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GOOD EPIDEMIOLOGICAL PRACTICE (GEP) PROPER CONDUCT IN EPIDEMIOLOGIC RESEARCH¹

**Prepared for the IEA Brazil meeting April, 2007 by Jorn Olsen
And we invite comments for all IEA members**

BACKGROUND

Research is ideally an activity devoted to the exploration of the laws of nature driven only by the desire to know the truth. In the real world other factors interfere with this ideal aspiration and produce “conflicts of interest”. Research often has to be funded, carried out and published and researchers like to promote their reputations. Research is done in an ambience of many competing issues.

Research results in public health should serve the public good but results may not be welcomed by all or much less please all. For example, findings of serious side effects of a given drug will be welcomed by those taking the drug but may seriously reduce the expected profits of the manufacturer. Or a promising hypothesis may not be supported by data. Opposing forces may lead the researcher astray from altruistically seeking truth and may even lead to violation of research ethical codes .

A Good Epidemiology Practice (GEP) paper written by a scientific organization will not prevent this but a GEP paper under discussion and used for educating young epidemiologists may prevent some unethical research and improper behavior. We need a code of practice when we do research and when we take part in the process of evaluating research and evaluating each other.

We also need arguments to make sure we obtain a reasonable balance between the opportunities for doing legitimate research of importance to public health. The aim of this document is to encourage a proper collegial conduct and to show how research of good quality may be done. The document has no legal status. It is a set of guidelines recommended by the IEA for the conduct of epidemiologic research and collegial behavior.

We recognize that guidelines should change with time as new problems and opportunities emerge. A document on GEP is meant to be regularly re-visited. This is especially important for a document that covers epidemiology in all parts of the world.

¹ This document is based upon a document developed for the IEA-European Federation. The documentation has been substantially modified and is now being considered for approval by all IEA councilors.

The Role of Ethics Committees

The IEA fully respects that research must rest upon accepted ethical standards but we advocate that these standards are applied in a way that take into consideration the balance between the risk involved in the research and the benefits provided by high quality research. Poor research may do more harm than no research. In other words, the quality of research has an ethical dimension.

Much of what epidemiologists do is to observe without involving risky, invasive procedures, to record and to make inferences based on the observations. Some of what we do may provide information which run counter to the aims of those doing harm. Ethical appraisals are often time consuming and costly and may pose serious threats to the validity of the studies that pass these committees. Experience has shown that ethical standards vary widely between different committees and large multicentre studies must follow procedures that are accepted by all committees thereby eliminating essential methodological requirements. We have, over a short time period in many countries, gone from almost no rules to very strict rules, and in some cases these rules are too strict for valid research.

The development of the practice for ethics appraisal of research has seldom involved epidemiologists. Rules have been made to regulate clinical randomized trials with invasive procedures and often major economic cost implications for the firms that produce the drugs to be tested. Although only a small part of epidemiologic research falls in this category, other epidemiologic research has often been subject to the same set of evaluation criteria. Most of epidemiologic research is “observational” based upon already existing data, data that are collected by means of non-invasive procedures or data that do require low risk procedures. It is unreasonable to treat all protocols alike without taking risk and benefits into consideration.

We argue that the benefits of research should be weighed against the risks of taking part in research which in many studies do not go beyond that of unwanted disclosure of personal data. We hope that consent to research can be given in a broad sense and without repeated consents in studies with repeated analyses over time. We expect bureaucratic procedures to be more streamlined, especially for research that involves several regions and thus a multiplicity of ethics committees. We suggest some epidemiologic research to be removed from ethics committees and instead be approved by people versed in data protection.

We know that researchers have violated important ethical standards but such examples should not lead to undue paternalism and bureaucratic obstacles that absorb unreasonable amounts of time and resources and impoverish epidemiological research.

ETHICAL PRINCIPLES OF RESEARCH

There are four general ethical principles for research:

- . • Autonomy (Respect for individual rights)
- . • Beneficence (Do good)
- . • Non-maleficence (Do no harm)
- . • Justice

Although these principles are well accepted, they must be seen in a broader context. Research is needed because people have the right to know about hazards to their health and to make evidence-based choices concerning treatment and prevention. From an ethical point of view, no research may occasionally be a better alternative to some research, but this is not the usual case. There are many epidemiologic research projects for which the ethical concerns for not doing the study are far greater than for doing the study.

