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Ethical guidelines in research: when *more* is not necessarily *better*...

The prevention of disease. What a laudable goal! Could this goal become unattainable because of unreasonable administrative constraints on research? I'm afraid the answer may be yes, unless we act now to rectify the situation.

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I have been a professor/researcher in the field of cancer epidemiology for almost ten years. I am interested in better understanding the causes of cancer and the possibilities for prevention. Epidemiologic research has already succeeded in saving millions of lives. As reflected in the cinema of the 1960s, smoking used to be perceived as a desirable activity. It was the same for over-exposure to the sun. The use of heavy doses of radiation for diagnostic purposes is another example. The identification and prevention of these factors, and many others, have had a marked effect on the health of populations. Must we stop there? Certainly not! More than ever, epidemiologic research makes use of methodological tools that should allow us to advance knowledge in the area of prevention. It is essential that we undertake studies that are solid and based on large numbers, often thousands, of individuals. In order to do this, we have to gather precise data, historical as well as current, concerning these individuals. The catch? There are many obstacles to overcome before we can contact these potential subjects, that is, the obstacles created by ethics committees. Let's make this perfectly clear. The application of ethical standards is essential to ensure that the fundamental rights of subjects are respected. During World War II, horrible abuse was committed in the course of unacceptable research conducted on subjects without their consent. This led, in 1964, to the Declaration of Helsinki, which has ever since defined the ethical principles of health research concerning human subjects. Unfortunately, even recently, health research has sometimes been tainted by the practices of some researchers who do not respect the scientific and ethical protocols that shape their research. Even though extremely rare, these situations have led ethics committees to formulate very restrictive guidelines in order to protect

subjects and to reassure the population. The interpretation of basic ethical principles, and especially the guidelines that are derived from them, are largely arbitrary, as we will see here. Now we are not only preventing theoretical abuse caused by research; we are also preventing epidemiologic research from progressing, and we are depriving the population of data that is crucial for the improvement of their health. We are at the point of over-protecting the subject to the detriment of beneficial research. And in this case, it is clear that "more" is not necessarily "better".

This opinion piece is meant as a simple description of the ethical practices that I have encountered during the past decade in the course of my research in Montreal. The report is, unfortunately, very grim. Despite the good intentions behind the application of ethical standards, the damage done to etiologic research is enormous. The situation has deteriorated throughout the years to a critical threshold. I am happy to be able to address a readership including administrators from the health care system. The alarm has sounded; we have to act now...

18 different recruitment protocols

Ethics committees do not agree on what is ethically correct or incorrect when it comes to epidemiologic research. In Montreal, for example, each of the 18 hospital and institutional ethics committees insisted that I operate differently for the same study. What is ethically correct for one ethics committee is not correct for any other committee. I have to apply 18 different recruitment protocols, and the consent form required by one committee is unacceptable to the others. Yet, isn't there only a single Truth.... rather than 18 Truths? To counter this problem, the MSSS recently tried to implement a system permitting the nomination of a "competent" ethics committee; following a consultation, this group would be charged with devising a single ethical procedure for all the ethics committees implicated in a single study simultaneously being conducted in many hospitals. What a relief for those involved in multi-center studies, which are often the norm in epidemiology! However, many ethics committees refused to participate. It was out of the question that one committee could decide for another. Each one insisted on keeping complete control over its decisions. We therefore find ourselves back where we started, with flagrant proof that ethics committees want to continue to apply their recommendations as they wish, founded on their own interpretations, highly variable, of the notion of risk.

