



ADELFF*



AEEMA*



ADEREST*



EPITER*

RECOMMENDATIONS FOR PROFESSIONAL STANDARDS AND GOOD EPIDEMIOLOGICAL PRACTICES

(VERSION FRANCE – 2007)

This version has been examined by the National Data Protection Authority, the National Council of Physicians, the National Committee for Ethics in Life Sciences and Health and the Committee on Data Treatment for Health Research.

These Recommendations were developed by a working group coordinated by Marcel Goldberg and composed of: Anne Chevalier, Annette Leclerc, Sophie Lesieur, Philippe Ricordeau, Rachid Salmi and Annie J Sasco.

The most useful science is that whose fruit is most communicable.

Leonardo da Vinci

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1 THE REVISION PROCEDURE

1.1 STAGES OF THE PROCEDURE

In December 1998, ADELFF (Association of French-speaking Epidemiologists), ADEREST (Association for the Development of Epidemiological Studies and Research on Workplace Health), AEEMA (Association for the Study of the Epidemiology of Animal Diseases), and EPITER (Association for the Development of Field Epidemiology), adopted *Recommendations for Professional Standards and Good Practices in Epidemiology*, for five years — a period that expired in December 2003.

During this period, the European Federation of the *International Epidemiological Association* (IEA) submitted a text entitled "*Good Epidemiological Practice*" to various European epidemiology societies for discussion.

The Board of Directors of ADELFF, which had taken the initiative in launching the first version, therefore commissioned a working group to propose a revision of the *Recommendations for Professional Standards and Good Practices in Epidemiology*, taking into account developments since 1998 as well as the work of the IEA. This group was established in 2003 and included:

- Anne Chevalier
- Annette Leclerc
- Sophie Lesieur
- Marcel Goldberg (coordinator)
- Philippe Ricordeau
- Rachid Salmi
- Annie J Sasco

The procedure to revise these *Recommendations* took place between 2003 and the beginning of 2006. Its several stages were similar to those that led to the adoption of the 1998 version by all French epidemiology associations (ADELFF, ADEREST, AEEMA, and EPITER).

1 - Development of a new version by the ADELFF *ad hoc* working group;

2 - Distribution to all ADELFF members and transmission to the other French epidemiology associations;

3 - Launching a debate on the version proposed by the working group, *via* ADELFF's web site; consultation with the CCNE (National Ethics Advisory Committee for the Life Sciences and Health), CNOM (National Council of Physicians), CNIL (National Data Protection Authority), and CCTIRS (National Advisory Committee on Data Treatment in Health Research). The other associations examined the text at the same time.

4 - Preparation of a revised version that took the comments received into account, including those of the other associations;

5 - Formal adoption of the new version by the ADELFF Board of Directors;

6 - Formal adoption of the new version by the other associations;

7 - Request to the CNIL for an opinion on the conformity of these Recommendations to the provisions of Act 2004-801, dated 6 August 2004, concerning the protection of individuals in relation to treatment of their personal data, modifying Act 78-47 dated 6 January 1978

related to computers, files, and liberties, article 11-3 of which stipulates that the CNIL "*at the request of professional organizations [...] shall give its opinion on the conformity to the provisions of the present law of proposed professional standards [...] tending to protect people in relation to the treatment of their personal data [...]. It assesses the guarantees provided by those professional standards that it previously recognized as consistent with the provisions of the present law, in regard to their respect for fundamental human rights [...]*".

In a letter dated 14 March 2007, the CNIL President authorized the examination of this text in relation to the provisions of the Act of 6 January 1978, as modified; because no regulations have yet been issued, however, the formal examination of conformity will take place after the publication of the relevant texts.

8 - Public distribution under the seal of all the epidemiological associations. A version in English will make possible its international distribution.

1.2 ORGANIZATION OF THE REVISED VERSION

The objective of this document is therefore to update the Recommendations, taking into account the changes in practices and laws, and at the same time, to integrate the principal new items proposed by the European Federation of the IEA.

The present version is divided into two principal parts, preceded by *Disclaimers* and a *Glossary*:

- 1 - Basic principles, core values, professional standards and good epidemiological practices.
- 2 - Good epidemiological practices: Detailed recommendations.

The first part provides a rapid introduction to the fundamental principles and core values that underlie the practice of epidemiology, in all its forms. The second proposes specific recommendations to investigators who are preparing, conducting, and disseminating the results of epidemiological studies, as well as to those who sponsor or fund such studies.

1.3 NATIONAL BACKGROUND

To help harmonize the professional standards and practices of epidemiology in Europe, both parts of the document seek to be as "universal" as possible. This text, while more detailed in various aspects, seeks to be consistent with that of the European Federation of the IEA, to which it will be transmitted.

For this reason, all explicit references to legislation, agencies or organizations involved in personal data protection or national ethical standards have been removed from the main text of the Recommendations. They were nonetheless prepared by a group of French epidemiologists and examined by the French authorities; their correspondence to French statutes and regulations justifies the subtitle "*Version France*".

The Recommendations mention types of bodies, agencies and organizations. In France they are the following:

Data Protection Authority: Commission nationale de l'informatique et des libertés (CNIL), established by Act 78-17, dated 6 January 1978, related to computers, files, and liberties, as modified; Comité consultatif sur le traitement de l'information en matière de recherches dans le domaine de la santé (Advisory Committee on Data Treatment in Health Research), as established by the dispositions of Act 78-17 dated 6 January 1978, as modified, and of decree 95-682 dated 9 May 1995, issued to implement section V-bis of this act and modifying decree n° 78-774 dated 17 July 1978; this committee must be consulted before transmission of any request to CNIL.

For some types of investigation, it may also be necessary to obtain authorization of the Comité de protection des personnes (Institutional Review Committee) with jurisdiction over the institution where the research will be conducted.

Moral authorities: This may be the Comité consultatif national d'éthique pour les sciences de la vie et de la santé (CCNE) described above, a local ethics or institutional review committee, or the Conseil de l'Ordre des Médecins (Council of the Physicians' College of France).

These Recommendations may be adapted to other national contexts by the epidemiology societies concerned.

2 DEFINITIONS

In the context of these *Recommendations for Professional Standards and Good Epidemiological Practices* (GEP), we define the following terms:

Anonymization - Process by which the identifying particulars of data are removed to make it irreversibly impossible to identify, directly or indirectly, the individuals to whom they relate.

Communication - Any presentation, in any form whatsoever, of the methodology or the results of an epidemiological study to individuals or organizations outside the team responsible for the study.

Confidentiality - The guarantee to subjects that all non-anonymized personal data will remain inaccessible, except through specific data protection procedures.

Data - Any item or combination of items of information collected and recorded during the study, either directly, from a person participating in the study, or from a third party's data base.

Data collection - The phase of an epidemiological study during which information related to individuals or groups of individuals is collected.

Data director - The person, public authority, department or body that determines the aims and resources of the study. The data director is especially responsible for data security and compliance with the ethical, professional, regulatory and legislative provisions for data treatment chosen and may delegate some of these powers.

Data integrity - The physical security of the data, that is, that it is not physically damaged, deformed or mislaid.

Funder - Any individual or organization, whatever their status, involved in financing all or part of an epidemiological study.