The quality of research should be good. Bad research may lead to wrong decisions that may have profound impact on people's health. We accept that the absolute truth is an unreachable goal but it should never the less be the goal to pursue when it is possible without violating ethical principles.

Respect for Individuals

Respect for individuals in research leads to accepting individuals right to refuse to take part in research; to be informed about the research subject and to be in a position where he or she can make up their own mind based upon the best possible information. The principle of informed consent rests on the principle of autonomy and respect for people who take part in research. Written informed consent should be obtained when the research involves risks and it should not primarily be obtained because it protects the researcher against claims for compensation if something goes wrong. Formal written consent seems unjustified if the research is done in settings that pose no threat to the potential participants, when it is stated that taking part is voluntary and it is obvious that no benefits are at risk of being lost if potential participants refuse to take part in the research, . Situations like these are often seen in studies based on self-administered questionnaires or telephone interviews where providing the data is giving de facto oral consent. There may also be situations where informed consent is impossible, difficult, or even unethical to obtain. There may even be situations where requiring specific information poses a threat to the participants and the validity of research, for example, in the use of already existing data.

The early guidelines of the Council for International Organizations of Medical Sciences (CIOMS) state that: http://www.cioms.ch/frame_guidelines_nov_2002.htm

Informed consent is consent given 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 includes three components:

1. Information. There should be adequate disclosure of information enabling the potential participant in research to make an informed choice.

There may, however, be a situation where it is justified that consent is given to a more general research purpose. In a case control study the disclosure of the specific hypothesis may make it impossible to get reliable recall data and in much of contemporary inductive genetic research the meaning of being informed about the aims of the study is not clear since these aims are very broad and change rapidly with new research findings.

2. Understanding. The individual should have the ability to digest and comprehend what he or she is told and to make a reasoned choice based on that information. Experience shows this ideal is difficult to achieve.

Too much and too detailed information may be given mainly to protect the researcher and his or her place of work. Understanding the main ideas and risks may be more important than being informed about all scientific details.

Consent. There should be a voluntary decision or agreement on the part of a capable person.

Research participants have the right to refuse to take part in a study but they also have the right to accept. As a general rule only research ethics committees or similar authorities may deny participants the right to choose for themselves whether they will take part in the research or not and they should exercise that right with great caution. It is especially important that people who may be responsible for the potential harmful exposures under study cannot deny the exposed people the opportunity to have the possible health effect of the exposure studied.

Beneficence, non-maleficence and justice may all be involved when considering whether subjects should be informed about all aspects of a study. In general, sufficient information must be given so that, when the interview or examination is completed, or when the research results are published, participants do not feel they have been misled. Information was insufficient if the participants at that stage regret they participated and think they would have made any other decisions had they been better informed.

Participants must have the right to withdraw their consent at any time during the study without being obliged to give any reasons for doing so. Non-participation or withdrawal of consent should never result in disadvantage for these individuals. Informed consent should be given freely without external pressure and without unreasonable inducements. There should always be an assessment of what incentives, if any, should be offered to potential respondents for participating in the study. Although the distinction is not clear-cut, a balance between reasonable reimbursements, such as travel costs, and unreasonable remuneration must be found.

Use of incentives that include more than actual costs is acceptable only in studies that carry no risk for the participants. In the clinical setting, where patients may not feel free to refuse a

request from their doctor to take part in a study, mechanisms to counteract undue influence must be set up, such as letting an outside person give the information or to wait until the patient is back in his/her own environment to ask for consent.

Although people have the right to say no, it should be possible to try to contact people who do not respond to an invitation at least once and in most situations twice.

Consent should not be required for use of information in the public domain, although countries and communities differ in their definition of what type of information about citizens is regarded as public. Data gathered for administrative purposes do not require consent from the subjects if getting consent could cause undue concerns, be impractical or too expensive. This type of research requires, however, that standards of data protection are followed to reduce all possible risks of disclosure of personal data.

Research ethics committees and other appropriate authorities should set the conditions for setting up biological research banks. If the samples are to be used for research not covered by the original consent, an ethics committee should decide under which conditions renewed consent is needed.

The research ethics committee or similar authority could, under special conditions, be given consent for children and other individuals who are temporarily or permanently unable to give informed consent by themselves.

It has been suggested that research data should be made available to the participants but there are some caveats to this principle. It could induce a threat to data security and requires a means of checking a person's identity beyond doubt. Furthermore, research tests are usually not of the same quality as diagnostic tests so providing uncertain data may do more harm than good.

