Clinical Trials – A Practical Perspective*. Edited by V. Barnett. John Wiley and Sons Ltd., Chichester, England, 2002, pp. 93-94.

ping should be considered, and it is usually appropriate to demand less rigorous proof of harm to justify early termination. In some cases, however, it may be appropriate to establish a harmful effect more definitively – for example, if a positive effect on the primary endpoint has been demonstrated or appears to be emerging, a precise assessment of a negative trend on a potentially important safety endpoint may be required for benefit-risk considerations. Another example would be when the product being tested is already in wide use and more definitive data may be required to support practice change recommendations.

The DSMB is also responsible for the interim review of serious and occasionally non-serious adverse events observed in the study, such as significant trends in laboratory parameters that may portend serious consequences. The sponsor may be requested to provide the DSMB with summaries of specific or all adverse events observed.¹⁸ This is particularly important when the event may result from the disease being treated as well as the study intervention itself. If an imbalance between groups emerges, concerns will arise that the adverse event may be due to the intervention rather than the disease itself. Since a potentially large number of adverse event categories may be observed and compared between the study arms, the interpretation of safety findings by the DSMB must be sensitive to the issues of multiplicity.

Although a DSMB should always review summary adverse event data, it will not usually review in detail every adverse event reported, or even every serious adverse event. This responsibility generally lies with the sponsor who reviews such events promptly and has the responsibility for reporting and communicating this information appropriately. The involvement of a DSMB in the review of individual adverse event reports will vary from case to case. The DSMB should always be prepared to review any individual event thought to be of major significance by the sponsor or study's medical monitor. The DSMB should learn in a timely manner of any cases for which unmasking of treatment code at the clinical site or by the treating clinician is thought to be necessary to provide an appropriate intervention.

¹⁸ The DSMB may define specific serious or non-serious events which it may consider important for it to monitor. These might involve known background morbidity (serious adverse events) or known serious expected adverse drug reactions (as identified in the Investigators Brochure or product label). Although some regulatory authorities may grant 'waivers' for the expedited reporting of serious related and unexpected possibly drug-related events, the existence of a DSMB does not automatically preclude the need for reporting in all countries (the EU for example, where 'SUSARS' are considered to be generally unpredictable). Where such serious events are not addressed in the protocol, Investigator's Brochure or DSMB charter, they are still required to be reported to the regulatory authorities within the standard 7 or 15 day time frame). A careful consideration of these documents can therefore minimise the need to unblind critical trial data when a DSMB is *involved*.

DSMBs are less likely to be established for small, short-term studies of interventions to relieve symptoms.¹⁹ The need for an outside group to regularly monitor data to consider questions of early stopping for efficacy or protocol modification is less compelling in this situation. For such products, however, an expert group to oversee all studies at all stages of development, monitor the developing safety database and make recommendations for the design of successive studies based on early results may be useful. Such a group may be particularly valuable when the patient population is at relatively high risk of serious events. The external group would independently evaluate individual events and overall event rates in ongoing studies and advise the sponsor of emerging concerns – monitoring considerations of this type are clearly more clinical than statistical.

¹⁹ Ellenberg, S.S. Monitoring Data on Data Monitoring, *Clinical Trials*. 1: 6-8, 2004.

Data Elements that Should Be Considered for Individual Adverse Event Reports

It is difficult to decide in advance exactly what specific data elements are necessary or sufficient to include on case record forms or serious AE report forms for adverse events occurring during clinical trials. ICH Guidelines E2A and E2B have indicated the most common data elements for routine data collection, as well as those that might be useful, especially for serious or special adverse events. The goal in collecting safety data is to learn as much about the drug as possible without overburdening investigators with unnecessary requests. Ultimately, the data will be converted into product information (package insert, SPC, etc.) that will be important for practitioners in advising their patients in the use of the product. A simple example of the kind of detail that can be useful is the following adverse reaction: early onset of nausea that disappears after one week on the drug.

