

Registration and ethics committee approval for observational studies:

Current status and way forward



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Abstract

Randomised controlled trials (RCTs) have always been recognised as the highest level of evidence in medical research. However, they cannot address the questions that one comes across in real-world clinical practice. Observational studies can answer such questions as they are based upon real data obtained from patient healthcare records, medical databases, and registries. Literature review has shown that observational studies are as important as RCTs and should be considered when making any clinical decisions. However, there is a lack of standard guidelines for registering and reporting observational studies, which may contribute to publication and reporting bias. Furthermore, guidelines differ on the ethical considerations for observational studies. This article discusses these issues, focusing on the current situation and gaps in the registration, ethics approval, and publication of observational studies.

Background

Randomised controlled trials (RCTs) investigate the efficacy of new interventions and are considered the gold standard in medical research. They are considered strong evidence in the hierarchy of evidence-based medicine (EBM) because of their well-defined study designs, compliance with strict protocols, and trans-

parency (Figure 1). However, RCTs are performed under tightly controlled conditions and, thus, their results are limited to the patients in experimental settings. Real-world clinical practice comes up with many different situations that might not have been tested in a clinical trial. There can be a new adverse event, an off-label indication, a co-morbid condition, or a co-

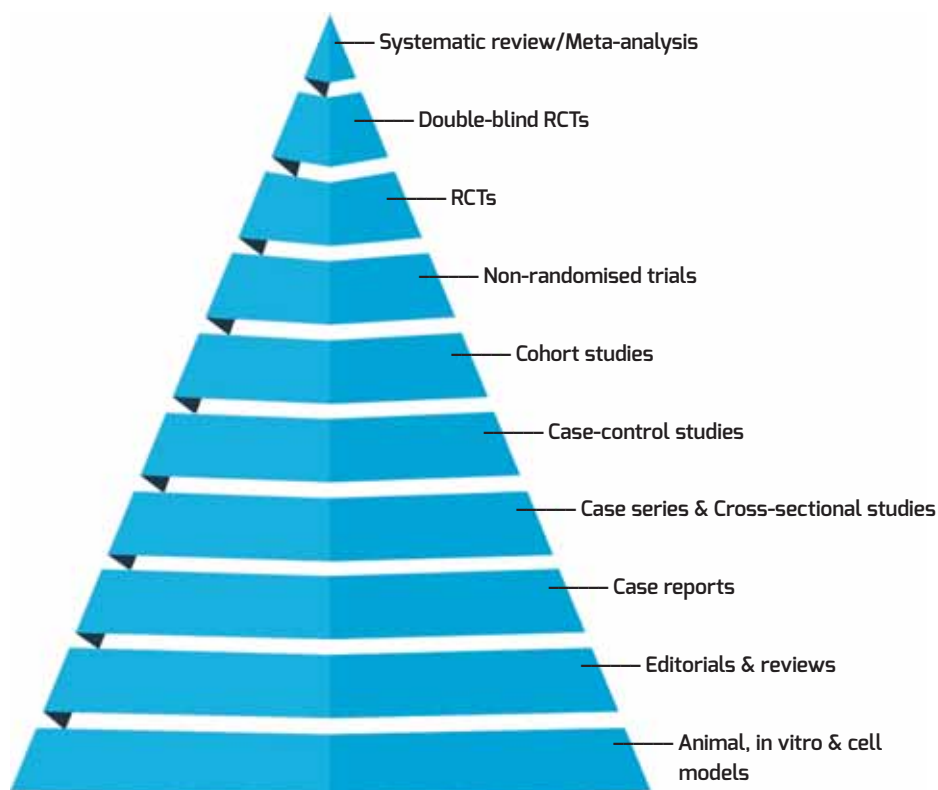


Figure 1. Level of evidence in medical research.⁴ The positions of randomised controlled trials and observational studies in the pyramid of evidence for medical research are shown.

medication that can change the course of the illness. In such situations, an observational study can provide answers to many questions and can supplement the clinical trial in applying the intervention to the general population.^{1–4}

In observational studies, the interventions are not determined by the protocol and are based on real-world clinical practices. These studies are based upon data obtained from patient health-care records, health care databases, and registries, and can be prospective or retrospective in nature. Observational studies can be of various types, including cross-sectional, case-control, and cohort studies; however, their main strength lies in the fact that they are more proximate to real-life evidence.^{1–3}

Going beyond randomised controlled trials: Where do observational studies stand?

