

R E V I E W

Retrospective observational studies: Lights and shadows for medical writers

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Abstract. A retrospective study (by definition non-interventional) is a purely observational review and/or reassessment of database records with the aim of analyzing previous events of interest. The ethical and scientific standards for conducting biomedical research with humans have been established in international guidelines. Nevertheless, the reporting of ethical considerations in human research is not yet agreed upon globally, although some progress has been made in recent years. If a study has been granted exemption from ethics approval, this should be indicated in the manuscript (including the reasons for the exemption) and, if formal review by an ethics committee is not available, a statement should be included indicating that the research was conducted according to the principles of the Declaration of Helsinki. Editors play an important role in adherence to these ethical requirements for all submitted and published research papers in their journals. This short review paper focuses on the main lights and shadows of ethical aspects for conducting retrospective observational studies in humans and implications for medical writers. (www.actabiomedica.it)

Key words: Retrospective studies, Ethical Committee, low-risk research, exemption, international variation, human, ICET-A survey.

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Introduction

A retrospective study (by definition non-interventional) is a purely observational review and/or a reassessment of database records to analyze events of interest that have already happened. Retrospective studies are carried out in health care settings, including but not limited to, hospitals. Various types of data sources may be available for conducting such reviews (e.g., patients' case charts, computerized registries and others), each with specific strengths and weaknesses (1). Importantly, such studies are used to answer specific clinical problems in a relatively easy and less expensive manner.

The ethical and scientific standards for conducting biomedical research with humans have been established in international guidelines. The International Committee of Medical Journal Editors (ICMJE) offers ethical recommendations and standards in reporting of research and helps authors, editors, and all other parties involved in biomedical publishing (2). The Declaration of Helsinki (<https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki>) advises that all research protocols must be submitted and approved by an independent research committee to ensure that the rights and interests of the subjects are protected (3,4). Moreover, all authors must disclose any financial and personal relationships with other people or organizations that could influence their work. Potential conflicts of interest do not necessarily preclude publication.

It is often unclear to the clinical investigator whether retrospective observational studies should be submitted to a research ethics committee (REC), mostly because no active or additional interventions are performed. Although observational studies do not involve interventions, they entail ethical concerns such as confidentiality and respect for basic patient rights according to good clinical practices. Nevertheless, the requirement of ethical standards for observational retrospective studies still varies among journals. Some journals provide general guidance and instruct authors to consult the editorial office on a case-by-case basis.

This short review paper focuses on the main ethical aspects for conducting retrospective observational studies in humans and highlights the implications for medical writers.

Ethical standards in scientific research

Ethical standards for conducting biomedical research in humans have been established through international guidelines. The new Regulation (EU) 2016/679 of April 27, 2016 (5), repealing Directive 95/46/EC, strengthens and synchronizes the rules for protecting individuals' privacy rights and freedoms, and the World Medical Association has developed the Declaration of Helsinki (<https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki>) as a statement of ethical principles for medical research involving human subjects; this also provides a guide to ethics committees regarding approval and informed consent (6).

The four key principles underpinning ethical research are (a) respect for autonomy, (b) beneficence, (c) non-maleficence and (d) justice.

Substantially, the two main ethical aspects for approval of clinical studies involving human subjects are that all the participants have the right to be informed in detail about the study and give informed consent, and that an ethics committee has approved the appropriateness of the project design before initiating the research.

The definition of informed consent given in Directive 2001/20/EC relating to the implementation of good clinical practice is as follows: "*Informed Consent is the decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation*" (7). Informed consent of parents/legal representative must be obtained in accordance with the legislation of the host country. The investigator must also obtain that consent when the child is able to give the assent.

Although patients' confidentiality and formal informed consent remain important ethical issues relating to record reviews, informed consent may not be obtained for individual routine analyses or diagnostic investigations beforehand because very often it is given

verbally, especially in patients with chronic diseases. Moreover, in multi-centre research protocols where the research is carried out at several institutions, obtaining ethical approval from several ethics committees often results in serious delays and conflicting demands (8). Therefore, it is mandatory that the researchers who participate in studies involving human subjects, tissues, or medical records, should be familiar with the contents of the Declaration of Helsinki, as well as their local and national research standards and regulations.

The regulatory framework governing an observational study

Ethics Committees (ECs) are multidisciplinary bodies constituted to evaluate clinical experimentation and research involving human subjects and routine patient care, from an ethical and scientific point of view, in order to ensure that these abide by the ethical standards and guidelines set by national and international committees (9). These rights are protected by international agreements, such as the Helsinki Declaration, which are translated into regulations for the protection of individuals and into the rules for good research practices at the level of each country. However, the organization of the ECs varies between countries.