CIOMS Working Group V developed a recommended set of data elements that should be sought during **follow-up of post-marketing**, mostly spontaneous, cases. For that purpose, the elements were prioritized according to three categories of cases: non-serious expected cases; serious-expected and non-serious unexpected cases; and serious unexpected and “special interest” cases.*

For safety monitoring during clinical trials, however, in practice it is desirable that most or all the data elements recommended be collected; if initially missing from the CRF, attempts should be made to determine them through follow-up. This is particularly important for suspected serious and special interest cases. The list given here is consistent with the entries in the sample serious AE reporting form in Appendix 8.

It is worth noting that in processing clinical trial safety data, non-serious AE cases are usually not examined in detail or analyzed until study-end

* See *Current Challenge in Pharmacovigilance: Pragmatic Approaches*, Report of CIOMS Working Group V (2001). Council for International Organizations of Medical Sciences, Geneva, 2001.

(or perhaps during an interim analysis). At that stage, all relevant CRF and other data will be incorporated into the analysis and evaluation (AE, demographic, etc.). It is thus critical that systems be in place to extract and merge data from the sponsor's various computer records and databases.

The recommended list of data elements given below is based on the CIOMS V list. Some of the elements have been modified, or new ones added to make them more pertinent for clinical trial safety monitoring (shown in *italics*). Several of the data elements listed are administrative in nature and would be collected for any clinical trial for general use (core study information), not for safety monitoring alone (e.g., the first 8 in the list). The other types of data elements might be classified as (a) core AE data (typical entries in a CRF), and (b) data for serious AEs or AE's of special interest (e.g., additional information that might be found on serious AE reporting forms used by investigators). Many if not most of the same data elements often occur on both the CRF and a special form for serious AEs. However, the data elements listed below are not sorted in any special way or presented in any order of priority or importance, since that will depend on the situation. It is a check-list for consideration but should not be considered exhaustive.

It is useful to recall that the minimum data elements (four) necessary to qualify a clinical trial (or spontaneous) case as valid and potentially reportable to drug regulators are: identifiable patient, identifiable reporter, one or more adverse reactions (or outcome, such as death), and a suspect drug.

- Country of occurrence
- An identifiable reporter
- An identifiable patient
- Patient demographics (e.g., age, sex, body weight, height)*
- Source type (physician or other medical professional)*
- Study drug or drugs (name or code, as appropriate)*
- Study code or protocol number*
- Setting (e.g., hospital, outpatient clinic, home, nursing home)
- Daily dose of suspected medicinal product and regimen
- Route of administration
- Indication(s) for which suspect medicinal product is administered*
- For concomitant medications: Daily dose and regimen
- Starting date of trial treatment (and if relevant, time of day of treatment, e.g., for an acute hypersensitivity reaction)
- Stopping date and time of treatment, or total duration of treatment

- ❑ One or more adverse events (investigator’s verbatim term(s))
- ❑ *Severity of AE (mild, moderate, or severe)*¹
- ❑ *Any action taken as a result of the AE (discontinuation from trial, dose reduction, etc.)*
- ❑ If serious, criterion or criteria for regarding the case as serious
- ❑ Full description of reaction(s) including body site and severity
- ❑ Starting date of onset of reaction (or time to onset)
- ❑ If date of onset not available, best available date or treatment duration
- ❑ Time lag from end of treatment if ADR occurred after cessation of treatment
- ❑ *Date AE disappeared/ended; if date not available, duration of AE*
- ❑ Patient outcome (at case level and, when possible, at event level); should include information on recovery and any sequelae
- ❑ Dechallenge information (if any)
- ❑ Rechallenge information (if any)
- ❑ Other etiologic information
- ❑ For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction(s)
- ❑ Any autopsy or other post-mortem findings (and/or indication if autopsy report and/or death certificate is available)
- ❑ Causal relationship assessment *by the investigator*²
- ❑ *Is the AE present/ongoing in the patient at the end of the trial (or after the patient’s last dose of drug)*
- ❑ Specific tests and/or treatment required as a result of AE, and their results
- ❑ Whether or not the hospital discharge summary is available if the patient was hospitalized
- ❑ Anything relevant to facilitate assessment of the case such as medical history (especially concurrent disease(s)), relevant drug history including allergies, drug or alcohol abuse, family history, pregnancy

¹ Some study sponsors may use a different gradation of severity, or none at all.