Benson et al compared observational studies with RCTs across 19 diverse treatments and found summary estimates of the treatment effects to be similar for both types of studies.⁵ Further, Concato et al identified meta-analyses of RCTs and observational studies for five clinical topics and found the summary estimates and 95% confidence intervals (CIs) to be similar. For example, the odds ratio (95% CI) was found to be 0.49 (0.34–0.70) and 0.50 (0.39–0.65), respectively, for RCTs and observational studies assessing the effectiveness of the Bacillus Calmette-Guérin vaccine against active tuberculosis.⁶ Furthermore, literature shows that observational studies are being used by the American Geriatrics Society, the Endocrine Society, and various other vitamin D expert groups to make recommendations on vitamin D supplementation.⁷

RCTs and observational studies need to be viewed together because their different study designs and methods are crucial to provide as much information as possible in terms of the safety, efficacy, and effectiveness of an intervention.^{8,9} RCTs might not give accurate answers in complex situations, for example the presence of confounding factors, interventions of long duration, larger patient populations, and use of concomitant medications. Observational studies can, and should, be used in such complex domains to explore the best practices in the real world; however, their findings should be considered with due caution.^{2,4}

There are instances where FDA decisions

have been based on observational study results, such as the Data Collection on Adverse Events of AntiHIV Drugs (D:A:D) study. The D:A:D study was conducted in 33,347 HIV-1-infected patients and showed that the risk of heart attack increased by 49% and 90%, respectively, with the use of didanosine and abacavir. On the basis of these study results, the FDA advised healthcare providers to evaluate the risks and benefits of HIV antiretroviral drugs, including abacavir and didanosine.¹⁰

Ensuring the quality of observational studies: What do the guidelines say?

To ensure the quality of observational studies,

various guidelines have been published by scientific and regulatory organisations. The guidelines identified in the literature along with their key objectives are summarised in Table 1.^{11–20}

Literature review shows that these guidelines are not all in agreement on standards of observational studies: There was no consensus for 12 out of the 23 elements discussed in the guidelines. This may contribute substantially to disparities in research and, thus, a low quality of evidence for patient care decisions, leading to poor healthcare outcomes. Moreover, there is a lack of standards for ethical considerations and dissemination. Only three out of nine guidelines addressed these aspects; however, no actions were suggested regarding implementation.¹¹

Table 1: Guidelines for observational studies

Guideline	Key objective
1 Agency for Healthcare Research Quality (AHRQ): Developing a Protocol for Observational Comparative Effectiveness Research ¹²	To identify the minimum standards and best practices for designing observational comparative effectiveness research studies
2 Comparative Effectiveness Research Collaborative Initiative: Observational Study Assessment Questionnaire ¹³	To assess the relevance and credibility of observational studies for informed health care decision making
3 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols ¹⁴	To consider the important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol
4 ENCePP Guide on Methodological Standards in Pharmacoepidemiology ¹⁵	To provide methodological guidance for researchers in pharmacoepidemiology and pharmacovigilance
5 United States Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment ¹⁶	To provide guidance on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs
6 Good ReseArch for Comparative Effectiveness (GRACE) Checklist ¹⁷	To provide a checklist for observational comparative effectiveness studies that are rigorous in design to help in decision support
7 GRACE Principles ¹⁸	To help decision makers evaluate the quality of observational research studies of comparative effectiveness
8 International Society for Pharmaco-economics and Outcomes Research (ISPOR) Good Research Practices for Retrospective Database Analysis Task Force Report ¹⁹	To provide guidance on framing research questions and reporting findings for retrospective epidemiologic and health services research studies
9 Patient-Centered Outcomes Research Institute (PCORI) Methodology Standards ²⁰	To provide guidance on various topics, including formulating research questions, data integrity and analysis, data registries, and systematic reviews

Ethical principles for medical research

As per the Declaration of Helsinki, medical research involves research on identifiable human material or data and needs to be continuously challenged to prove the efficacy, effectiveness, or quality of prophylactic, diagnostic, and therapeutic procedures. The design and results of all clinical studies should be publicly available and are subject to ethical standards. Furthermore, all experimental procedures involving human beings should be well-defined in a protocol, which needs to be approved by an ethics committee.²¹

The two most important points to be considered are registration of clinical studies and ethics committee approval of any study involving human beings. In this article, we discuss the current status of these two points in reference to observational studies, as well as future implications.

Registration of observational studies: Current situation and gaps

Registering clinical trials is not only ethical but also has a scientific rationale. It provides global access to information, reduces duplication, enables monitoring for adherence to ethical principles and regulations, improves the credibility of the information, accelerates knowledge creation, and ensures transparency of research.²²

As per Food and Drug Administration Amendments Act (FDAAA) 801 requirements, there is no mandatory requirement for observational studies to be registered on ClinicalTrials.gov, unlike RCTs.²³ Thus, observational studies are quite vulnerable to publication and reporting bias, owing to selective reporting, misinterpretation of analyses, and lack of regulations related to their registration and reporting. This undermines the overall validity of observational studies and provides a rationale for registering them.^{22,24}