Individual rights concerning the treatment of personal data - Provisions that allow people asked to participate in a study or their representative: to refuse the recording of data about them, to have access to the data about them, to have it rectified where appropriate, and to refuse to waive their privilege of confidentiality

Peer evaluation or validation - The evaluation of an epidemiological study, at any stage, by peers unrelated to the research team; it may be specific or general, i.e. it may concern particular aspects of the methodology proposed or used, at the request of the principal investigator or of any other person, or it may concern the design, implementation, analysis and publication of the study as a whole.

Peers - Experienced epidemiologists recognized as such by the profession as a whole.

Personal data - Any data item, in any form, with which it is possible, directly or indirectly, to identify the persons to whom it applies.

Personal data treatment - All operations involving the collection, recording, development, modification, storage and destruction of personal data and all operations

related to their use including their cross-referencing, comparison, consultation or communication.

Preliminary study – The evaluation of data collected during an epidemiological study or series of studies, carried out with a view to establishing basic study hypotheses or identifying priorities or directions for future study.

Quality control – The entire program intended to guarantee compliance with the relevant standards, especially GEP standards. Quality control applies to all stages of the study, from the development of the study protocol to the publication of the results and the filing of the data used or produced during the study.

Results – The results of an epidemiological study, regardless of whether they are published, including the conclusions that may be drawn or the interpretations that may be made based on one or more such studies.

Standard procedures - Documents containing instructions relating to the methods to be used to conduct specific operations or studies.

Principal investigator – The member of the study team who is ultimately responsible for the design, implementation, analysis, documentation and communication (by publication or any other means) of an epidemiological study.

Study documents – All documents or data, in any form, on the basis of which it is possible to determine how a study was designed, conducted and analyzed, and any document, in any form whatsoever, containing data collected during the study, including the computer codes or manuals necessary for anybody who might wish to conduct further analysis or re-analysis of the documents or data.

Study protocol – Documents containing all the technical details of the design, implementation, analysis, documentation and publication of the results of an epidemiological study. The study protocol includes all the procedures developed or used during the study and any changes made to the initial protocol.

Study team – Any form of organization, of any status, including informal or *ad hoc* groups, that takes part in or contributes to the design, data collection, implementation, analysis or publication, in all or in part, of an epidemiological study, or which is responsible for the filing and storage of data used or produced during such a study.

Subcontractors – Any individuals or organizations treating personal data on the instructions of and on behalf of the data director. They must provide sufficient guarantees to ensure that all security and confidentiality measures are implemented.

Subject – Any individual included in a study about whom data — personal or otherwise — are collected.

Third party – Any individual or organization, whatever their status, that does not belong to the study team.

3 DISCLAIMERS

Before presenting the Recommendations, it is useful to review the definitions of epidemiology and epidemiologists.

The scientific discipline of epidemiology studies, in particular, different factors relating to the onset of diseases and health events or phenomena, their frequency, mode of distribution, natural history, and the means necessary to prevent and treat them.

Epidemiologists, regardless of their status and employer, are scientists who by their education, degrees, experience and professional practice are qualified to conduct epidemiological studies. This qualification may be officially acknowledged by a specific university diploma or by a competent authority made up of experienced epidemiologists recognized as such by the profession.

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These recommendations, like their preceding version, form a whole applicable to all forms of epidemiological practice. They concern two basic aspects: professional standards and good epidemiological practices. They can be used for studies of both human and animal health.

They are intended above all to facilitate dialogue between epidemiologists and the people they work with. They must be understood by all those who commission epidemiological studies or use their findings. They provide a framework intended to help epidemiologists and their partners work together, while respecting the core values of our discipline.

These are recommendations by which all epidemiologists must abide, regardless of their field or personal status or employer (public or private). In no way, however, do they replace epidemiological expertise acquired on a case-by-case basis and confirmed by *a priori* and *a posteriori* peer review, i.e., by experienced epidemiologists recognized by the profession as a whole. Because of the variety of techniques used in epidemiology these recommendations contain a number of principles, which must be implemented with discernment and adapted to the context and the nature of each study. These recommendations should not be used as a strict set of rules, for epidemiological practices are subject to constant development and innovation, as befits a dynamic discipline: omitting a procedure that is listed in this document, or using one that is not, might be a perfectly "good practice" in a specific context, if it is justified.

This document is not a code of ethics as such. While it is natural for an association of specialists in a discipline to fix rules governing professional conduct and good practice, it does not have the authority to define the ethical principles governing its work. Such principles are based on broader considerations than those governing a scientific discipline, and the discipline must comply with the general ethical principles defined by the relevant bodies responsible for them. Their role is reviewed in this document.

4 PART I.

**BASIC PRINCIPLES, CORE VALUES, PROFESSIONAL
STANDARDS AND GOOD EPIDEMIOLOGICAL
PRACTICES**

4.1 THE CONTEXT OF EPIDEMIOLOGY PRACTICE

The objective of this document is to develop recommendations that make it possible to follow universally agreed-upon ethical principles while practicing epidemiology of high quality. They are proposed as a reference for all types of epidemiological investigations, whether they involve research, description, surveillance, assessment, intervention or any other form of epidemiology, including collaboration, communication and peer assessment. **This document uses the term "epidemiology" in this sense, extended to all forms of practice.**

The Declaration of Helsinki defines the internationally recognized ethical principles of clinical research. It resulted from a series of meetings of the World Medical Association between 1964 and 1989. The Declaration concerns primarily experiments in clinical research and does not cover the diverse schemes of observational studies often used in public health. Nonetheless, the ethical principles established by the Declaration of Helsinki (last updated in 2004 in Tokyo) apply to all medical research on human subjects, and thus epidemiological studies of human being must follow them. These principles are reinforced by WHO recommendations about the ethics of biomedical research on human beings.¹ More precisely, four main ethical precepts apply to epidemiology:

- Respect each individual (autonomy);
- Do good (beneficence);
- Do not harm (non-maleficence);
- Be fair (justice).

Although these principles are recognized in the context of experiments on human beings, they must be envisioned in a broader sense that includes epidemiology. Individuals have the right to know the risks that threaten their health and to make rational evidence-based choices about treatment and prevention. This is not possible without epidemiology. Accordingly, not conducting epidemiological investigations is often unacceptable from an ethical point of view.

Moreover, the quality of epidemiological investigation must be high. A poorly conducted investigation may lead to erroneous decisions that may profoundly affect individuals' health. The quality of epidemiological investigation thus has ethical dimensions that must be taken into account.

Epidemiologists, like scientists in other disciplines, must have as an ideal the value of free enquiry and the will to contribute to improving knowledge. Their behavior as a profession must be equitable and just. Epidemiological investigations have an important role in democratic societies and all epidemiologists must make their contributions according to their own experience. An epidemiological study is a better solution than abstention only if the results have scientific credibility and provide social benefits or improve our understanding of the occurrence of different diseases in populations.

¹ *International Ethical Guidelines for Biomedical Research Involving Human Subjects. CIOMS-WHO, 2002.*

4.2 PRINCIPLES OF PROFESSIONAL STANDARDS IN EPIDEMIOLOGY

The end goal of epidemiology is to increase knowledge about health and especially public health: knowledge about the health status of the population, the mechanisms that determine it, the factors that threaten it, and the methods and interventions appropriate for improving it. This discipline includes experimental research (such as randomized controlled trials), non-experimental research, and different forms of applied investigations intended to improve population health.