² Some sponsors may require this for non-serious events, or for adverse events of special interest, as well as for serious events.

Causality Criteria and Threshold Considerations for Inclusion of Safety Data in Development Core Safety Information (DCSI)

Whether assessing an individual AE case or a series of related cases for causality, there are basic criteria that can be brought to bear on the assessment. Aside from regulatory reporting criteria, causality assessments contribute to the information needed to decide when the threshold has been reached for adding new adverse reactions and other safety data to the relevant reference safety document, in this case the Investigator's Brochure (IB) or Development Core Safety Information (DCSI).

The following lists are derived from three key documents: (1) *Guidelines for Preparing Core Clinical-Safety Information on Drugs*, Second Edition, *Including New Proposals for Investigator's Brochures*, Council for International Organizations of Medical Sciences, Geneva, 1999, p. 29 (CIOMS Working Group III/V), (2) FDA's Clinical Review Template (CDER, Office of the Center Director), Section 7.0 Integrated Review of Safety (<http://www.fda.gov/cder/mapp/6010.3pdf>; effective 9 July 2004), and (3) the more detailed Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (January 2005; see <http://www.fda.gov/cder/guidance/3580fnl.pdf>). The CIOMS III/V Group proposed a ranking of importance for the criteria related to causality, based on a survey of its members; however, that work dealt mainly with post-marketing AE reports. Although it is tempting to prioritize the various items (which ones are the most important or most convincing), such an ordering may depend on the specific product development program and trial conditions.

Furthermore, not all reports of a given event will necessarily meet all, or the same, criteria. Rather, multiple reports will manifest a spectrum of applicable causality criteria of varying strengths. Clinical judgment is essential to assess the weight of evidence. An important factor in this

judgment is to ensure that fewer and less stringent criteria for including new ADR information in the IB/DCSI are applied for events that might have a significant adverse outcome for the trial participants.

Although the lines of evidence listed below are useful for either (or both) individual case or aggregate data causality assessments, the CIOMS Working Group strongly believes that whenever possible, analysis of aggregate data should be used for robust determination of product-event relationships and changes in the safety profile.

Evidence from Individual Cases

Positive rechallenge

Definitive (i.e., clearly defined, well documented specific case histories)

Time to onset plausible

Positive dechallenge

Lack of confounding risk factors

Amount and duration of exposure consistent/plausible with cause and effect

Corroboration of the accuracy of the case history

Case clear-cut, easily evaluated

Co-medication unlikely to play a role

Investigator's causality assessment

Lack of alternative explanation

Evidence from Multiple Cases

Positive outcome in targeted safety study(ies)

Consistently higher incidence vs placebo or active comparator (whether statistically significant or not)

Positive dose-response (fixed or escalating dose studies)

Higher incidence vs comparator(s) of event-specific patient discontinuations

Earlier onset and/or greater severity in active vs comparator group(s)

Consistency of pattern of presenting symptoms

Consistency of time to onset

Consistent trends across studies

Consistent pattern of clinical presentation and latency

Previous Knowledge of AE or Drug/Class, Including Metabolites

Recognized consequence of overdose

Rarity of event in comparable untreated populations or indications

Event is commonly drug-related (e.g., neutropenia, Stevens-Johnson Syndrome)

Pharmacokinetic evidence (e.g., interactions)

Known mechanism

Recognized class effect

Similar findings in animal or *in vitro* models

Closeness of drug characteristics to those of other drugs known to cause the AE

Appendix 8

Sample Serious AE Report Data Collection Form for Investigators

COMMENTARY:

The CIOMS Working Group is not proposing this form as a standard. It is a format and content presented for possible consideration by those who would like a sample template. When developing any form for AE data collection, careful consideration should be given to what are the necessary and desirable data elements for the situation. For example, the form below does not include a field for “race”, a concept that is subject to debate and possible privacy/confidentiality restrictions, but might be pertinent in certain settings. Also, please note that the choices for causal relationship to study treatment in section C.3 (“No reasonable possibility” or “Reasonable possibility”) are preferred by some to the more traditional “Not related” or “Related”; the former terms imply more judgment and less certainty, which comports with the known difficulty of establishing causality for individual cases; see chapters 4 and 7 for more discussion. Any form used should be designed to support electronic regulatory reporting of cases, especially under ICH Guideline E2b. See Appendix 6 of this report for more discussion of specific data elements.

A. STUDY INFORMATION			
1. Study Drug Name/Code:	2. Protocol No:	3. <input type="checkbox"/> Initial <input type="checkbox"/> Follow up	4. Country:
B. SUBJECT INFORMATION			
1. Initials:	3. Age:	5. Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female	7. Height: <input type="checkbox"/> cm <input type="checkbox"/> in
2. Number:	4. Date of Birth: (MM/DD/YYYY) / /	6. Weight: <input type="checkbox"/> kg <input type="checkbox"/> lb	8. Pregnancy: <input type="checkbox"/> Yes <input type="checkbox"/> No 9. () wks
12. Indication for use			10. At the onset of initial AE: <input type="checkbox"/> Outpatient <input type="checkbox"/> Inpatient 11. Inpatient Admission date: (MM/DD/YYYY) / /
14. Concom. Disease			13. Date of AE diagnosis: (MM/DD/YYYY) / /
15. Relevant Past Medical History, including allergies/risk factors			

C. EVENT INFORMATION								
1. Event(s)	2. Onset date (MM/DD/YYYY)	3. Severity	*4. Seriousness (See below)	5. Outcome (Date: MM/DD/YYYY)	6. Dechallenge If study drug stopped, did event improve or disappear?	7. Rechallenge If study drug restarted, did event reappear?	8. Relationship to Study Drug	**9. Possible Cause of SAE other than study drug (see below)
	/ /	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8	(Date: / /) <input type="checkbox"/> Recovered <input type="checkbox"/> Not recovered <input type="checkbox"/> Unknown <input type="checkbox"/> Recovered with sequelae	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/> Unknown Rechallenge Dose ()	<input type="checkbox"/> No reasonable possibility <input type="checkbox"/> Reasonable possibility	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8
	/ /	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8	(Date: / /) <input type="checkbox"/> Recovered <input type="checkbox"/> Not recovered <input type="checkbox"/> Unknown <input type="checkbox"/> Recovered with sequelae	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/> Unknown Rechallenge Dose ()	<input type="checkbox"/> No reasonable possibility <input type="checkbox"/> Reasonable possibility	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8
	/ /	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8	(Date: / /) <input type="checkbox"/> Recovered <input type="checkbox"/> Not recovered <input type="checkbox"/> Unknown <input type="checkbox"/> Recovered with sequelae	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/> Unknown Rechallenge Dose ()	<input type="checkbox"/> No reasonable possibility <input type="checkbox"/> Reasonable possibility	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8

*4: Seriousness: Check the applicable numbers in the above "Seriousness" box
1. Death 2. Life-threatening 3. Involved hospitalization 4. Prolonged hospitalization 5. Involved persistent disability 6. Congenital anomaly 7. Important medical event (e.g., seizure, blood dyscrasias) 8. Non-serious (does not meet above criteria)

**9: Possible cause of serious AE other than study drug: If "No reasonable possibility" checked in box C.8 (Relationship to Study Drug), specify other possible cause of AE.
1. Disease under study 2. Medical condition(s) 3. Lack of efficacy/worsening of treated condition 4. Study drug withdrawal-effect 5. Concomitant or previous medication 6. Erroneous administration of treatment 7. Protocol-related procedure 8. Other, specify.

