

Ethics and observational studies in medical research: various rules in a common framework

Frédérique Claudot^{a,b,c}, Laywer, PhD; François Alla^{d,e}, MD, PhD; Jeanne Fresson^{f,g}, MD; Thierry Calvez^{h,i}, MD; Henry Coudane^a, MD, PhD; Catherine Bonaïti-Pellié^{j,k,g}, MD, PhD

a: Nancy-University, Faculty of Medicine, Department of Forensic Medicine and Health Law, Nancy, France;

b: University Hospital, Pole strategy, medical resources, Nancy, France;

c: Comité de protection des personnes Est III, Nancy, France

d: University Hospital, Epidemiology, Nancy, France;

e: Nancy-University, Faculty of Medicine, Public Health School, Nancy, France;

f: Maternité Régionale Universitaire, Epidemiology, Nancy, France

g: Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, Paris, France

h: INSERM, U720, Paris, F-75013 France;

i: Université Pierre et Marie Curie-Paris 6, UMR S720 Paris, F-75013 France;

j: INSERM, U535, Villejuif, F-94817 France

k: Univ Paris-Sud, IFR 69, UMR-S535, Villejuif, F-94817 France

Corresponding author:

François Alla, Epidémiologie, Hôpital Marin,

CHU de Nancy, C.O N°34, 54035 Nancy cedex, France.

f.alla@chu-nancy.fr

Abstract

Background: Research ethics have become universal in their principles through international agreements. The standardization of regulations facilitates the internationalization of research concerning drugs. However, in so-called observational studies (i.e. from data collected retrospectively or prospectively, obtained without any additional therapy or monitoring procedure), the modalities used for applying the main principles vary from one country to the other. This situation may entail problems for the conduct of multi-centric international studies, as well as for the publication of results if the authors and editors come from countries governed by different regulations. In particular, several French observational studies were rejected or retracted by United States peer reviewed journals, because their protocols have not been submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC).

Methods: national legislation case analysis

Results: In accordance with European regulation, French observational studies from data obtained without any additional therapy or monitoring procedure, do not need the approval of an IRB/IEC. Nevertheless, these researches are neither exempt from scientific opinion nor from ethical and legal authorization.

Conclusion: We wish to demonstrate through the study of this example that different bodies of law can provide equivalent levels of protection that respect the same ethical principles. Our purpose in writing this paper was to encourage public bodies, scientific journals, and researchers to gain a better understanding of the various sets of specific national regulations and to speak a common language.

Introduction

International rules for pharmacological research

Research ethics developed over the course of the 20th Century as a reaction to the discovery of scandalous conditions in which certain experiments on human beings were being carried out. Since then, respect for individual rights has become a constant concern, and its principles have become quasi-universal in research: respect for the dignity of individuals, respect for the integrity of their persons, for their personal autonomy through the rule of informed consent, for their privacy and their private life... These rights are protected by international agreements, such as the Helsinki Declaration **(1)**, which are translated into regulations for the protection of individuals and into the rules for good research practices on the level of each country. With regard to pharmacological research, important standardization work was carried out under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions. The principles and rules defined by the ICH have been adapted into national laws, for example, in Europe, by virtue of the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. According to the ICH, the objective of such harmonization is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health **(2)**. Unfortunately, this standardization applies only to drugs, which is only one of the fields of clinical research.

Non pharmacological research

There are many other kinds of research. We may mention evaluation trials without

medications (medical devices, for example), physiopathological researches, and epidemiological researches. Universal principles such as the Helsinki Declaration apply to all these other kinds of “non-pharmacological” research. However, the modalities of their application vary from one country to another. This situation may entail problems for the conduct of multi-centric international studies, as well as for the publication of results if the authors and editors come from countries governed by different regulations. This situation refers particularly to so-called observational studies, i.e. collected retrospectively or prospectively, from data obtained without any additional therapy or monitoring procedure.

Issue and objectives

In fact, as underlined in a recent editorial (3), observational studies that may have respected the laws in effect in the country where they were performed, were rejected by international journals because they did not respect the laws of the country where the journal is published. We wish to demonstrate through the study of an example from a European country that different national bodies of law can provide equivalent levels of protection that respect the same international ethical principles cited above. Our purpose in writing this article was to encourage public bodies, scientific journals, and researchers to gain a better understanding of the various sets of specific national regulations and to speak a common language.