The professional standards that govern the practice of epidemiology are based on rules about the scientific and methodological quality of studies, the quality and confidentiality (as well as the ownership) of the data, conflicts of interest, reuse of data, and the use and communication of study results. If studies do not comply with these rules, their implementation and continuation become contrary to professional standards, which themselves are part of the more general rules of health ethics.

The principal rules of professional conduct that apply to all forms of epidemiological practice are enumerated in the following paragraph.

The professional and technical independence of epidemiologists in the exercise of their scientific activity is an inviolable principle that must be the basis of relations between the epidemiologist and the funder, public or private, of an epidemiological study, regardless of their relationship — employer-employee or another type of contract. In particular, the professional status or work contract of epidemiologists should not include any condition incompatible with their professional and technical independence, or any clause that might prevent them from doing their job in conformity with good epidemiological practices. When epidemiologists conduct their activity within a regulated profession or belong to a body regulated by a particular status, they must personally ensure at all times that the rules applying to that profession or status cannot be opposed to their independence, or to compliance with good epidemiological practices.

When an epidemiological study is initiated and conducted in accordance with the recommendations set forth in this text, no one has a right to exert an influence, direct or indirect, on the epidemiologist, for example concerning communication of the results.

It is epidemiologists' responsibility to take all steps possible to meet the criteria of quality, probity and rigor that correspond to the state of the art. These criteria make up what we call good epidemiological practices.

When an epidemiological study is conducted within a particular community (ethnic or social group, organization, etc.), it must be organised according to ethics rules that respect the moral and material interests and the specific regulatory provisions of the community concerned, insofar as possible under the professional and scientific standards and regulations set forth herein. It is unacceptable to conduct epidemiological investigation in populations or in vulnerable groups without an ethically justifiable reason; any epidemiological study concerning vulnerable people or involving risks for the research participants must meet the requirements of the relevant ethics committees.

Epidemiologists may legitimately refuse to undertake an epidemiological study if they consider that the chances of obtaining valid results are too slim. In this event, they must explain their decision (e.g., unjustified hypotheses, lack of power, difficulty in evaluating exposures, etc.). Similarly, if they decide to go ahead with such a study, they must justify its utility.

Epidemiologists have a personal responsibility to comply and ensure compliance with the rules for protection of personal data, which is not limited simply to their obligation to protect confidentiality; these rules also concern respect for the aims of the study, the obligation to collect only data relevant to these aims, not to save data for longer than necessary for the study, and to respect the subjects' individual rights. More generally, like all scientific investigators, epidemiologists must comply with all laws applicable in their field — those relevant to the protection of personal data and those involving public health and standards for health-care professionals.

It is the personal responsibility of epidemiologists to:

- provide to people asked to participate in a study clear, complete and effective information about the study's objectives and protocol, thus allowing them, when they want, to refuse to participate
- communicate the results of their work by all appropriate means; with scientific rigor, and without introducing interpretations that are either understated or overstated;
- rectify the scientific facts established by their studies insofar as possible when they are not accurately reported and this is brought to their notice, even when those responsible for the inaccurate reporting are third parties, scientists or otherwise;
- ensure that research participants (subjects or their representatives, people who contributed to the data collection, etc.) are informed of the findings in an easily comprehensible form;
- plan in the study protocol to inform, when pertinent, the subjects of the individual results relating to their health, with recommendations for management when appropriate. Should they deem it unwise to divulge these results, they must inform the principal investigator, who shall consult the data protection authority to determine whether it is acceptable not to inform the subjects concerned. They may also consult the physician concerned or an appropriate moral authority (ethics committee);
- make every effort to explain to other professionals in the health field the methods used and the results obtained, to facilitate their use.

Generally, epidemiologists must seek the truth in good faith, without harming or compromising anyone's integrity.

4.3 THE FIELD OF APPLICATION OF GOOD EPIDEMIOLOGICAL PRACTICES (GEP)

These GEP Recommendations apply to all forms of epidemiological studies. These generally involve either no or very little risk to participants and are therefore outside the jurisdiction of ethics committees. Nonetheless, it is possible that epidemiological studies or parts thereof may also be regulated by the Code of Good Clinical Practices (GCP) or Good Laboratory Practices (GLP). In such cases, compliance with these guidelines is also necessary.

These recommendations concern feasibility studies, preliminary studies, pilot studies, and full-scale studies of every kind. They apply from the first phase of the study (protocol development) through its completion, to the report and publication of the results and the conservation of the scientific documents relative to them.

These recommendations also apply to review studies, multicenter studies, combined analysis of individual studies, meta-analyses and calibration studies.

These Recommendations apply regardless of who the sponsor or funder may be and regardless of the affiliation of the study, in either the public or the private sector.

These Recommendations concern the most common GEPs. They are not always necessary or sufficient. Good judgment should be applied in each specific situation. Only epidemiological expertise based on peer evaluation can determine the justification for departures from standard GEP.

4.4 DO GOOD, DO NO HARM

Individuals have the right to make decisions and choices for themselves and therefore the right to know the risks for their health, the prevention measures available and the way to obtain optimal treatment in the health care system. One of the aims of epidemiology is to increase the likelihood that the individual and collective choices made will improve health.

Although the risk of damage is usually low, an essential ethical principle is the moral obligation to do no harm, physically or psychologically, to participants in epidemiological surveys. This is especially important because most such subjects receive no personal benefits and often have no disease requiring treatment.

Epidemiological study participants must be treated with respect. The study's objectives, methods and results must be accessible to all participants in an appropriate form.

4.4.1 Protection of personal data

Epidemiologists often use personal data and must therefore respect the confidentiality of the subjects. Working with personal data is a privilege that calls for a high degree of data protection. Beyond the requirements established by the data protection authorities, epidemiologists must develop working standards that reduce as much as possible the risks of violating confidentiality. Unintentional communication of personal data may further limit the future options of other investigators, even though no participant is harmed.

4.4.1.1 Information to potential participants

The principles of doing good, doing no harm, and doing justice are all elements that may be involved in analyzing the amount of information to be provided to subjects about all aspects of the study. Sufficient information must be provided so that when the interview or examination is performed, subjects do not feel that they have been led in a direction other than where they thought they were going and particularly not in a direction to which they would have refused to participate. Principal investigators must therefore keep study participants properly informed to the extent possible. If there are any potential risks, in particular, they must be informed. Generally, it is desirable to provide clear, complete and effective information to the people concerned in a written document, thus allowing them to refuse the use of their data for epidemiological purposes.

It can happen that during the collection or verification of data about study participants, investigators may discover information previously unknown to the subject that has repercussions on their health, that of their family members or their animals, and on their family or social life or rights. Examples of such information are the discovery of a disease, of susceptibility to a disease, exposure to a toxic product, or sometimes ruling out the diagnosis of a disease the subject thinks he or she has.

Epidemiologists should not define their approach to such a situation on their own. If the situation may be anticipated at the time the protocol is prepared, a preliminary opinion on the appropriate conduct should be requested from the data protection authority to enable the planning of appropriate information; an appropriate moral authority (ethics committee) may also be consulted. If such an unforeseen situation occurs during the study, the opinion of these authorities must be requested on a fast-track basis to determine the appropriate response.