Currently, ClinicalTrials.gov allows the registration of observational studies and provides specific data elements to be filled in for registration. In Europe, the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) is publicly available for registration of post-authorisation studies to improve the transparency of observational research.^{25,26}

Over the past few years, the number of observational studies registered per year has

increased and observational studies now represent about 15% of all studies on ClinicalTrials.gov. Around half of these studies are from North America (50%), followed by Europe (20%) and Asia (13%), and 85% are funded by non-industry sources. However, the number of observational studies registered is still considered low, exposing observational studies to reporting bias.^{24,27}

Some of the challenges in the registration of observational studies include:²⁴

- Most of the studies registered are prospective in nature, and there is a need to establish methods for registering other types of studies, such as retrospective studies
- The timeframe for registering observational studies needs to be defined, along with the attributes that should be mentioned
- Whether or how to register sub-studies or secondary studies using the same prospective data
- Defining the data elements for reporting different types of observational studies

To ensure complete transparency of observational studies, these issues need to be properly addressed. This requires discussions among all stakeholders, including sponsors, regulatory authorities, and the public.²⁴

Ethics committee approval of observational studies: Current situation and gaps

Although it is clear from the Declaration of Helsinki that research protocols must be approved by an ethics committee before the start of any experimental procedure, the situation is a little confusing for observational studies. Some countries may waive the requirement for ethics committee approval of observational studies because there is no experimental intervention.²⁸ Currently, ethics committee approval is needed for all research in Canada, including the review of

patient records.²⁹ By contrast, retrospective studies are excluded from the code of ethics approval in Turkey.³⁰

Ethics committee approval of observational studies has been a topic of great debate. This is well illustrated by the differences in opinion in the literature. While Orchard (2008) argued that most observational studies are not ethically sensitive and that ethics requirements are an unnecessary barrier, others (Moser and Röggla, 2008) disagreed, stating that ethical requirements are important to prevent bad practices in research.^{31,32}

Observational studies and publications

Differences in guidelines on observational studies may lead to serious confusion when it is time to publish them. This is illustrated by a case in which manuscripts based on various French observational studies were rejected or retracted by US peer-reviewed journals because the protocols had not been approved by an ethics committee. As per French law, which comes under the European regulations, only biomedical research involving an intervention and not performed in the normal medical follow-up of patients needs ethics approval. The authors of the French studies stated that ethics approval was not sought as the studies were performed using routine techniques. However, this was against US requirements and, thus, the studies were rejected. One important point to consider here is that even if there is no requirement for ethics approval of such studies in France, it is compulsory to have an ethics opinion.³³

In 2004, an international initiative, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), was launched to provide guidance on the reporting of observational studies. The STROBE guidelines include a complete checklist of items that need to be addressed when reporting observational studies (e.g. study design, participants, and results), but there is no mention of ethical requirements and regis-



Table 2: Statements to be included in manuscripts based on observational studies, as per the ICMJE recommendations and journals' author instructions³⁵⁻⁴⁰

Organisation/ Journal	Statement
ICMJE	"The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). 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."
BMJ	"Every research article submitted should include a statement that the study obtained ethics approval (or a statement that it was not required), including the name of the ethics committee(s) or institutional review board(s), and the number/ID of the approval(s)."
JAMA	"For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section. For those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki should be followed."
PLOS ONE	"Methods sections for submissions reporting on any type of observational and field study must include ethics statements that specify: permits and approvals obtained for the work, including the full name of the authority that approved the study; if none were required, authors should explain why."
Lancet	"Studies on patients or volunteers need approval from an ethics committee and informed consent from participants. These should be documented in your paper."
Springer	"The following statements should be included in the text before the References section: Ethical approval "Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards." For retrospective studies "Ethical approval: For this type of study formal consent is not required."

Abbreviations: BMJ, British Medical Journal; ICMJE, International Committee of Medical Journal Editors; JAMA, Journal of the American Medical Association

tration.³⁴ However, the International Committee of Medical Journal Editors (ICMJE) along with specific international journals clearly mention the ethical requirements and considerations when submitting observational studies for publication (Table 2).³⁵⁻⁴⁰

Ultimately, the Committee on Publication Ethics recommend ethics approval for all observational studies or suggests that a supporting letter be requested from the ethics committee in cases of exemption (where ethics approval is not required).^{41,42} It should be understood that regulatory authorities and legal bodies are not enemies of research but are working towards improving research practices to the ultimate benefit of patients and society.²⁸

Key messages

- Observational studies are as important as RCTs and play an important role in real-world evidence.
- Currently, there are no standard guidelines on registration and ethics committee approval of observational studies.
- It is not mandatory to register observational studies and obtain ethics committee approval before study start.
- There are no standards on dissemination of data from observational studies, and this creates confusion in the publication process.
- