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Comments on 2006 CIOMS draft "Special Ethical Considerations for Epidemiologic Research" as proposed supplement to the updated 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects

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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 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects.

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 1,000 members represent 30 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 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects 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 thanks the Council for requesting comments from ISPE on the 2006 draft Special Ethical Considerations for Epidemiologic Research. ISPE generally welcomes the proposal to abandon the separate 1991 CIOMS International Guidelines for Ethical Review of Epidemiological Studies (and the 2005 draft for revision of these guidelines) to be replaced by this supplement to the Biomedical Research Guidelines. This will help to convey that non-experimental biomedical studies are at par with experimental studies. Because the 2002 guidelines are so clearly written with experimental studies in mind, however, several points of the guidelines need to be termed as "if appropriate" in the next revision of the parent guidelines even if clarified by the Special Ethical Considerations for Epidemiological Research supplement.

All studies, including interventional ones, rely on observation of individuals. What separates analytic from interventional studies is the intervention or the experiment, not the observation per se. The main ethical issue directly related to participants that arises in experimental studies (whether epidemiological or not) is the safety of the participant against the potential harm by the intervention selected. There are innumerable examples of participants in experimental studies being grievously harmed or killed by the intervention. In contrast, the main ethical issues directly related to participants that arise in the context of non-experimental studies pertain to participant privacy, and such losses of privacy, especially those that cause genuine harm to the participant, appear to be relatively rare.

Following this rationale, CIOMS might consider making this distinction more explicit by avoiding the term “Epidemiologic” and replacing it with “Non-experimental” in the title and restricting the special guidelines to this kind of studies.

Specific Comments

1. Introduction

   a) line 25: ISPE suggests adding epidemiological investigations of drugs, vaccines, diagnostics, and devices as an important example to improve public health:

   *It can also be reasonably maintained that there is an ethical imperative to make greater use of the tools of epidemiology to improve public health, and that, conversely, failing to carry out epidemiological investigations of the many agents**, therapeutics,** and circumstances to which people are currently exposed would be [wrong] unethical.*

   b) line 28: ISPE suggests adding scientific standards:

   *At the same time, it is essential that this new knowledge, and the changes for the good that it prompts, be derived from studies conducted according to recognized **scientific and** ethical standards.*

   c) line 58 – 60: ISPE strongly disagrees with and therefore suggests deletion of the statement that “***~~Because of their merely observational nature, epidemiological studies in the past were widely regarded as not raising any significant ethical issues and were commonly carried out without approval of an ethical review committee~~***” Members of ISPE have been involved in non-experimental research of effects and side-effects of therapeutics using ad hoc studies and administrative database studies in several continents for decades. Ethical review of study protocols has always been a central part of this experience and is a central part of the societies guidelines for Good Pharmacoepidemiologic Practice.

2. Epidemiological research: types of studies.

   a) line 94 – 96: ISPE acknowledges the difficulties in defining the various aspects of epidemiologic studies. The distinction between 4 main types (line 56 and 96) seems very unusual and not optimal. If a distinction needs to be included at all, ISPE proposes to separate the following fields of epidemiology: descriptive, analytic, and interventional. All studies, including interventional ones, rely on observation of individuals. What separates analytic from interventional studies is the intervention or the experiment, not the observation per se. ISPE suggests using the terms experimental and non-experimental instead of interventional and observational to make this distinction and its far-reaching ethical consequences more explicit.

   b) line 132 – 134: The major important disadvantages of case-control studies are neither unique to this type of study nor do they apply to all case-control studies. ISPE suggests deleting this sentence because the guidelines should not be intended to be a tutorial on relative values of different study designs. The same deletion should apply to the description of limitations related to cross-sectional studies.

3. Commentary on guideline 1 (line 258 – 262): the whole paragraph is a commentary on guideline 2. Also, it is unclear why emergency research should be ***typically*** designed prior to the emergency.