The editorial, published in the American Journal of Respiratory and Critical Care Medicine, was entitled: "Do All Types of Human Research Need Ethics Committee Approval?" (3). This question was asked following the rejection or retraction by United States peer reviewed journals of several French observational studies, whose protocols have not been submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC). Basically, according to French law, consistent with a European directive (4), only biomedical research needs an approval from an IRB/IEC, called *Comité de protection des personnes* (CPP) in

France. Biomedical research is defined as research requiring intervention (like a treatment), or a constraint (for example a blood sample), not envisaged in the normal medical follow-up of the patient. On the contrary, research carried out on data from the usual management of the patient is not considered as biomedical research, but as observational research. This involves data obtained retrospectively (e.g. from medical records), *post hoc* analyses from data obtained for another goal (i.e. data obtained from patient usual care or from another research), or new prospective data. A questionnaire is not considered as an intervention on a person, with the exception of some questionnaires which could jeopardise psychological integrity (for example in the field of psychiatry).

These observational studies do not need the approval of a CPP. Nevertheless, in French legislation, consistent with a European directive (5), these observational researches are neither exempt from scientific opinion nor from ethical and legal authorization. Two national authorities, the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS) and the Commission nationale de l'informatique et des libertés (CNIL), are responsible for authorizing or rejecting entry (automated or not) of data identifying individuals, directly or not.

In the first example cited in the editorial (3), the authors wrote in the methods section “*All tests were performed for clinical purposes using routine techniques, thus ethical approval was not sought.*” This statement is not in accordance with the French legislation. Indeed, the approval of an IRB/IEC is effectively not necessary for this type of study in France, but it compulsorily requires an ethical opinion because of the use of personal health data. Thus, since the authors had not solicited those two national bodies, they would have complied with neither international ethical principles nor French law; in this case, the editor was right not to accept this paper.

International principles and rules concerning observational research

The Helsinki declaration

More generally, this raises the question of compliance of French law regarding observational research with international benchmarks, first and foremost with the Helsinki Declaration **(1)**. This question is especially important for French researchers, since the Helsinki Declaration is the ethical standard for the International Committee of Medical Journal Editors: “*When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000*” **(6)**.

Indeed, the Helsinki Declaration applies to all types of medical research, including observational research: “*Medical research involving human subjects includes research on identifiable human material or identifiable data.*” It is thus clear that the opinion of an ethics committee is also required for research on identifiable data. Thus, a literal application of these principles may lead to the rejection of articles that do respect the applicable French law! However, the Helsinki Declaration does not specify the *nature* of this ethics committee. For medical drug research, the international standard, drafted by the ICH, is the IRB/IEC. These committees were defined as groups that have been formally designated to approve, monitor, and review biomedical and behavioural research involving humans with the aim to protect the rights and welfare of the subjects. In the United States, the Food and Drug Administration (FDA) and Health and Human Services (HHS) regulations have empowered IRBs to approve, require modifications in (to secure approval), or disapprove research. An IRB performs critical oversight functions for research conducted on human subjects that are scientific,

ethical, and regulatory.

The Council for International Organizations of Medical Sciences (CIOMS)

For other types of research, it is not univocal; the main international standards were drafted by the CIOMS in collaboration with the World Health Organization (WHO). In particular, the CIOMS published International Ethical Guidelines for Biomedical Research Involving Human Subjects (7). This document indicates that all research must benefit from both scientific and ethical expertise: *“All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. (...) Ethical review committees may function at the institutional, local, regional, or national level, and in some cases at the international level. (...) The ethical review committee is responsible for safeguarding the rights, safety, and well-being of the research subjects. Scientific review and ethical review cannot be separated: scientifically unsound research involving humans as subjects is ipso facto unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of subjects` and researchers` time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must either carry out a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound.”* Thus, other models besides the IRB/IEC can be valid for observational research.

What is the French system?

As mentioned in the introduction, observational studies require the advice of the CCTIRS and the authorization of the CNIL for the treatment of personal health data. The only studies which are exempt from this rule are those that are conducted by professional health workers

on their own patients, provided that data are not transmitted to anyone else (monocentric studies), or the studies in which data are totally anonymous (i.e. without any identifier, even a number). In all other cases, persons included in the study must be personally informed through a written document of the objectives of the study and on the treatment of data, as well as on their right to object, of access and of rectification. In retrospective studies, it may happen that persons are deceased or impossible to re-contact. In such a case, it is possible to obtain a derogation to the duty of information.