A multiplicity of intervenors

In order to better understand the situation, let's take as a concrete example a study that I am presently conducting in Montreal. This study requires the recruitment of 1500 patients recently diagnosed with cancer, and 1500 control subjects who do not have this disease. These persons must be representative of the same base population. I must identify the potential

subjects, patients as well as controls, according to very precise eligibility criteria. I then invite them to take part in an interview during which I question them on many aspects of their life experience, such as their dietary habits, lifestyle, chemical exposures at work or elsewhere, and others. This scientific approach implies several crucial steps. I have to identify the subjects eligible for the study, be in a position to invite them to participate, and strictly apply the study protocol approved by my scientific peers and by the granting agency, in order for the study results to be valid. Each of these steps calls upon different intervenors, and each of these has the power to influence the progress of the study and its scientific quality.

1. *Institutional review board* – The university with which I am affiliated must first of all rule on all ethical aspects of the project. An institutional review board examines in detail the study protocol and all the related documentation, and makes specific recommendations concerning the study protocol and the consent forms to be used with the subjects. Following a series of useful exchanges, this committee issues me a certificate of ethics approval along with ethical guidelines; this allows the university to then transfer the funds provided by the granting agency to initiate the study.
2. *Hospital ethics committees* – My study requires that patients be recruited from many hospitals, which is the case for population-based epidemiological studies. I must therefore apply independently, with distinct application forms, in each hospital in order to obtain approval to carry out my study there. It appears strange, yet the recommendations of the institutional review board and the other hospital ethics committees are completely ignored. We start from zero with each committee. No one is interested in what the other committees have suggested concerning the method of identifying patients, obtaining the approval of the treating physician, the approach to the patient inviting participation, the study documents, or the consent forms. The consent form required is different for each hospital, even though each form is devised with the same objective in mind, i.e., to ensure that the participants' fundamental rights are respected throughout the project. Another strange fact is that the committees require me to use different consent forms for the control subjects. I therefore have many different versions of these forms for a single group of controls who were not recruited in the hospitals. Should I pick one at random to use?
3. *Hospital scientific committee* – Many hospitals evaluate the scientific value of projects that will take place on their premises. This procedure is certainly appropriate in the context of a project that was not evaluated and approved at the outset by scientific peers. On the other hand, we have to question seriously the relevance of a scientific re-evaluation by the hospital of a project already approved by an accredited granting agency. The latter has already approved the

scientific value and the protocol of the project in detail, by calling upon many researchers (who are often recruited nationally or internationally) in order to provide specific expertise in the area of the study. Is a hospital scientific committee really in a position to modify a scientific protocol, one which has already been approved by the panel of experts assembled by the granting agency, based on specific expertise and absence of conflict of interest?

4. *Hospital management committee* – This committee evaluates the costs and the needs, in services and hospital personnel, that might be engendered by the research project. Financial spin-offs from the project can be taken over by the researcher, which is completely justified.
5. *Director of Professional Services (DPS)* – Article 19.2 of the law concerning health and social services establishes that the DPS of an institution has the right to authorize a professional to take cognizance of the file of a user for the purposes of research. In this case, the DPS is consenting in place of users with whom it would be difficult to communicate to request their consent. This authorization is crucial for epidemiologic research, because it allows the researcher to identify the subjects potentially eligible for the study, and to determine diagnostic parameters. According to the law, the DPS can refuse authorization if he or she believes that the project does not respect ethical standards or does not meet generally recognized standards of scientific integrity. In any case, in spite of the positive recommendations concerning my study from hospital ethics committees after detailed examination, some DPSs rejected, without explanation, these recommendations. It was therefore impossible to implement my research project in these hospitals.
6. *Treating physician* – Many epidemiologic approaches require the recruitment to a study of subjects newly diagnosed with a disease. Systematically, ethics committees request that treating physicians act as intermediaries between patients and the researcher. The method of approval of the treating physician recommended by a committee can take several forms:

Approach #1 – The treating physician must recruit the patient for the study him- or herself. The physician must keep our study in mind, verify that the patient meets the eligibility criteria, present the study to the patient, respond to questions the patient might have concerning the study, have the patient sign the consent forms, and return them to the researcher. Most doctors simply cannot take on these tasks, over and above their clinical activities. Furthermore, this approach carries with it certain ethical risks. Most of the time, the treating physician is not directly involved in the study and is not therefore in a position to respond adequately to

questions, which is a necessary condition for obtaining informed consent from the subject. Moreover, the treating physician may choose not to present a study from an external group of researchers, preferring to introduce another study in which he, or perhaps one of his colleagues, is participating. This approach, which we have tried to use but without success, inevitably brings with it a methodologic bias, because most of the eligible subjects will not be invited to participate in the study. In very rare circumstances, it is desirable that the treating physician inform us that he prefers that we not approach a particular patient, for a very precise reason (psychological difficulties, for example). But a unilateral recommendation that renders the treating physicians, as many as 100 for one study, responsible for the recruitment of patients, makes it impossible to undertake etiological epidemiologic research.

Approach # 2 – The treating physician must give us written authorization before we can invite each of his patients to participate. This is the approach preferred by the ethics committees. We have tried to implement this approach, but without success. We receive only a small fraction of the authorizations from the physicians, through lack of time. The sample of patients recruited this way for the study is not representative of the totality of the patients, causing the study to be biased.

Approach # 3 – The physician must inform us only if he wishes that we not approach a patient who is eligible for the study. This way of proceeding is the only one that has proved functional, because it leaves up to the researcher the responsibility for the steps in recruiting patients, all the while allowing the doctor to advise us not to approach a patient, if he judges it necessary.

When ethics committees are presented with evidence that the treating physician cannot act as a functional intermediary between the researcher and the patient, they sometimes recommend that another member of the hospital staff, a nurse, for example, act as a replacement or representative of the physician. It is clear that this does not work, either, for the same reasons as for the physicians.

In the past, we have been contacted by patients who were extremely upset because they could not take part in a study that they learned about through another patient, and that they judged to be important. In fact, it was impossible to invite them to participate in our study because their physicians did not give us their approval, or because the doctors did not inform their patients of the study, whether from lack of time or other reasons. The questioning of such a patient is nevertheless legitimate: how is it

that someone (here, the treating physician) who is not his legal representative, has the right to make, for the patient, the decision to participate or not in a research project? Why can patients not decide for themselves something which is their concern above all? Doesn't this approach interfere with fundamental rights? Will the patient's treating physician continue to act, one year or five years later, or perhaps forever, without any time limit, as their intermediary for all types of research?

Some physicians push even farther their power to prevent their patients from participating in a study, for reasons other than medical. One doctor did not believe the hypothesis of the study (which was scientifically supported by peers) and would not allow any of his patients to be approached. Another feared a patient would initiate a lawsuit, if he learned that his doctor had given us authorization to approach him. He subsequently incited all his colleagues to withhold authorization for their patients.

7. *Medical department head* – certain committees require us to obtain authorization from the heads of the departments concerned before beginning a study in a hospital. The department head may favour certain projects over others that he judges to be similar, and to ensure that patients are not over-solicited for research projects.
8. *Patients* – Patients often wish to understand the causes of their disease. They are also ready to help with research, in the hope that others may be spared such an experience. In Montreal, once the seven preceding steps have been gone through (that is, ethics committees, authorization of the department head, the treating physician, etc.), more than 85% of the patients that we are able to invite to participate, accept. This suggests that the patients themselves are very favourable to research and that it is wrong to build a system that unduly restricts their access to research activities.

Unacceptable delays

Unfortunately, management of the ethical aspects of epidemiologic research on cancer is more difficult in Quebec than elsewhere. In fact, the Fichier des tumeurs du Québec, which registers all new diagnoses of malignant tumors, has a delay of approximately three years from the actual dates of diagnosis. It cannot, therefore, be used to identify new cases of cancer for epidemiologic studies. This situation is notably different from that in other Canadian provinces, such as Ontario, Manitoba, or British Columbia, where a central registry allows identification of new patients with only a few weeks' delay. This means that epidemiological research in Quebec is extremely difficult and expensive, and in the end hardly competitive nationally or internationally, because we have to identify eligible patients for our studies one by one, in each hospital in the study area.

