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March 2005 draft of the revision of the 1991 CIOMS International Guidelines for Ethical Review of Epidemiologic Studies

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The International Society for Pharmacoepidemiology (ISPE) is very pleased to have the opportunity to offer our perspectives and suggestions, and submits for your consideration the following comments on the *March 2005 draft of the revision of the 1991 CIOMS International Guidelines for Ethical Review of Epidemiologic Studies*.

About ISPE

ISPE is an international, nonprofit, professional membership organization dedicated to promoting the health of the public by advancing pharmaco-epidemiology, the science that applies epidemiological approaches to studying the use, effectiveness, values and safety of pharmaceuticals. ISPE is firmly committed to providing an unbiased scientific forum to the views of all parties with interests in drug, biologics, and devices development, delivery, use, costs and value, adverse and beneficial effects, and therapeutic risk management. Moreover, the Society provides an international forum for the open exchange of scientific information among academia, government, and industry and for the development of policy; a provider of education; and an advocate for the fields of pharmacoepidemiology and therapeutic risk management.

The Society's more than 800 members represent 45 countries. ISPE members work in academic institutions, the pharmaceutical industry, government agencies, and non-profit and for-profit private organizations. ISPE members are researchers with background and training in epidemiology, biostatistics, medicine, public health, nursing, pharmacology, pharmacy, law, and health economics.

Our comments are based on a careful review of the March 2005 draft of the revision of the 1991 CIOMS International Guidelines for Ethical Review of Epidemiologic Studies by the Society's membership at-large as well as by ISPE Fellows, Past Presidents, members of the Board of Directors and Executive Committee and Public Policy Committee.

General Comments

ISPE is impressed by the result of the CIOMS revision process and thanks the Council for requesting comments from ISPE. ISPE specifically commends CIOMS for clearly identifying epidemiological studies using medical records as an exception to requiring informed consent. The following specific comments are mainly based on the unique perspective of ISPE. We hope that these comments are valuable to the CIOMS International Guidelines for Ethical Review of Epidemiologic Studies Core Group and that these ideas can be included in the final version of the guidelines.

Specific Comments

1. Commentary to Guideline 1: ISPE suggests defining the scope of "epidemiological research" covered by the guidelines upfront, if not already done in the preamble. Many would not automatically include interventions (first mention: commentary to Guideline 2, page 6, line 198) as part of epidemiological research. Furthermore, non-experimental research, especially based on data already collected for other purposes (recorded clinical data as found in electronic health records at primary, secondary and other points of healthcare data storage often used in pharmacoepidemiology), has a different (usually lower) propensity for harm for individuals compared with experimental research (interventions).

2. Commentary on Guideline 1, page 4, line 111: ISPE proposes adding "adequate knowledge of the pertinent scientific literature **and results are made widely available, for example by publication in a peer-review journal**.".

3. Commentary on Guideline 1, page 4, line 123: suggest changing "does not pose a risk" to "does not pose **a medical [or physical]** risk".

4. Commentary on Guideline 2, page 8, line 187 – 196: ISPE suggests adding on line 191: "… and the ethical review of research protocols. **Populations covered by automated health databases should ideally have a ethical review committee in which expertise with this type of research is present and that ensures patient data confidentiality and protection procedures as well as the public health value of the research (e.g. the Data Access Review Committee for the Canadian Saskatchewan Health database, the Scientific and Ethical Advisory Group for the UK General Practice Research Database.** In …".

5. Commentary on Guideline 2, page 7, line 219: Since epidemiology is the key discipline in epidemiological studies, ISPE suggests reversing the order of specialties for the review of such studies: "should normally include **epidemiologists, physicians**, ….".

6. Commentary on Guideline 2, page 8, line 237: ISPE suggests adding **prisoners and employees** as examples of vulnerable populations that should be considered to be heard by an ethic committee (see also 13., 20.).

7. Commentary on Guideline 2, page 8, line 253 - 256: ISPE suggests adding intellectual conflicts to be aware of: "… from a single sponsor of handful of sponsors **or as a consequence of long-time research lines or support of specific hypotheses**;".

8. Commentary on Guideline 2, page 8, line 263: ISPE considers the need for a uniform fee for all projects of comparable complexity impractical in many

settings, e.g. for academia or publicly funded projects compared with industry funded projects. ISPE suggests changing to “fee … is uniform for all projects of comparable complexity **and comparable funding sources**”.

9. Commentary on Guideline 2, page 9, line 266-298: ISPE welcomes the specific considerations regarding multi-centre research involving multiple ethical or scientific review committees, especially the mention of “review may be substantially facilitated by agreement among centres to accept the conclusions of a single review committee”

10. Commentary to Guideline 3, line 388: ISPE suggests adding "full **or expedited review, as appropriate**, by the ethical review committee…".