C. EVENT INFORMATION (continued)

<p>9. Description of the event: Include signs, symptoms and treatment of the event, as well as any relevant laboratory data. Whenever possible, assign a diagnosis supported by signs and symptoms.</p>	
<p>10. Did the AE result in discontinuation of the subject from the study? <input type="checkbox"/> No <input type="checkbox"/> Yes</p>	
<p>11. Date of dropout: (MM/DD/YYYY / /)</p>	
<p>If outcome of event was death: 12. Date of death: (MM/DD/YYYY) / / 13. Cause of Death: ()</p>	
<p>14. Autopsy: <input type="checkbox"/> No <input type="checkbox"/> Yes 15. Autopsy date: (MM/DD/YYYY) / /</p>	
<p>16. Autopsy results: : Details Attached? <input type="checkbox"/> No <input type="checkbox"/> Yes</p>	
<p>17. Has the subject previously experienced this sign(s)/symptom(s)/disease(s) during the study? <input type="checkbox"/> No <input type="checkbox"/> Yes</p>	
<p>18. If so, provide details:</p>	
<p>19. Has the subject experienced this sign(s)/symptom(s)/disease(s) prior to this study? <input type="checkbox"/> No <input type="checkbox"/> Yes</p>	
<p>20. If so, provide details:</p>	
<p>21. Has a serious AE report been made previously for this patient? <input type="checkbox"/> No <input type="checkbox"/> Yes</p>	
<p>22. If so, for what event(s) and when? ()</p>	
<p>21. Date of AE occurrence: (MM/DD/YYYY / /)</p>	
<p>23. Hospital discharge summary attached? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not applicable</p>	

E. LABORATORY TESTS RESULTS (Please attach lab data or describe here)

(Specify if results relate to Baseline, During administration, At the time of AE, follow-up to AE, etc.)

F. REPORTING INVESTIGATOR'S COMMENT ON CAUSALITY

Explain your reasoning for attributing the event(s) to the cause chosen.

G. INFORMATION ON REPORTING INVESTIGATOR			
1. Name:	2. Title:	3. Specialization:	4. Location (study site):
5. Address:	6. Telephone:		
7. Investigator's signature:		8. Date signed: (MM/DD/YYYY) / /	

FOR COMPANY USE ONLY	
a. Date this report initially received: (MM/DD/YYYY)	c. Local No:
b. Database No:	

Appendix 9

Databases for Epidemiology and Pharmacoepidemiology

The list of database sources shown below is derived from a standard list under continuous development by the International Society for Pharmacoepidemiology and is provided with their permission. Some URLs were not available. (see http://www.pharmacoepi.org/resources/summary_databases.pdf)

For additional information on various databases, see BRIDGE (Benefit-Risk Information for Drug Evaluations) at www.dgiinc.org.

Database Resources - Databases (List contributed by IPSE members)	Country	URL
British Columbia Healthcare Utilization Population Research Unit	Canada	http://www.gov.bc.ca/healthservices
Saskatchewan Health Databases	Canada	http://www.phru.medicine.dal.ca
Odense University Pharmacoepidemiological Database (OPED)	Canada	http://www.health.gov.sk.ca/
Pharmacoepidemiological Prescription Databases of North Jutland (PDNJ)	Denmark	http://www.sdu.dk/health/research/units/clinpharm.php
Finland Medical Record Linkage System	Denmark	http://www.clin-epi.dk
PEDIANET	Finland	
Sistema Informativo Sanitario Regionale Database-FVG Region (FVG)	Italy	http://www.pedianet.it
Health Insurance Review Agency Database	Italy	
Integrated Primary Care Information Database	Korea	http://www.hira.or.kr
InterAction Database (IADB)	Netherlands	http://www.ipci.nl
PHARMO Records Linkage System	Netherlands	
Medicines Monitoring Unit (MEMO)	Netherlands	http://www.pharmo.nl
Primary Care Clinical Informatics Unit-Research (PCCIU-R)	Scotland	http://www.dundee.ac.uk/memo
Base de datos para la Investigacion Farmacoepidemiologica en Atencion Primaria (BIFAP)	Scotland	http://www.abdn.ac.uk/general_practice/research/special/pciui.shtml
Swedish Centre for Epidemiology	Spain	http://www.bifap.org/
General Practice Research Database (GPRD)	Sweden	http://www.sos.se/epc/epceng.htm#epid
GPRD through Boston Collaborative Drug Surveillance Program (BCDSP)	UK	http://www.gprd.com/
IMS Disease Analyzer (MediPlus)	UK	http://www.bcdsp.org
Prescription Event Monitoring (PEM) Database	UK	http://research.imshealth.com
The Health Improvement Network (THIN)	UK	http://www.dsru.org/main.html
	UK	http://www.epic-org