To sum up, if we make a list of all the vulnerable points between the funding of an epidemiologic study (judged to be of high priority) and the recruitment of subjects for such a study, the result is frankly disturbing. Let's take, as a concrete example, the study that I am currently conducting in Montreal on the environmental causes of diseases of the prostate. In total, 3 universities, 15 hospitals, 15 hospital management committees, 15 department heads, 10 ethics committees, 10 scientific committees, 10 DPSs, and 120 treating physicians are involved. Each one of these intervenors has the power to allow or to refuse the researcher permission to recruit the 1500 patients and 1500 controls necessary to conduct the study adequately.

The implications: two and a half years of full-time work by the team of researchers, including meetings with numerous doctors and committees, unceasing written correspondence, negotiations, explanations, etc., with the impression that we are starting from zero every time in order to convince every one of these intervenors of the importance of the study, and of the fact that it must be undertaken in such a way as to maintain scientific rigor. Is this really what the population wants? The risk that we are running now is not abuse resulting from research. Rather, it is the danger that research is becoming for all practical purposes impossible, as a result of the application of too restrictive principles of basic ethics.

Ethical issues in epidemiology

Epidemiology remains a discipline presenting particular issues from the point of view of ethics. Unfortunately, a framework of standards allowing us to understand and manage ethical aspects in this context does not exist. The committees charged with making decisions almost always, therefore, refer to standards applicable in related sciences, notably clinical research, which deals with completely different ethical and methodological issues. For example, clinical research often makes use of recruitment of patients by the treating physician or his colleagues. Furthermore, this type of research is not necessarily based on recruitment of subjects who are representative of the base population.

Very recently, the Interagency Advisory Panel on Research Ethics presented a proposal for the second edition of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*. This new edition contains many improvements and clarifications, and provides a framework of standards for research involving aboriginal people, qualitative research, clinical trials, human tissues, and human genetics. Once again, we find nothing here concerning epidemiologic research. As in the first edition of 1998, there is nothing offered to guide ethics committees in their future evaluations and recommendations concerning epidemiologic studies. How is it that nothing was done, in the context of a major revision, to provide epidemiologists with a framework of standards based on expertise in ethics and in epidemiology? This important omission was officially noted by

epidemiologists at the time of the pan-Canadian consultative process concerning the new proposal. We were told in response that, if we wished the new edition to contain a section covering ethical issues relative to epidemiology, we would have to write it ourselves. I do not share this opinion. Epidemiology should have been treated initially by the consultative group in the same manner as the other disciplines, by calling upon a group of epidemiologists, ethicists, jurists, physicians, patients, and others. This would have permitted the establishment of a concrete proposal, one which could be openly commented upon by the appropriate scientific community. This omission might possibly result from a lack of resources on the part of the revision committee; if so, this absolutely must be remedied.

It is not advisable in ethics to project an image of laxity, even if this concept is completely subjective. The stricter your neighbour is, the more you feel you must raise the bar as high, or even higher, for yourself. The more restrictive we are, the more we have the impression that we protect the population, and the better we feel. This debatable idea is at the origin of excessive restrictions on the part of ethics committees. These committees call upon the notion of protection, but also of control. Faced with ethics committees, the researcher who wishes to maintain scientific rigor often has the feeling that he is considered guilty, and that he therefore has to prove his innocence.

Unfortunately, the current ethical climate has important repercussions for research. First of all, it is injurious to the population, because it prevents important studies from being undertaken. All my experienced epidemiologist colleagues, like myself, are losing interest in conducting new population-based studies in which the science is put in question by unreasonable demands from ethics committees. We are left with having to recruit subjects for studies that risk being seriously scientifically compromised because of the requirements of ethics committees. Is that really ethical?

EPIGRAPH

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