11. Commentary to Guideline 3, lines 376-389: the commentary allows for the sponsor country and the host country Institutional Review Boards (IRBs) to each review different aspects of a study. In the US, under a Federalwide Assurance (FWA), IRB A may "rely" on another IRB B (using a procedure outlined by the Office for Human Research Protections (OHRP)). But if the IRBs decide to do this, then IRB B is responsible for the full review of the study (all aspects), although IRB A is kept informed about the outcomes of the reviews. We understand that the intent of guideline 3 is to have IRBs review the aspects for which they are best suited/have capacity for, but we have not heard of IRBs splitting reviews as suggested in this commentary.

12. Guideline 4.1, page 12, line 399 – 400: ISPE suggests adding “Waiver of informed consent is to be regarded as generally uncommon and exceptional **(although it might be common and therefore unexceptional in certain areas of research, e.g. pharmacoepidemiology)**, and must in all cases be approved …”.

13. Commentary on Guideline 4.1, page 13, line 417-425: ISPE suggests adding **vulnerable populations, e.g. prisoners, employees, etc.** as examples where the safeguard of independent review is particularly important.

14. Commentary on Guideline 4.1, page 15, line 466-67: ISPE suggest deleting the sentence "As a general rule, both the subject and the person obtaining consent should sign a consent form." since this statement appears earlier verbatim (line 457 – 458)

15. Commentary on Guideline 4.1, page 16, line 505-513: ISPE suggests adding the use of “claims data” and registry data as examples for studies usually conducted without explicit, individual informed consent “personally identifiable private data (including data derived from biological samples, medical records, **and recorded clinical data as found in electronic health records at primary, secondary and other points of healthcare data storage**)”.

16. Commentary on Guideline 4.1, page 16, line 509: ISPE suggests changing "this proposed failure to obtain consent" to "**this request for a waiver of informed consent**".

17. Commentary on Guideline 4.1, page 16, line 586: ISPE suggests adding "In no case, however, may the permission of a community leader or other authority substitute for individual informed consent, **when informed consent is required**".

18. Commentary on Guideline 4.2, page 20, lines 657 – 667: This seems overly restrictive about research use of samples from other studies where subjects have given permission for future use. ISPE is not sure whether there is a basis for requiring new informed consent even when informed consent has been granted to use the samples "for future research", the scope of this future use is covered by the initial informed consent, any agreed upon procedures for notification of results are taken care of, and the source of the data is acknowledged in reports and publications. These points need to be covered in an agreement for future use of samples from other studies.

19. Commentary to Guideline 11, page 39, line 1280: suggest "**efficacy and effectiveness**" instead of "efficiency".

20. Commentary to Guideline 13, lines 1468-1475: the commentary lists various classes of vulnerable subjects who must be afforded special protections if they are involved in research. This is the only mention of prisoner subjects in the extended discussion of these types of subjects (discussion specific to children, persons with mental or behavioral disorders, women, and pregnant women continues under Guidelines 14-17). ISPE suggests mention of prisoners as examples in previous sections (see 6. and 13., above) and that specific guidance about the special considerations/protections needed for prisoner subjects in epidemiologic studies are added in a separate guideline.

21. Guideline 17, page 51, line 1683-1687: The second paragraph of the guideline "Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus" clearly only applies to experimental research (interventions). If applied to non-experimental research where information on pregnancy is often not available, this would practically exclude women of childbearing age to be enrolled in any non-experimental study not addressing health needs of pregnant women or fetuses. ISPE therefore suggests rephrasing to "**Interventional** research in this population …". This should also be made clear in the commentary (line 1691): "The justification for **interventional** research …".

22. Commentary to Guideline 18, page 52, line 1723-1737: ISPE suggests adding the need for identifiers at a person specific level as a prerequisite for longitudinal research, i.e. one of the most important epidemiological study designs (cohort studies). ISPE suggest rephrasing the first sentence

"**Longitudinal** research relating to individuals and groups **usually relies on** the collection and storage of information….".

23. Commentary to Guideline 18, page 52, line 1745 – 1752: ISPE strongly suggests adding the following to the definition of anonymous (line 1746): "… except by a code or other means known only to that person **or a third party independent from the investigator authorized by the appropriate ethical review committee**." If CIOMS does not agree with this added statement defining *anonymous*, then this method to conduct epidemiological research in agreement with current good practice needs to be added as a 4th category (e.g. *pseudo-anonymous*) here, since it is not covered by any of the definitions presented.

24. Appendix 1., 12., page 66, line 2179-2180: In non-experimental research, it might be adequate in certain situations to study a group of individuals without formal power considerations. ISPE therefore suggests adding "The number of research subjects needed to achieve the study objective, and how this was statistically determined, **if applicable**".

This Statement, having been ratified by ISPE's Board of Directors [once a final statement has been ratified], represents the consensus views of this society.