4.4.1.2 Informed consent

According to the recommendations of the Council for International Organizations of Medical Sciences (CIOMS): "Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation."

Informed consent thus includes three dimensions:

Information: subjects must be given sufficient information to allow them to make a reasoned choice; in some situations, to prevent engendering bias, the competent data protection authority can authorize the principal investigator not to reveal all of the study objectives.

Understanding: Subjects must be able to understand what is said to them and to make a thoughtful decision based on this information.

Consent: There must be a voluntary decision or agreement by an individual capable of making this decision.

4.4.1.3 Voluntary participation

Consent must be given freely without outside pressure and without any unreasonable arguments. When incentives are used, they must always be assessed. Although the distinction is not always very clear, there must be a balance between reasonable reimbursement, for example, for transportation expenses, and excessive remuneration. The use of incentives that exceed real costs is acceptable only in studies that include no risk to the participants.

In a clinical context, where patients may not feel free to refuse the request to participate in a study suggested by their physician, efforts must be made to avoid this influence, for example, by having the invitation to participate made by a person from outside the healthcare system.

Because participants in most public health studies have many opportunities to refuse to participate, incentives must not be judged on the same basis as in clinical trials.

In the case of doubt about the legitimacy of incentives for participation, the data protection authority must be consulted in advance; a competent moral authority (ethics committee) can also be consulted.

Subjects must have the right to withdraw their consent at any point during the study, even without any apparent reason. Non-participation or refusal to participate must not create any disadvantages for these subjects. Insofar as possible, all this must be stated clearly in the initial written document inviting participation.

4.4.1.4 Rules governing the applicability of consent

If the study requires subjects to complete a questionnaire and adequate information was provided to the subject, consent is said to be "*simple*" and written consent is not necessary, because responding to the questionnaire implies consent.

"*Express*" consent (written authorization by patients or their representatives) must be obtained in some cases, for example, to collect and store biological material with identifiers attached. The appropriate data protection authority shall establish the conditions for this procedure. Use of samples for research not covered by the original consent requires a request to the data protection authority, which decides if new consent is necessary or if the analyses can be performed on anonymized samples.

In some circumstances, when it considers the circumstances justify it, the data protection authority can authorize an exception to the collection of consent (for example, subjects lost to follow-up or use of personal data already collected for a purpose not initially associated to the epidemiological study, when consent may be too difficult to obtain).

Consent is not necessary in situations of overriding public health imperatives. Nonetheless, in all circumstances, preliminary authorization from the data protection authority must always be obtained to use information without obtaining consent.

For children and others who are temporarily or permanently incapable of providing informed consent themselves, consent may be provided by a third person independent of the body implementing the treatment or study. This may be parents for children, legal representatives, or healthy proxies designated by the subjects involved. In all cases, the data protection authority must be consulted.

4.4.1.5 Data security

The principal investigator and data director have important obligations for data security and confidentiality. They must both take all useful precautions in view of the nature of the data and the risks presented by the treatment, to preserve data security and especially to prevent data from modification, damage, or accessibility to unauthorized third parties. For these purposes, it is essential that the principal investigator define a security policy and that the data director ensures that all necessary measures are taken to ensure compliance by everyone with access to the data.

4.4.2 Publication must not harm

Premature publication of the results must be avoided. Particular care must be taken to avoid publication of data that may lead to discrimination against vulnerable groups.

4.4.3 Need for a protocol

Every epidemiological investigation requires the development of a protocol that can be assessed by a competent body to ensure that subjects do not participate in a study that began at the onset with important methodological defects.

4.5 ACCOUNTABILITY – CONFLICTS OF INTEREST

4.5.1 Scientific integrity and conflicts of interest

A conflict of interest is a situation in which epidemiologists have or may have a personal interest sufficient to influence their professional judgment during their official duties.

Epidemiologists must never have a conflict of interest that is unknown to their collaborators, funders or study subjects. Consequently, epidemiologists must report to the competent moral authority (ethics committee) any and all conflicts of interest — real, apparent or potential. All funders and sponsors of a study must be known. There is no justification for secrets.

4.5.2 Scientific and legal responsibilities

The responsibilities of and relations between individuals and organizations contributing to the design, implementation, analysis and publication of the findings of an epidemiological study, or involved in the filing and storage of the data used or generated during the study, must be determined before data collection begins. All individuals and organizations (principal investigator, study team, funder, public or private body implementing the study) involved in the tasks listed in the study protocol are individually responsible at their level for proper compliance with these GEP recommendations. These responsibilities are both scientific and legal and involve compliance with all applicable legislative or regulatory dispositions.

It is essential to specify these different points from the beginning of negotiations with the funder, public or private. A written document must specify that the results will be published, regardless of what they are; in some cases, a moral commitment of the parties may suffice. The funder must recognize the epidemiologists' independence, which must be maintained throughout the study.

4.6 STUDY PROTOCOL

4.6.1 Definition of protocol

The protocol is the cornerstone of an epidemiological project: it is the document that describes the study's aims, methods, population and planned analyses. It should also cover administrative and legal questions, possible difficulties and limitations, calendar and deadlines, and how the results will be communicated. Writing and following a good protocol is an ethical duty for scientists, and defining and conducting studies without the resources and scientific competence necessary must be considered unethical. The protocol must also reflect the basic ethical principles and core values of epidemiology mentioned above.

4.6.2 Principal objectives of an epidemiological study protocol

The principal objectives of the protocol are to:

- Justify the need for the study, that is, explain why in the current state of knowledge the study should be performed.
- Define the study objectives and show that they correspond to the identified need.
- Demonstrate that the methods proposed to meet the objectives are adequate.
- Demonstrate the feasibility of the proposed study, that is, that the study can successfully be completed in the time planned and with the resources available.
- Demonstrate that the investigator has the competence necessary to conduct the proposed study.
- Demonstrate that appropriate provisions, meeting legal requirements, have been made to protect participants' personal data.

4.6.3 Use of protocol

The protocol must be written before the study begins.

The protocol is an instrument to justify the proposal for the purposes of obtaining the necessary financial resources and authorizations.

It serves as documentation for all those who participate in the study.

It must be accessible to all persons involved in the study, especially those who will be included in it.

4.6.4 Protocol characteristics

Since epidemiological studies may have a wide variety of study designs, it is impossible to present a standard model appropriate to all studies. Nonetheless, the protocol must be sufficiently detailed to serve as the study's basic document.

It must specify the study aim and the questions to which it seeks answers. For some epidemiological studies, nonetheless, all the study objectives cannot be specified in a document accessible to the subjects, because revealing all the hypotheses may bias the investigation when the respondents know both their exposure and their health status. The data protection authority must review the protocol when researchers propose selective information.

The protocol must show that the investigator knows the relevant scientific literature about the study topic.

The protocol should include information about the study calendar and deadlines, publications and authors' lists. In addition, the protocol must refer to these Recommendations for professional standards and good epidemiological practices.

The protocol must be treated as a confidential document by those who read or assess it.

4.7 STUDY CONDUCT

4.7.1 Adhering to the study protocol

The authorizations required in any field, including for the protection of personal data, must be obtained before the study begins.

All epidemiological studies must be conducted, analyzed and, where applicable, published in conformity with the study protocol.