BRIDGE Database of Databases	US / Europe	http://www.dgiinc.org/html/frameset.htm
Case-Control Surveillance Study	US	http://www.bu.edu/slone/
Constella Health	US	http://www.constellagroup.com/health_sciences/
Framingham Heart Study Database	US	http://www.nhlbi.nih.gov/about/framingham/index.html
Group Health Cooperative of Puget Sound	US	http://www.centerforhealthstudies.org/
Harvard Pilgrim Health Care	US	http://www.harvardpilgrim.org
Healthcare Cost & Utilization Project (HCUP)	US	http://www.ahrq.gov/data/hcup/
Healthcore (Wellpoint/Blue Cross/Blue Shield)	US	http://www.healthcore.com
Henry Ford Health Systems (HFHS)	US	http://www.henryfordhealth.org
HMO Research Network (HMORN)	US	http://www.hmoresearchnetwork.org
IMS LifeLink	US	
IMS National Disease and Therapeutic Index	US	http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_44000160_44022368,00.html
United Health Care - Ingenix Epidemiology	US	http://www.epidemiology.com
Integrated Healthcare Information Solutions (IHCS) National Managed Care Benchmark	US	http://www.ihcis.com/information_services/databases/
Kaiser Permanente Medical Care Programs	US	http://www.dor.kaiser.org/
Kaiser Permanente Northwest	US	http://www.kpchr.org/public/studies/studies.aspx
Lovelace Center for Pharmacoeconomic and Outcomes Research (CPOR) Managed Care Database	US	http://www.lrri.org/cr/cpordata.html
MarketScan	US	http://www.medstat.com/1products/marketscan.asp
US Medicaid and Medicare Databases	US	http://www.cms.hhs.gov/data/contacts.asp
Medical Expenditure Panel Survey (MEPS)	US	http://www.ahrq.gov/data/mepsix.htm
National Ambulatory medical Care Survey	US	http://www.cdc.gov/nchs
National Death Index	US	http://www.cdc.gov/nchs/r&d/ndi/ndi.htm
National Health and Nutrition Examination	US	http://www.cdc.gov/nchs/nhanes.htm
National Health Care Survey	US	http://www.cdc.gov/nchs/nhcs.htm
National Health Interview Study	US	http://www.cdc.gov/nchs/nhis.htm
National Hospital Discharge Survey	US	http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm
National Natality Survey	US	http://www.cdc.gov/nchs
National Nursing Home Survey	US	http://www.cdc.gov/nchs/about/major/nnhsd/nnhsd.htm
NDC Health's Intelligent Health Repository	US	http://www.ndchealth.com/index.asp
Nurses Health Study	US	http://www.channing.harvard.edu/nhs/
PharMetrics	US	http://www.pharmetrics.com
Pregnancy Health Interview Study	US	http://www.bu.edu/slone/
Slone Survey	US	http://www.bu.edu/slone/
Solucient Databases	US	http://www.solucient.com/solutions/Solucient_Databases.shtml
Surveillance Epidemiology & End Results	US	http://seer.cancer.gov/
Vaccine Safety Datalink	US	http://www.cdc.gov/nip/vacsafe/
Veterans Administration Databases	US	http://www.virec.research.med.va.gov

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