In general, the National Medical Ethical Committee has the authority to judge an application for the entire country. A Regional Medical Ethical Committee has the authority to judge a medical research protocol for a particular region or state but not for the entire country. In many countries a local hospital Ethical Committee called the Institutional Research Board (IRB) needs to judge the medical research protocol as well (9). In accordance with the Federal Drug Administration (FDA), the IRB has the authority to approve, disapprove, monitor, and require modifications in all research activities that fall within its jurisdiction as specified by both the federal regulations and institutional policy (10).

In Austria, studies involving the collection of retrospective medical records are classified as “Nicht-interventionellen Studie” and require only notification to the central entity. In Belgium an approval by the Regional Committee is mandatory for retrospective

studies using already available data. In Italy, studies involving the collection of retrospective medical records need to be registered at the A.I.F.A (Agenzia Italiana del Farmaco) and site-specific Regional Committee approval is required. In the Netherlands, retrospective patient file research does not fall under the diction of medical research. In Switzerland, retrospective patient chart studies require neither notification nor approval by Regional Ethics Committees (11).

In the UK, according to the NHS Health Research Authority, the first step is to determine if a project is classified as research (an attempt to derive generalizable or transferable new knowledge), warranting EC review or not. If none of the following three criteria (randomization of participants to different groups, changing treatment/care from accepted standard of care, purpose of the project being to produce generalizable or transferable findings) are met, then this study is not considered research. In this case, submission to EC is not needed since this retrospective observational study is classified as clinical audit (designed to compare provided care against predetermined standards) or service evaluation (designed to measure quality of current service without reference to a standard) (12). Therefore, a simple process of registration and approval as a clinical audit by the hospital is adequate, requiring limited time and resources.

de Lange et al. (13), in a survey covering 16 European countries, have reported a large variety of ethical processes from either national ECs', regional ECs' or IRBs' approval regarding an identical study protocol. In most countries, more than one level of ethical approval (EA) had to be completed. Sometimes local IRBs are stricter than their national ECs. The time between applying for EC and the first decision varied between 7 and 300 days.

In March 2022, the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) (14) promoted a survey on nationwide ethics committee regulations with regard to retrospective observational studies, containing seven questions. The main answers reported by 21 Researchers of 13 countries are summarized in Table 1.

Substantially, EA approval is mandatory in 9 out of 13 countries, the time between applying for EA and the first EC decision is extremely variable (from 2-4

Table 1. ICET-A survey on regulations of retrospective observational studies (ROS) in 13 countries.

Country	Is Ethics Committee approval needed for ROS ?	How long do you have to wait for receiving the decision of Ethics Committee for ROS ?	Do you know if publishers in your country require Ethics Committee approval for ROS ?
Bulgaria (2 centers)	No	=	Not needed
Cyprus (2 centers)	Yes	2-4 weeks	No
Egypt (2 centers)	Yes	1-2 months	Most of them
Greece (1 center)	Not mandatory, if the study can be included in the general approval already obtained for ROS.	1-2 months	Not all of them
Iran (2 centers)	Yes	3 weeks	Yes
Italy (3 centers)	No (1) Not mandatory (1) Mandatory for drug exposure studies (1)	3-6 months	Not all of them
Kingdom of Saudi Arabia (1 center)	Yes	4-6 weeks	Yes
Oman (2 centers)	Yes	4-6 weeks	Yes
Qatar (2 centers)	Yes	3-6 months	Yes
Spain (1 center)	Yes	2 months	Yes
Sri Lanka (1 center)	Yes	3 months	Yes
Turkey (1 center)	Yes	2 months	Yes
UK (1 center)	Not mandatory. The possible requirement for ethical approval needs to be discussed on a case-to-case basis.	50 days	(§)

Legend: (§) Some retrospective studies undergo ethical review and approval. A large proportion is registered as clinical audit or quality improvement project with the intention of comparing clinical practice against a set of standards and criteria (defined as optimal practice) and making recommendations to improve quality of services. The key question is about the extent and scope of data collection and whether they are under the umbrella of describing real-life clinical practice or there is a broader scope.

weeks to 6 months) and not all editorial publishers require EC approval (including project identification code, date of approval, and name of the ethics committee or institutional review board) for retrospective observational studies.

In summary, the process for obtaining EA for retrospective observational studies may be a daunting task (15). Some researchers have argued that the waiting time between applying for EA and the first decision is unjustified because it may create significant

delay and cost, may prevent some research, and can translate into potential harm to patients (16).

Therefore, an improved and uniform regulation of the exemptions from ethics review for retrospective observational studies, considered at “low-risk” in different jurisdictions, is desirable in order to help doctors working in small hospitals and to facilitate more efficient use of resources for researchers’ and ethics committees’ (16,17). Although there is not a clear definition of patients at “low-risk”, we may consider in this category patients who were informed of the possibility of research being performed on their data and did not object, provided their personal data would remain strictly confidential and anonymised (or at least not identifiable).

Are the ethical and endorsed statements regularly applied in clinical research?