4. Commentary on guideline 2 (lines 269 – 280): ISPE suggests rephrasing the paragraph to be more specific about the term “anonymous data”: *Some observational studies, such as those utilizing publicly available or anonymous data, may not be subject to prior review and approval by an ethical review committee under the regulations of local jurisdiction.* ***Such databases are often publicly available through a scientific research contract or available for a fee-based contract and the data accessible to researchers are de-identified and anonymous. These data and the studies conducted using these data may not always require ethical review and approval (e.g. insurance databases which allow data to be purchased could be analyzed without ethical review, and often are within industry, government, etc – populations covered by automated health databases should ideally have a ethical review committee [see also suggested commentary on guideline 3]). However, if a linkage to individual patient identity information in such a database is needed for a special research purpose (eg, review medical records, contact patients for scientific data collection) then the study protocol must be reviewed and approved by an ethical committee before the study commences.***

5. Commentary on guideline 2 (lines 282 – 287): this paragraph is not specific to non-experimental research and furthermore redundant because it is already a commentary of the parent document. ISPE suggests deleting the whole paragraph.

6. Commentary on guideline 3: ISPE suggests specifically addressing the issue of automated health databases:

   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 such a setting, ethical review by this committee will be sufficient without the need for additional review in the country of the sponsor (if applicable).

   Lines 307 – 311: ISPE suggests adding therapeutics here:

   In industry-sponsored research on possible occupational hazards ***or therapeutics****, the protection of classified information on products and production processes, as well as material or intellectual property interests, should not prevail over the primary interests of identifying potential health effects and of communicating the research results to all involved parties and to the scientific community.*

7. Commentary on guideline 4: ISPE strongly suggests pointing out that in certain fields of research, like pharmacoepidemiology, waiver of informed consent is the rule rather than the exception. ISPE suggests adding the following sentence at line 323:

   It should be pointed out that in such settings and the research fields that rely on such data, e.g., pharamcoepidemiology, waivers of consent are the rule rather than being uncommon or exceptional.

8. Commentary on guideline 5: It is unclear why investigators should justify why particular items that clearly have no meaning for non-experimental research are not relevant. ISPE strongly suggests adding that items 7, 12, 13, 16, 21, 22, 23, 24, and 25 do not generally apply to non-experimental research and thus would not need to be included in any informational materials as default (without investigator's justification).

9. Commentary on guideline 6: ISPE suggests adding:

   The need for renewal of informed consent is clearly less pronounced in non-experimental compared with experimental studies.

10. Commentary on guideline 7: ISPE suggest adding:

Because participants in non-experimental studies often do not directly benefit from their participation, the issue of compensation might be more relevant or slightly different compared with experimental research.

11. Commentary on guideline 8: ISPE suggests adding:

    In epidemiologic studies, it is important to publicize any vital public health information in a timely, comprehensive, understandable, and responsible manner. On the other hand, it is important that immature data not be released, as they may produce more panic and harm than help to the public. Attention should be paid to prevent the distortion of results, especially in communicating to the media.

12. Commentary on guideline 11: ISPE suggests adding:

    Although randomization is the preferred method for assigning subjects to the various arms of a clinical trial, non-experimental methods, such as cohort and case-control studies to evaluate therapeutics, may often be justified scientifically and ethically.

13. Commentary on guideline 17: ISPE strongly suggests pointing out that the second part of guideline 17 is irrelevant for non-experimental studies and verbatim application of this part would make non-experimental studies with women of childbearing age very restrictive:

    The second part 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" does not apply to non-experimental research.

14. Commentary on guideline 18: ISPE suggests adding the word "may" (line 602 – 603):

    *Health authorities **may** have the right to inspect study records, and a sponsor's compliance audit staff may require and obtain access to confidential data.*

15. Commentary on guideline 19: ISPE suggests adding that:

    In studies without intervention and with minimal potential harm to participants, there might often be no need for insurance of participants.