Do Good, Do No Harm

Individuals have the right to choose between different preventive and therapeutic actions. To use this right they need to know about health hazards related to the different procedures in order to obtain optimal treatment in the health care system. Without research they cannot exercise these rights. One important aim of epidemiological research is to improve people's opportunities for making choices that will improve their health.

The most basic ethical principle is the moral obligation to cause no harm, whether physical or psychological, to the people who participate in epidemiological research. Although the risk of harm to those who participate in an epidemiological investigation is usually minimal, most people who take part in public health epidemiological research gain no personal benefit and often do not have a disease that needs treatment. In recognition of this altruism, people who take part in research should be treated well and with respect. Important findings from the research should, therefore, also be made available in an understandable form. A study may reveal information on individuals of importance and value for

these individuals alone. Such data should be made available for the participants. In research that involves no risky invasive procedures, the greatest risk to individuals is a disclosure of personal data that could be misused by the media, an employee, an insurance company or someone else.

RULES FOR GOOD RESEARCH BEHAVIOR

While data collection and recruitment of volunteers to research in many countries fall under legal procedures, there are many other areas of activities that are not guided by legal principles. In the following we present IEA guidelines for these activities under the headings: working with personal data, data documentation, publication, exercise of judgment. The list should be seen as a starting point to which new elements may be added.

Working with Personal Data

Working with personal data donated by participants to research is a privilege that should be honored by making the best possible scientific use of data and by making sure personal data are kept confidential.

Do not work with data that have overt personal identifiers. Data with overt personal identifiers are only needed during data collection and in part of the data cleaning process. Use a study-specific running number to identify your data and keep the link between overt personal identifiers (like names, addresses, phone numbers, social security numbers) locked in a safe with access limited to the person responsible for data security. This person should also make sure that all back-up copies are kept safe. After the study is over, data should be kept in a safe for the time period required by law to document published results. Exchange and sharing of data or reuse of existing data will usually require additional permissions from the relevant authorities.

Data analyses should be done in designated areas where doors and windows can be locked.

Do not send personal data by ordinary mail or in any electronic form unless data are encrypted. Data should be sent by personal courier or as recommended/special delivery mail.

As a researcher you are bound by professional secrecy. You must not reveal personal information you obtain by having access to research data to anyone outside the scientific research team. All participants in the project should sign a contract of professional secrecy and should agree in writing to strictly adhere to the national rules set for working with data. The principle investigator is responsible for making sure all members of the team are aware of these rules.

Identifiable personal data should never be stored on computers outside the research establishments and the files containing personal identifiers (name, security numbers, addresses, telephone numbers etc) should be stored in locked cabinets or rooms separated from the data used for analysis. Back up copies must be subject to the same degree of data security and personal data should only be sent from one place to another by secure methods.

The people responsible for working with data should be identified throughout the study period. They are responsible for the legal conditions being followed and the implementation of good practice rules.

Publication of data should only be in the form of anonymous tables where no individual can be identified.

Epidemiologists often use personal data and people's right to privacy must be respected. Working with personal data is a privilege that calls for a high degree of data protection, especially in situations where data are used without personal consent. Over and above the requirements set up by the data protection agencies, epidemiologists should set up a working standard that secures as little risk of disclosure of personal information as possible.

We encourage each country to set up standards for data protection for all research organizations that have access to personal data, since unintended disclosure of personal data can harm individuals. Disclosure of personal data is a violation of the trust that must exist between the epidemiologists and the people who take part in research and a violation of this agreement may impair future options for other researchers even in situations where none of the participants suffered any harm.

Premature publication should be avoided, and particular care should be taken to avoid publication of data that may lead to discrimination against vulnerable groups in society. Publication of unfavorable data from small vulnerable groups may stigmatize these groups and cause harm.

Data Documentation

Data documentation includes all phases of the study, from its planning, conduct and to its publication. The research protocol is a key document to obtain good documentation.

The Research Protocol and Conduct of a Study

The research protocol is the cornerstone of an epidemiological research project, where the purpose of the study, the hypotheses, the design, the source population, and the planned analyses are described. Administrative issues, ethical considerations and possible problems and limitations are also addressed in the protocol.

The primary objectives of the protocol are to:

1. justify the need for the study - i.e., why the study should be conducted, given the current state of knowledge;
2. demonstrate the appropriateness of the proposed methods for testing the stated hypothesis;
3. demonstrate the feasibility of doing the study as proposed - i.e., that the study can be completed successfully in the specified time and with the available resources;
4. demonstrate that the investigator(s) have the ability and skills to conduct the proposed study and are aware of all limitations in the design.