Failure to report on informed consent and approval by an ethics review board has been described to be frequent in clinical research, even in prestigious journals.

Yank and Rennie (18) investigated the ethical protections of clinical trials published in five top medical journals: The Lancet, JAMA, BMJ, The New England Journal of Medicine, and Annals of Internal Medicine. Sixty articles per journal per period were randomly selected and assessed for rate of reporting on informed consent and on EC approval. Informed consent was not reported in 79 articles (26%) published before 1997 vs 53 (18%) published after 1997 ($P = .01$), and EC approval was not mentioned in 93 (31%) before 1997 vs. 54 (18%) after 1997 ($P = <.001$). Neither protection was described in 48 articles (16%) published before 1997 vs. 28 (9%) after 1997 ($P = .01$). In subgroup analyses, those journals with the worst initial rates generally improved the most.

Munung et al. (19) assessed the extent of research ethics approval and informed consent reporting in publications from Cameroon and indexed in PubMed from 2005-2009. He found that 57.53% reported ethics approval, 70.78% informed consent, and 50.68% both ethics approval and informed consent.

In 2016, Hiroi et al. (20) surveyed the ethical and endorsed statements of 10 peer reviewed medical

journals with impact factors of 10 or more. General medicine, oncology, endocrinology, cardiology, gastroenterology and hepatology journals were the target of study. The authors found that some journals provided general guidance on anonymous and personally unidentifiable studies and gave instruction to authors to consult the editorial office on a case-by-case basis.

In this context, it is evident that a significant proportion of articles involved in clinical research lack reporting of ethics committee approval and written informed consent, although improvements have been observed over time.

Open problems

On the one hand, the principle of autonomy, with an emphasis on informed, autonomous decision-making of patients themselves, has in recent years supplanted the principle of non-maleficence as the primary principle guiding the practice of scientific research on humans. On the other hand, it can be argued that EC in retrospective observational studies can pose an overburdening demand on researchers, and may discourage researchers from undertaking potentially significant projects. The only possible harm involves personal privacy issues, but in many cases the physicians and scientists would be reviewing patient records they had written themselves and have free access to anyway. A practical approach to the matter of applications to ethics boards for relatively simple retrospective studies could be that individual medical researchers may be licensed by institutional review boards to perform retrospective clinical studies at their institution in their medical field (essentially being allowed to use retrospectively anonymised data of their own patients). Finally, part of the solution could lie with editorial boards which may be better situated than ethical boards in safeguarding privacy of patients by preventing publication of potentially identifiable data (16).

What action should be taken if authors cannot obtain ethics approval for a study that is merely retrospective (“non-interventional”) if they are working in a small or private clinic not affiliated to a university? Should strict ethical criteria also be applied to patients

diagnosed and routinely treated according to national and international guidelines?

The ICMJE (2) has clearly mentioned that submitting publications based on observational studies requires ethical approval, or at least a letter from an EC. If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included. This procedure is also reported in the guidelines to authors by some international journals (21).

Discussion

A clinical study is considered observational or non-interventional if it meets the following criteria: a) it does not involve a novel specific medicinal product or it involves a medicinal product that has received marketing authorization; b) the product will be used in accordance with the marketing authorization and c) the study will be conducted per standard of care (22).

The publication of retrospective research is crucial because it allows the spread of scientific knowledge, comparison of different methods of treatment, may have an impact on epidemiological surveillance, evaluation disease progression and survival, or offers the stimulus to design prospective studies.

It is often unclear to the clinical investigator whether retrospective observational studies in patients with no identifiable personal data should be submitted to an EC, mostly because no active or additional interventions are performed (23). Recent assessments have shown marked variations between research areas in the proportion of articles lacking information on external ethics review.

The proportion has been reported to range from 6% in nursing research (24) to 48 % in pediatric surgery (25), 50% in otolaryngology (26), and 31% in five prestigious medical journals in the mid-2000s (27). Articles with only one or two authors were associated with a high risk of not reporting on ethical approval. The chance of someone in the research group being experienced in ethics regulations would be greater in a larger team (27).

Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights (2). Although

retrospective observational studies do not involve interventions, and precautions are taken to protect the patients' privacy and confidentiality, ethical considerations are not yet uniform globally, although it is acknowledged that some progress has made in recent years. If a study is granted an exemption from requiring ethics approval, this should be indicated in the manuscript (including the reasons for the exemption). If no formal ethics committee is available and the retrospective study is intended to benefit the subjects of the study, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be reported in the manuscript. Therefore, Editors play an important role as "gatekeepers not only of good science but of responsible science" (28) for all submitted and published research papers in their journals.

In conclusion, the decision on whether to proceed to ethics review in case of retrospective studies depends on individual IRB, journal guidelines and editor's discretion, in accordance with the Declaration of Helsinki. It could be helpful if mandatory steps are added to online submission portals so that during submission authors can conform each of these components.

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