4.7.2 Analysis

The data collected or obtained during an epidemiological study must be analyzed in conformity with the study protocol. Nonetheless, data collected in a study may legitimately be analyzed to evaluate hypotheses that were not explicitly formulated in the initial protocol, or for a secondary purpose different from that originally intended. Any significant change from the statistical methodology described in the study protocol must be expressly mentioned in any publication or presentation of the study results.

4.7.3 Quality control for the study

Standard procedures must be developed to guarantee the quality of the data collected, obtained, produced or published during or as part of an epidemiological study.

4.7.4 Filing and archiving data

During the study period, it is imperative that a filing system be organized and made secure to guarantee the confidentiality of personal and easily accessible data and enable the filing of and convenient access to personal data and more generally to all study documents.

After study completion, personal data can be stored only in anonymized form that does not in any case allow the identification of individuals.

4.7.5 Stopping a study for reasons beyond the control of the principal investigator

When a study must be stopped before its completion for reasons beyond the control of the principal investigator (his or her inability to continue the study, decision by funder or public or private body organizing the study), the director must, if able to do so, seek the opinion of a recognized professional society of epidemiologists about the study fate; such a recognized society can also raise the issue itself if necessary. It may recommend that the study be continued or that all of the existing documents be archived under the supervision of another director. The data protection authority that initially authorized the study must be consulted according to the legal procedures in effect to agree to the conditions proposed for continuation or archiving.

4.7.6 Access to documents related to the study, for re-analysis or validation

The study documents may be analyzed, assessed, commented or used, including in other studies or meta-analyses. Editors of scientific journals to whom a publication is submitted, other investigators or any interested physical or moral person must be able to have access, in order to proceed to their own evaluations, on condition that their motivation and their scientific quality be at least as justified and rigorous as that in the original protocol. Any transmission of personal data must be anonymized, in compliance with all applicable legislative and regulatory provisions.

4.8 PUBLICATION OF RESULTS

4.8.1 Dissemination and other publication of the study results

The broadest possible publication of the results of epidemiological studies is sure to benefit the scientific and public health community. Moreover, it is contrary to the collective interest

not to make the results obtained available, or to prevent them from being taken into account, for example by public decision-makers or by the authorized representatives of the community in which the study was conducted.

Withholding information or refusing to divulge results can be justified only by exceptional circumstances — for example if the methodological problems encountered during the study deprive the results of all meaning. It must be realized that when testing a hypothesis, all results — positive or negative — are equally important and therefore that refusal to publish results must not be based on the fact that the results obtained show no statistically significant correlations. Refusal to divulge or publish research results, including negative results or results that reveal no significant statistical correlation, may also lead to a bias in the conclusions obtained in summary studies, by meta-analysis or other means. The results of the research must consequently be published without delay, critically and in good faith, with adequate documentation. Observations that contradict the principal results must always be presented in the text.

When it is not possible to present or publish all of the results or conclusions of an epidemiological study, for reasons related either to insufficient space or insufficient time, the principal investigator must guarantee that all who may be interested in the complete results or conclusions can have access by a simple request.

The principal results must be provided to those who participated in the study or to their representatives, as well as to other members of the community where the study took place, in an appropriate form, such as a letter, newsletter or local newspaper article. If possible, they shall be informed personally, at a meeting, or by letter, newsletter or any other appropriate means. The information should be presented in a form that is easy to understand.

4.8.2 Rules for publication

4.8.2.1 Obligation to publish

All study results, regardless of whether the funders are public or private, are under the scientific supervision of the epidemiologist who is the principal investigator, and not of the funder, and the results must always be made public if their scientific validity is sufficient. All requests to hide the results or change or attenuate the content of a report or to delay publication must be categorically rejected.

4.8.2.2 Obligation to assess publications

As a general rule, the results of a study should be submitted to a journal with independent peer review before they are made public or the media are informed. In some circumstances, a study's results are presented as a study report that must then be assessed by independent peers before being made public. Epidemiologists should not inform the press of a study's results until the results are available in a publication or an accessible peer-reviewed report or presented and discussed during a scientific conference in the presence of peers

The only exceptions to this principle are epidemics and other emergencies. For example, epidemiologists may discover a health risk that requires rapid correction measures; as they thus become advocates for the protection and restoration of health, their advocacy must be based only on objective scientific data. It is nonetheless highly desirable that in situations where the public health interest of the results prevents proceeding to a normal review, an

independent organization recognized by peers should, insofar as possible, be asked to conduct an appropriate critical review of the study before it is made public.

4.8.2.3 Impartiality of publications

Such publications must describe every aspect of the study in an honest and balanced manner, without taking any other interests, especially nonscientific, into account. Epidemiologists must not exaggerate results in the aim of increasing the likelihood of further funding for future research or to make their articles more attractive to journal editors. Published results generally constitute only a small part of the information available, and some bias may affect the choice of data published, in selecting results that agree with the epidemiologist's point of view and not mentioning those that contradict it. This type of partiality or bias must be avoided.

The authors of epidemiological articles must comply with the rules of the better journals in their reporting of possible conflicts of interest. The definition and order of authors must comply with good practices for scientific publication.

4.8.3 Participation in the evaluation of protocols and articles

Epidemiologists acting as peers in the review of protocols submitted for preliminary evaluation before funding or implementation or of epidemiological articles presenting study results must be aware of the importance of their role as guarantors of the scientific quality of studies and advisors to journal editors. They must avoid any bias during the review process for an article or for funding. One of the foundations of public confidence in epidemiological results is that epidemiologists judge their own work and ideas and those of their colleagues with impartiality. Reviewers judge the originality, scientific quality, and clinical importance or public health consequences of studies and especially assess the entire article for its publication in a journal.

Epidemiologists who review research protocols or manuscript in proposal form or who review their colleagues' work must be able to assess whether they are sufficiently competent to agree to do this review. Reviewers must not agree to review articles if they will be in a conflict of interest situation because they work too closely with one of the authors or because they compete in the same domain. Reviewers must respect the confidentiality of the research ideas of the authors whom they review and must do the work within a reasonable time. They must not try to block a proposal or grant application because of personal interest.

Recommendations for reviewers have been made by the Council of Biology Editors and adopted by several scientific journals.

5 PART II

**GOOD EPIDEMIOLOGICAL PRACTICES: DETAILED
RECOMMENDATIONS**

We have brought together in this part the most detailed guidelines to provide additional useful information on diverse points in Part I. These points complement the general recommendations and follow the outline of Part I, with a cross-reference to the number of the paragraph concerned in Part 1.

5.1 INFORMING THE PEOPLE CONCERNED (4.4.1.1)

Principal investigators must describe to research participants or subjects, in a written document and to the extent possible: (1) the type of data collected or transmitted; (2) the objectives of the study and the planned utilization of the data; (3) the recipients of the data; (4) their right of access and correction; (5) their right to object to the use of data about them. It is not usually necessary to obtain written consent from subjects in observational epidemiological studies, but it may nonetheless be essential in some situations, as for the collection of identifying biological samples. People are deemed to have provided informed consent to participate in a study only after an affirmation that they received appropriate information in writing, they understood it, and they consented unambiguously in writing.

If there are legitimate reasons for not divulging some information (seriousness of the prognosis, nature of the population studied, object of the study), the principal investigator shall consult the data protection authority to assess whether it is acceptable not to inform the subjects concerned. The subject's physician or a competent moral authority (ethics committee) may also be consulted.

In cases where the personal data used for the epidemiological study were initially collected for another purpose, the information mentioned above must be communicated in writing to the individuals concerned, if possible and to the extent that this can be done under reasonable conditions. If such communication does not appear feasible, approval must be sought from the data protection authority. In any case, the data protection authority and any body that may have given an opinion about the initial study must be consulted for its opinion before the implementation of the newly proposed study.

5.2 PROTECTION OF PERSONAL DATA (4.4.1)

5.2.1 Anonymization

All data or information collected during the study must be rendered anonymous as soon as possible after its collection, except when the identification of the people concerned is necessary to the proper execution of the study.

A data item or information is considered anonymous when it may no longer be used directly or indirectly to identify the individuals it concerns. In all cases, the data must be rendered anonymous before they are placed in storage.

5.2.2 Data security

Principal investigators are responsible, among other things, for the security and processing of the data collected. They must have the resources necessary to perform these tasks properly.

They must ensure that appropriate steps have been taken to limit access to personal data exclusively to those persons who need this access for their work on the study. We will consider the following principal procedures:

- every precaution must be taken to safeguard the data and make sure, among other things, that they are not altered, damaged or communicated to unauthorized third parties;
- personal data in any form — especially written, graphic, as words or computer codes, vocal recordings or electronic signals — must be stored in a closed and locked space, access to which is controlled by the principal investigator or an investigator working under his or her direct supervision;
- measures must be taken to ensure the confidentiality of the information, including separate storage of the code identifying the corresponding subject list and limited access to it;
- all appropriate measures, such as encrypting data with a specific algorithm or passwords, input and output files, physical and logical separation, must be used to prevent: (1) onsite or remote access to the data by unauthorized persons; (2) onsite or remote access to the data by authorized people without the recording of each access; (3) access to the data during transmission by open computer networks;
- a list of all persons authorized to have access to data collected or produced by or resulting from an epidemiological study must be drawn up before data collection begins and must be updated on a regular basis throughout the study; at its conclusion, this list must be stored and filed with the rest of the study documents so that it is easily accessible;
- all people with access to personal data must first sign a written agreement stating that they: (1) guarantee that they understand and accept the reasons for which they have access to these data; (2) agree not to reveal any data that would allow the direct or indirect identification of any individuals or any information about these data, to a member of the study team not authorized to have this knowledge, or to any third person; (3) undertake not to do anything or to let anyone else do something that might lead to a violation of the participants' privacy rights in their personal data; (4) state that they are aware that any violation of these provisions can lead to the application of sanctions;
- access of authorized people to personal data must involve verification of their identity.

5.2.3 Studies involving multiple contacts

When an epidemiological study design involves multiple contacts between members of the study team and the same participant throughout the study, appropriate procedures must be set up to avoid the multiplication of such contacts by people with access to the subject's personal data.

5.2.4 Communication of personal data

Before any presentation in any form or publication of epidemiological study results it is essential that all appropriate precautions be taken to: (1) prevent the knowledge of any personal data by any unauthorized individuals; (2) and guarantee that if these data are transmitted to others, the subjects of these data receive the information required by the procedures described in these Recommendations or provided their informed consent to this

disclosure, in accordance with the procedures described in these Recommendations. These measures do not apply when nominative transmission is mandatory for public health reasons.

5.2.5 Relations with third parties holding personal data

When the study involves collecting personal data from third parties who already have it in their possession or collect it specifically for the study, principal investigators must ensure that the third parties are willing to participate (except when nominative data transmission is compulsory for public health reasons, following existing legal and regulatory dispositions. Accordingly, the third parties concerned must be informed of: (1) the study objectives and the planned use of the data;(2) the nature of the data likely to be transmitted; (3) the recipients of these data; (4) the procedures intended to guarantee confidentiality and data security; and (5) authorizations by the data protection authority.

Except in special circumstances explained in the study protocol, third parties who agree to take part in data collection for the study must be kept informed by the principal investigator of the study's progress and results.

5.2.6 Violations of security procedures

Any failure to comply with the instructions herein must be reported without delay to the principal investigator, who must then: (1) notify the data protection authority that data protection provisions were violated; (2) describe in the greatest possible details the circumstances of the violation; (3) inform the data protection authority of the measures taken or envisioned to limit as much as possible the consequences of the violation; and (4) propose to the data protection authority solutions to avoid a repetition of this violation.

Furthermore, if the violation concerned is particularly serious, or likely to affect the professional obligations of the funder, principal investigator or any participant in the study in any capacity whatsoever, the funder, principal investigator or team member concerned shall inform the data protection authority to enable it to take any steps it deems necessary to remedy the situation.

In all cases, together with the above measures, the principal investigator may take legal action in the appropriate courts that he or she considers justified.

5.2.7 Unplanned use of personal data

In the event that investigators wish to use non-anonymized data for a study with a purpose other than that of the study for which the data were originally collected, they must apply in writing and explain their intentions to the data protection authority. Participants must also agree, after information.

5.3 SCIENTIFIC AND LEGAL RESPONSIBILITIES (4.5.2)

5.3.1 Competence of the study team

Members of the study team and any subcontractors must have the necessary training, practice and experience in epidemiology or in other disciplines involved in the study concerned, to carry out competently and professionally all the tasks assigned to them by the study protocol and all directions they receive during the study.

5.3.2 Responsibility of the principal investigator

Principal investigators assume overall responsibility for the design, implementation, analysis and publication of the study, and for the sorting and filing of the data generated or used during the study. Any person who agrees to accept the responsibility of principal investigator must be prepared to devote enough time to the study to make sure that it is conducted in accordance with these recommendations and with all other applicable legal or regulatory measures.

In particular, principal investigators must ensure that the study team and any possible subcontractors understand the tasks for which they have operational responsibility, that they are capable of performing these tasks successfully, competently and professionally, and that they know and understand the provisions of these Recommendations, as well as any other applicable legislative or regulatory measures.

They will verify, *inter alia*, that the members of the study team responsible for collecting data, including those working part time, are trained before they start work on the study and are monitored subsequently to make sure they do their work properly. The training and monitoring must extend to all aspects of data collection, from its onset to the transmission of the data to the team members responsible for data entry and analysis.

Moreover, when several persons on the team have similar tasks, simultaneously or not, their role and relation should be defined specifically in advance and one team member should be responsible for coordinating the work.

5.3.3 Responsibilities of the data director

The data director may be a different person from the principal investigator when the latter belongs to a public authority, department or body that determines the study's aims and resources. The data director is responsible especially for data security and compliance with the ethical, professional, regulatory and legislative provisions for data treatment decided upon; he or she may delegate some of this power to the principal investigator.

5.3.4 Responsibilities of the funder

Any individual or organization, of any status, who contributes financially to an epidemiological study must do so in accordance with the rules laid down initially and demand from the outset that the study be carried out in keeping with the principles of these Recommendations and with any other applicable legislative or regulatory measures.

The contracts, or any other form of commitment entered into by any or all members of the study team, funders and institutions or employers on whom they depend must be in keeping with these Recommendations, including the rules governing publication.

5.3.5 Changes in responsibilities

When changes are made to the responsibilities incumbent on the team responsible for the study as defined in the initial study protocol, for example concerning the protection of personal data or the scientific supervision of the study, the reasons for such changes must be stated in writing by the public or private body implementing the study and transmitted to the competent authorities who initially examined and authorized the study.

5.3.6 Ownership of data

The members of the team responsible for the study, the study funders and their institutions or employers must explicitly agree on the provisions governing data ownership. Under no circumstances should these provisions hinder the progress of the study, its interpretation or the dissemination of the results under the responsibility of the principal investigator, in conformity with the principles laid down in these recommendations. In particular, the conditions governing subsequent access to data for re-analysis or validation must be established in conformity with these recommendations.

5.3.7 Responsibilities for publication (also related to point 4.8)

The publication of the results of an epidemiological study is a scientific task. Every stage in the process leading to publication must therefore be carried out accordingly. In particular, each member of the study team who participates in the publication of the results of the study is personally responsible for ensuring that the publication is consistent with the principles of these Recommendations.

If manuscripts are distributed to be reviewed prior to publication, even to the study funders, the members of the study team must decide whether or not to heed any remarks the funders or any reviewers who read the manuscript may make. Furthermore, their decision must reflect and be motivated by scientific considerations alone.

5.4 THE PROTOCOL (4.6)

5.4.1 Prior approval of a study design

Independently of the control procedures required by any applicable legal and regulatory provisions, preliminary validation is strongly recommended: it will make it possible to compare different scientific viewpoints and provide multiple angles of illumination on the procedure; it can therefore help ensure the absence of flaws in either methodology or professional practices.

Internal validation

One form of prior approval required for most epidemiological studies should be carried out by the members of the organization to which the principal investigator or study team members belong. Its purpose, at least in part, is to determine whether the studies envisioned are consistent with the organization's procedures and compatible with its resources, particularly in the context of its public health priorities. It is the organization that should determine whether validation is necessary and what form it should take.

Ethical validation

A second form of advance approval also carried out by the members of the organization to which the principal investigator and/or study team members belong, concerns the ethical questions raised by the study project. The principal investigator must ensure that the study corresponds to the professional practice rules described above and that it corresponds to the rules applicable to the team members who practice a profession regulated by particular ethical rules. This ethical validation should, where applicable, take into account any remarks made by authorized representatives of the community where the study takes place.

5.4.2 Protocol content

The design of the study must be described in sufficient detail and in its entirety in the study protocol. The study protocol must include all the elements necessary to understanding and implementing the study. It is not possible to draw up an exhaustive list of every item which must be included in an epidemiological study protocol, for it must always be adapted to a particular context. It is possible, however, to list the information most frequently included in a protocol, while stressing that this list is by no means either exhaustive or exclusive and that the items comprising it are not necessarily essential in every protocol and that dispositions not in this list may well be part of a protocol:

- A title describing the study purpose.
- The name, address, degrees, job title, and experience in epidemiology and in the specific study topics of the principal investigator and other study team members.
- The names, addresses and titles of subcontractors, where applicable.
- The name, address and titles of the person in charge of the automatic processing of study data, and the categories of staff responsible for actually processing the data and of those who will have access to it, even for quality control.
- A summary of any commitments or activities of members of the team responsible for the study that might be a source of conflicting interests, and the justification of the conditions in which their participation in the study remains possible without infringing these recommendations.
- Identity of the study funders and the justification of their financial involvement.
- A summary clearly explaining the objectives of the study, the main features of its design and strategy and the statistical analysis plan.
- The origin and nature of the personal data intended to be collected as well as the need for these data and their pertinence to the study objective.
- A statement of the research hypotheses and how they can be tested (and how accurately) by the methods set forth in the study protocol.
- If the study is a preliminary study as defined above, an explicit statement to this effect and an explanation of the reasons for which these particular study methods were adopted.
- A sufficiently complete review of the relevant literature, made and presented so that a third party can assess the context and significance of the proposed study and the methodological problems to be taken into account or given special consideration.
- The results of any pilot study already undertaken, or, if the study in question is a pilot study, the criteria according to which it will be decided to undertake a full-scale study after the pilot study.
- A complete and sufficiently precise description of the planned study methods, including its overall design and strategy and the planned procedures for selecting subjects and for entering and verifying data.
- Reference to the size of the sample population to be studied, including, where applicable, the reasons for the choice of this sample size. When such calculations are

impossible, the investigator must discuss the problem of the expected quantity of information. A sample size that is theoretically insufficient is not necessarily an obstacle to the performance of the study, because scientifically valid studies can be conducted, even with a small sample size; they help accumulate facts in time and space.

- The variables of interest chosen according to the study objectives, including especially an explanation of their limitations.
- A description of the methods used to gather all the data needed for the study, and the methods used for studying any biases.
- Description of the statistical methods used for data analysis, showing that these methods are appropriate for answering the questions the study seeks to answer; this must not, however, prevent the subsequent use of complementary methods.
- Description of the principal limitations inherent in or resulting from the study design, data source, and statistical methods.
- A description of the criteria used to interpret the study results and to assess their potential accuracy.
- A description of the methods used to inform subjects and to comply with their right to object to any data collection, except for any justified exceptions, and accepted by the data protection authority.
- A description of the procedures followed to protect subjects against any risks, for example, to protect their legal privacy rights, and the quality control procedures used to protect data confidentiality and integrity and to ensure the quality of data collection.
- A description of all possible risks that the study might involve for the subjects.
- A description of the quality control and verification procedures envisioned.
- The study schedule, including the starting date for data collection, the dates of the proposed control points and the completion date of the study.
- A description of the plans for communicating the study's results.
- A description of the plans for the filing of the data and other documents obtained or produced during the study, including an accurate description of the data and documents filed away and the criteria on the basis of which third parties will be allowed access to the data or documents.
- A complete and reasonably detailed assessment of the budget required for the entire study, including the publication phase.
- A statement of the individuals or entities who will have ownership of the study documents before and after these documents are classified and filed.
- Proof of the approval of the bodies entitled to issue authorizations and opinions for the performance of the study.

5.5 STUDY CONDUCT (4.7)

5.5.1 Adherence to the study protocol (4.7.1)

Any departure from the study protocol must be reported in writing, including a description of the reasons for the change, and in particular those related to the quality of the study or to a request from the funder or any other party involved. Insofar as is reasonable and depending on their importance and their nature, modifications to the study protocol should undergo the same formalities, opinions, authorizations and controls as the protocol itself.

Data collected in a study may legitimately be analyzed to evaluate hypotheses that were not explicitly formulated in the initial protocol, or for a secondary purpose different from that originally intended. In such cases a new protocol corresponding to the new analysis should be drawn up and, if possible, submitted for the same approvals as the initial protocol; at the very least all the documents and publications relating to the new analysis must mention the initial study.

5.5.2 Data collection and verification

Quality control of all data collected or obtained during an epidemiological study must be implemented as rapidly as possible, precisely and intelligibly, with the indication of the team member with the best knowledge of the circumstances and conditions in which the data in question were collected or obtained.

In this respect, the study protocol must include a sufficiently detailed description of the methods and procedures by which the data were collected or obtained. Any change in these procedures or methods, and any change in the filing of the data thus collected or obtained, must be stated in writing by the member of the study team on whose initiative the change was made, with a sufficiently detailed description of the reasons for the change, whatever they may be.