The CNIL, an independent national ethical committee protecting human rights

In 1978, an independent national administrative authority, the CNIL was created to look after the protection of personal data and privacy. Among other things, its role is to authorize or reject entry (usually computerized or intended for computerization) of data identifying individuals. More particularly, in terms of ethics, Article 1 of the Law of 1978 says: “Information technology should be at the service of each citizen. (...) It shall not violate human identity, human rights, privacy, or individual or public liberties.” **(8)** The CNIL has 17 members. Twelve of them are elected by the assemblies (National Assembly and Senate) or the highest French courts (Supreme Court, State Council, Public Finance Court, Economic and Social Council) to the jurisdiction of which they belong. The Commission does not receive instructions from any authority. It is responsible for informing people of their rights and obligations, authorizing "at risk" treatments such as handling of personal health care data, and ensuring compliance with the law by monitoring information technology applications. It uses its monitoring and investigative powers to file complaints. Additionally, it oversees information systems, ensuring that all precautions are taken to avoid data being altered or shared with unauthorized people. The CNIL may implement various graduated sanctions: warnings, notices, fines up to € 300,000, or injunctions to stop treatment.

The CCTIRS, a committee providing expertise on methodological aspects

With regard to research in the human health field, the second committee, the CCTIRS was set up in 1994. This committee is made up of 15 members qualified in the field of research in health care, in epidemiology, genetics and biostatistics. Its role is to give the CNIL advice on the reasons for the handling of personal data and on their justification with respect to the goal of research. Its expertise focuses on methodological aspects. All observational research projects must obtain the approval of this committee prior to receiving authorization from the CNIL. In 2007, the committee reviewed 608 protocols. Only 165 (27.1%) were accepted without revision, 241 (39.6%) were accepted with minor modifications, 150 (24.7%) were accepted with major revision and re-review, and 11 (1.8%) were definitely rejected. A non negligible number of protocols, 41 (6.7%), were not given a formal advice for various reasons, but most of the time because the application was not really a research protocol and the committee considered that it did not come under its responsibility.

Conclusion

Thus, the observational research regulation is very stringent in France and even goes beyond the international benchmarks. The IRB/IEC model, drafted and implemented in the context of the assessment and authorization of medical drugs, is perhaps not the most appropriate for observational research. The International Epidemiological Association (IEA), in the current draft of good epidemiological practices, suggests that "*some epidemiologic research to be removed from ethics committees and instead be approved by people versed in data protection*" (9), thus a model similar to the French one. Some French researchers may find the system somewhat complex and may be tempted to escape its requirements. We strongly encourage them to take all necessary regulatory steps and to specify this in their method. If

necessary, the French IRB/IEC (CPP) could determine that a study does / or does not require its approval. Under these conditions, there is, in theory, no ethical obstacle to international publication. Finally, we can see through this example how important it is to establish standardization between countries or, at least, to speak a common language concerning all categories of biomedical research in human subjects (with or without health products, whether interventional or observational), and not only interventional clinical trials of medicinal products, as recently emphasized during a European Commission-European Medicines Agency Conference (10).

References

1. World medical association (WMA). Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. [Online]. 2004 October 9 [cited 2007 July 10].

Available

from: <http://www.wma.net/e/policy/b3.htm>

2. ICH. Official web site. [Online]. [cited 2008 February 3]. Available from:

<http://www.ich.org>

3. Lemaire F. Do all types of human research need ethics committee approval? *Am J Respir Crit Care Med.* 2006;174(4):363-4.

4. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

5. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

6. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. [Online]. February 2006. [cited 2007 July 10]. Available from:
<http://www.icmje.org/>
7. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects. [Online]. 2002 [cited 2007 July 10]. Available from: http://www.cioms.ch/frame_guidelines_nov_2002.htm
8. Act n°78-17 of 6 January 1978 on Data Processing, Data Files and Individual Liberties (Amended by the Act of 6 August 2004 relating to the protection of individuals with regard to the processing of personal data). [Online]. 2004 [cited 2007 July 10]. Available from:
www.cnil.fr/fileadmin/documents/uk/78-17VA.pdf
9. IEA. Good epidemiological practice (GEP) conduct in epidemiologic research [Online]. 2007 January 9 [cited 2007 July 10]. Available from:
<http://www.dundee.ac.uk/iea/GEP07.htm>
10. European Commission-European Medicines Agency. Report on the Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future. [Online]. 2007 November 30 [cited 2008 February 3]. Available from:
<http://www.emea.europa.eu/pdfs/conferenceflyers/clinicaltrials/report.pdf>