The protocol serves as:

- an instrument to justify the project when applying for money or permissions (do not pretend you will do research activities you are not sure you can do);
- as documentation for those conducting the study (usually a more detailed protocol will be needed for that purpose and this documentation should be updated over the course of the study to document all changes in the protocol over time).

A study protocol should always be available before the study starts. Since epidemiologic studies may involve many designs, it is not possible to present a standard structure for a protocol that could be used in all situations. Nevertheless, the protocol should be sufficiently detailed to serve as documentation for the study. The protocol should demonstrate that the researcher knows the literature well. It is often useful to include power calculations in the protocol but it is acceptable to do studies with smaller numbers than the power calculations indicated. The widespread misuse of probability (p) values that may lead to unjustified statements such as 'non significant results equal no difference between the compared groups' is not an argument for not collecting valuable data that in combination with other published data may be used to reach a conclusion. In any case single studies are rarely sufficient to make decisions and consensus is usually reached by gradually obtaining information that modifies prior beliefs until a justified cue for action is reached.

It is also advisable to include agreements on time schedule, publications and authorship in the protocol.

The protocol is the intellectual property of the investigators and should be treated as such. It should be considered a confidential document by those who read or review the protocol. It should also be stored and kept after the study has ended. For randomized studies there are now procedures for archiving protocols before the data collection starts, partly for being able to document that study hypotheses were made prior to the data analyses.

Storage of data

Once data have been collected, the process of data cleaning starts. Since this part is subject to manipulation of data and thus of results of the study, it is important that this process is transparent to others than the researchers themselves. Data cleaning should involve as few recodings as possible when these recodings may be questioned by others. The recoding rules should be stated in the protocol and raw data (without any manipulations) should always be stored together with the cleaned data.

These data files should then be stored in a safe and kept for a time period of not less than 5 years after results are published. The data documentation is part of this archiving procedure and the IEA supports the establishment of public archives for research data.

Data documentation should at least make it possible for others who were not involved in the study to replicate its published findings.

Publication

The general principle is that research of importance for other people's health should be published, unless the researchers find the study to be of insufficient quality. Sometimes a good design described on paper does not work in practice. If the researchers themselves have no confidence in their results, the results should probably remain undissemated. However this course should rarely be taken and it is always unacceptable to avoid publishing results if they do not fit with expectation and hypothesis, or if they do not fit the financial interest of the sponsor. Before a study starts it should be made clear to all members of the research team that the research is done with the aim of being published. Many colleagues have experienced substantial pressure from private funding sources with an economic interest in certain results when these results were not reached. This had led to a wide spread debate about "conflicts of interest". The IEA supports disclosure of "conflicts of interest", not only "conflicts of financial interest."

Researchers should have no undisclosed conflict of interest with their collaborators, editors, sponsors or participants in research. Thus, researchers must disclose actual, apparent or potential conflicts of interest to the Ethical Review Committee. All sponsorship of research should be publicly acknowledged – it is difficult to justify secrecy. All results of a study, whether government or industry-sponsored, should be the intellectual property of the investigators, not the sponsor. Results should always be published if they address issues of relevance for public health. Requests to withhold findings, to change or tone down the content of a report to produce a misleading or delayed publication should be categorically refused.

It is essential to acknowledge these issues at the start of negotiations with the sponsor, whether private or governmental. There should be a written document that states that the results will be submitted for publication regardless of outcome. The sponsor must acknowledge the independence of the investigators and this relationship must be maintained throughout the study.

The IEA recommends that when research of public health importance is sponsored by a private contractor that has a personal interest in a given result and that interest may be in conflict with the interest of the public, a buffer funding structure should be established. The buffer could be a public research organization the purpose of which would be to ensure the data are analyzed, interpreted and reported in good faith and that the researchers publish results without pressure to deviate from what the data show.

The epidemiologist should not inform the press about the findings of a particular study, unless the full scientific report is available to the public. It is unacceptable to inform the public at a stage when no one has had the opportunity to challenge the findings. Under normal circumstances no information is given to the media before the findings have been subject to peer review. Only for a limited set of good reasons (emergency, epidemic, etc.) can this principle be waived. For example, investigators may discover health hazards that demand rapid corrections and therefore have an obligation to protect and restore health. In this event, their advocacy must be based on objective, scientific data only, and these data should be made available for others to scrutinize.

National epidemiologic societies could take up the responsibility to perform ad hoc reviews in

situations where findings have a public health interest that overrides the principle of the normal review process.

Epidemiologists that have access to information of major public health interest should not delay public release of such data, once the evidence has been reviewed by a competent body, usually a journal with a peer review procedure. Withholding such information is a violation of the principles of non-maleficence and autonomy.

Epidemiologists should not exaggerate their research results with the aim of increasing the likelihood of obtaining future research funding or making their paper more attractive to editors. We also encourage editors not to highlight key findings in a manner that obscures critical reservations. We strongly stress the need for caution when writing press releases or when communicating directly with the public. Epidemiologists should be wary of making poorly supported conclusions. History shows that most research results are wrong or not fully right, and epidemiology does not make an exception to this rule.

Published results are usually only a small part of the information available and it is important that what is selected is selected in good faith. It is poor scientific practice and misleading to select only what agrees with the point of view of the investigator while omitting parts which contradict prior beliefs.

It is advisable to publish the main results in a form that reaches the participants of the study and other interested members of the community where the study took place (e.g. a newsletter, local newspapers etc.). As stated, this type of publication should await publication in peer reviewed journals.

Raw data should be made available to journal editors if requested and to colleagues who want to verify already published results. Conditions for external access to data must of course respect rules for data protection and intellectual property for those who collected the data.

Authorship should follow the Vancouver rules stating that all authors have to take an active part in several phases of the research and should be willing to be responsible for the final research product website address.

Exercise of judgment

A conflict of interest is a situation in which a researcher has or could have a private or personal interest sufficient to influence the objective exercise of his/her professional judgment towards his/her official duties. These conflicts of interest should be taken into consideration when epidemiologists are asked to provide advice or opinions.

Experienced epidemiologists spend a substantial part of their working time evaluating others' work. They do this work for editors, funding agencies, or for users of epidemiologic studies.

External reviewers of epidemiological manuscripts and applications for funding should recognize that they play an important role as guardians of scientific standards and advisors to the journal editors and the funding agencies. Referees judge the originality, scientific

reliability, clinical or public health importance, and overall suitability of the paper for publication in the journal or for the funding agency. This peer review process is of fundamental importance for the quality of the epidemiologic research in general.

Epidemiologists who review research protocols, manuscripts in draft or colleagues' work should ask themselves if they are suitably skilled to review the document. A reviewer should not accept an invitation to do peer reviews if he/she lacks competence in the area of research or if he/she feels that he/she has a conflict of interest due to working too closely with one or more of the authors or being a competitor in the field. The reviewer should respect the intellectual property of the author's research ideas and not delay the review process or try to stop a project or a grant in order to obtain personal gain. The review should respect the intellectual property rights of those who wrote the paper or the grant proposal.

It is important that we do not pretend to be experts in areas where we are not. One of the cornerstones of public and collegial confidence in epidemiological research and in epidemiologists is the assumption that epidemiologists will judge their own work and ideas, and those of colleagues, impartially, with skills, knowledge, and in good faith.

Research serves important tasks in a democracy and everybody should be given the opportunity to contribute with their experience. The IEA does not support that epidemiologic research is restricted to people with certain educational backgrounds. Scientific findings should be reviewed based upon their own merits.

There are general guidelines for referees, which have been adopted by several scientific journals. [website link](#).

Scientific Misconduct

Any large scale study provides ample opportunities for manipulation and interpretation of data. Scientific misconduct is any deviation from interpretations not done in good faith and with the aim of being as [unbiased](#) as possible. It should be realized that if we cannot be trusted there is little value in our research. We recognize that external pressures to publish and to get research funding are severe risk factors for scientific misconduct, as are the editor's desire for simple 'take home messages'. In spite of these risk factors the whole discipline rests upon scientific honesty, helped by severe sanctions for documented misconduct. We encourage all countries to implement safeguards against misconduct by making research data available for other researchers and to remind co-authors and supervisors of their responsibility. Recent examples indicate that epidemiologic research is not immune to the most severe form of misconduct, namely, fabrication of data. More information is available at www.ieaweb.org/RapidResponses_21.htm.

Conclusion

Epidemiologic research is needed in health care, disease prevention and health promotion. This research should be of good quality, done in a timely manner and follow recognized ethical standards. Ethical evaluations should take into consideration the risk of not doing research as well as the risk of doing research.

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