5.5.3 Analyses (4.7.2)

Any departure from the statistical methodology described in the study protocol must be expressly mentioned in any publication or presentation of the study results. This also applies when analyses not mentioned in the initial protocol are conducted, especially when they correspond to scientific objectives not mentioned in the initial protocol.

All analyses conducted during or as part of the study must be reported and sorted so that they can be identified, classified under relevant headings (according to the object of the study), used in accordance with the study objectives and found at all times to verify and evaluate them when necessary. This sorting may consist in any form of filing or temporary storage during the study conducive to the fulfillment of these objectives.

5.5.4 Quality control of the study (4.7.3)

Standard procedures

Standard procedures must be developed to guarantee the quality of the data collected, obtained, produced or published during or as part of an epidemiological study. These procedures must apply to the collection, validation and coding of data, to the evaluation of the error rates likely to affect the data, to the principal aspects of the statistical analysis, to

the methods used to analyse the material collected (chemical, pharmacological, etc.), and to the methods used to file and store the data and documents.

Quality controller for the study

If possible, a physical person, whose participation in the study is limited to this role alone, must be appointed by the principal investigator as quality controller for the entire study. As often as necessary and in keeping with the timetable and procedure defined in the study protocol, the quality controller must verify that the study is conducted in conformity with the study protocol and the applicable standard procedures and make any observations on these points that he or she considers necessary. The principal investigator must then reply in writing to the observations made by the quality controller. This reply must include a detailed description of the measures envisioned to remedy to the problems raised by the quality controller.

5.5.5 Filing and archiving data (4.7.4)

Contents of files or archives and access to them

During the study period, a filing plan, an index (by investigator, by material, study type and type of data exploitation) and when necessary because of the multiplicity of studies undertaken towards a single objective, a correspondence table must be prepared and accompany the filing of the aforesaid data, documents and more generally, materials collected, produced, analysed and obtained during an epidemiological study, including, when applicable, - for example in meta-analyses -, materials obtained from other teams.

The files from an epidemiological study must contain at least the following:

- the study protocol, together with any changes made to it;
- the overall report of the study results, if it exists, as well as all presentations, reports and articles related to the study;
- correspondence and other documents related to the study, including all correspondence and exchange of documents relating to the question of personal data protection;
- the computer file related to the study and any information required in order to understand and repeat the data processing operations used, in keeping with these Recommendations;
- copies of the questionnaires or any other data collection tools used during the study, together with all the notes taken by the researchers (particularly those who conducted interviews) and the computer print-outs (including the execution codes of all tables, graphs), analyses and interpretations contained in the final report; and copies of the publications or presentations of the study results.

These documents and data may be kept in any form, including electronic, that is likely to facilitate their subsequent utilization.

After study completion, personal data can be stored only in anonymized form that does not in any case allow the identification of individuals.

When the data and documents used during the study are no longer likely to be analyzed, evaluated, commented or used, even in other studies or meta-analyses, they may be stored

in archives, after a reasonable lapse of time, in keeping with applicable legal and regulatory provisions.

5.5.6 Access for purposes of reanalysis or validation (4.7.6)

Any interested physical or moral person should have access to the study documents for purposes of reanalysis or validation, on condition of:

- compliance with the applicable legal and regulatory provisions, especially those concerning the protection of personal data; any transmission of personal data must be in anonymized form.
- consideration of the interest of the study team members of in first (but not exclusive) publication or presentation of the results and the conclusions to which they lead;
- compliance with these Recommendations, especially the procedures of advance approval and prior validation;
- the written authorization of a moral body competent in the field covered by the study (panel of peers, i.e. experienced epidemiologists in the field concerned or, where applicable, specialists in other disciplines concerned by the study) having no vested interest in the study and approved by the principal investigator. This accord must be given only on the basis of an established protocol and specifying in particular: the status of the person requesting access, their competence and interests in the field of study concerned, their reasons for requesting access, what they expect to do with the findings of their re-analysis and how they intend to publish them;
- a guarantee that all the documents related to the re-analysis, including the original application for access to the data, will be communicated in full to any interested party or legal entity for discussion, subject to the principles of these Recommendations.

This rule shall apply regardless of whether or not the documents related to the study are filed or archived. It shall also apply to documents of studies that were discontinued.

5.6 PUBLICATION OF RESULTS (4.8)

5.6.1 Content of the presentation or publication

All presentations or publications of the results of epidemiological studies must, where appropriate, include the following information, unless it is readily available in another document that has already been published and is listed as a reference or is easily accessible to any interested party:

- identity of the study funders;
- dates at which the study was designed, begun, and completed;
- relevant information concerning the design of the study — including the type of survey, how the subjects were selected, the size of the sample population, the data collection and processing methods used, including methods to adjust for or control confounding factors and biases, statistical methodology and the choice of presentation of the results;

- the methods of informing subjects and compliance with their right to refuse to participate, or the justification of any failure to meet this obligation; insofar as possible, refusals to participate must be counted and the number mentioned;
- changes related to the study protocol and standard procedures, and in particular any changes likely to affect the results of the study presented;
- a synthesis of the overall results of the statistical analyses and whether the statistical associations shown were significant or not;
- any sources of bias and the way in which they were taken into account or corrected for;
- results of sensitivity analyses, describing the effects of any biases at the individual or group level;
- evaluation of the plausibility of the results of the study, particularly when pertinent on the biological level, and the biological mechanisms that may account for the results reported;
- consistency or inconsistency of the study results with those of other studies of the same topic;
- other factors that must be taken into account to place the results in perspective and interpret them in a balanced way;
- the precautions taken to avoid direct or indirect identification of the subjects;
- pertinent references.

Every precaution must be taken to ensure that the communication of the study results does not permit identification of the subjects.

When presenting the results of epidemiological studies, it is important to avoid too systematic, too understated or too overstated a presentation. Compliance with the principles and values set forth in these Recommendations should make it possible to avoid such errors and the problems they may cause.

All publications must be signed by the actual authors of the study, as a public sign of their joint and individual responsibility. In keeping with the rules of scientific publication, publications should be signed only by those who made a substantial contribution to the design of the study or the analysis and interpretation of the results and a substantial contribution to the drafting of the paper or its critical assessment. Furthermore, the version actually published should be submitted to their approval. It is the responsibility of each person who signs a paper to ensure that all the others who sign it fulfill these conditions and that no one who does fulfill them has been omitted. Participation in the raising of funds or the collection of data does not warrant mention as an author of the publication

5.6.2 Dissemination and other publication of the study results (4.8.1)

Intermediate results - Study discontinuation

The intermediate results of the study, i.e. the preliminary or partial findings, analyses and conclusions formulated by the members of the team responsible for the study prior to its completion, may be presented or published only subject to the advance approval procedures set forth above. Intermediate results must always be explicitly presented as such. In any

case, the intermediate results as well as the data, either raw or already treated, or the data, results, analyses and conclusions that can be derived from these intermediate results cannot be transmitted to a third party or used in other studies unless this transmission or use is expressly foreseen in the protocol and is expressly approved by the principal investigator.

In cases where the study is discontinued for any reason, the presentation or publication of any preliminary or partial results or conclusions from it may be presented or published subject to compliance with the procedures for advance approval described above. The data or results from a discontinued study must be identified as such in any subsequent publications or presentations.

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