16. Commentary on guideline 20: ISPE suggests adding pharmacoepidemiology to the list (line 666 – 667):

    *This further extends to capacity in very specialized domains of epidemiological research studies such as **pharmacoepidemiology,** genetic, occupational, or social epidemiology.*

17. Commentary on guideline 21: ISPE strongly disagrees with the notion that there should be a general need to take action in a non-experimental study when conditions are detected that are not related to the study but that need treatment (lines 672 – 673 and 679 – 682). Such actions do not only contradict the scientific principle of non-experimental studies but might also interfere with local laws about the provision of medical services. It is obvious that any action taken in obese participants would clearly interfere with a valid estimation of the complex association between diet, body weight, and cancer in a non-experimental cohort study on diet and cancer. The corresponding considerations for repositories (line 901 – 910) are more specific and relevant to epidemiologic research. ISPE suggests the following changes:

    a) line 672 – 673: *This guideline and associated Commentary are generally applicable to* ***experimental*** *epidemiological research* ***only***.

    b) line 679 – 682: ~~***In addition, investigators should specify what action they will take when medical conditions are detected within a study population that are not related to the study but that need treatment, for instance, obesity or hypertension when recruiting subjects in an observational cohort study of diet and cancer.***~~

    Although there might be rare instances in which assessments performed within a non-experimental epidemiologic study might need to be communicated to the individual participants, e.g., very high blood glucose or potassium values detected in a blood sample; such communication should be rare and exceptional to avoid any interference with standard behaviour or treatment and needs to be specified in the protocol.

18. Commentary on guideline 22: ISPE suggests rewording so that independently applies to analyze, prepare, and publish (line 716 – 719):

    As the persons directly responsible for their work, investigators should not enter into agreements that interfere unduly with their access to the data or their ability to ***independently*** *analyze the data* ~~***independently***~~*, prepare manuscripts, or publish them.*

19. Commentary on guideline 24 (lines 889 – 892 and 897 – 900): ISPE suggests rephrasing to allow for analyses within broad categories of research without additional informed consent and ethical review as often encountered in cohort studies:

    a) line 889 – 892: ISPE acknowledges that this is a difficult area. ISPE does, however, challenge the assertion that the third conceivable solution (open ended donation of the sample to be used for biomedical research) "*is highly debatable and [likely to be] unacceptable under the ethical standards applied in several countries*". In light of rapidly evolving technologies, including whole

genome studies, it is impossible in cohort studies usually collecting data on outcomes over decades to foresee scientific approaches to be used e.g., 20 years after the genetic materials have been collected. Any restriction of future methods reduces the possible scientific benefit and thus adversely affects the benefit to risk ratio of a study. ISPE suggest replacing this sentence with:

~~This solution is highly debatable and [likely to be] unacceptable under the ethical standards applied in several countries.~~ Investigators should discuss the wording of the consent form with the ethical review committee taking advantages and disadvantages of broad categories of consent into account.

b) line 897 – 900: The sentence "In no case can a clearance given by an ethical review committee to enroll people in an epidemiological study and to establish a repository also be regarded as a clearance to carry out an actual study using the samples in the repository; a new clearance is required after scientific and ethical review of every specific study protocol" suggests that multiple ethical reviews are always required - one for enrolling samples into the repository and another for each specific study submitted for use of the samples in the repository. ISPE strongly suggests adding: ***"Protocols describing broad categories of research, if approved by an ethical review committee, can preclude the necessity for investigators to return to the ethical review committee for clearance to conduct each new individual study that falls within the parameters of the original approved protocol. Ethical approval for research use of the samples may occur at the same time that ethical approval for collecting samples for the repository is obtained. The custodian of the samples in the repository is responsible for ensuring that the samples are used only for the purposes - defined either broadly or narrowly - that were approved by the ethical review committee. Additional ethical review and approval is needed if the collected samples are used for a new research project that is not included in the originally approved protocol."***

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.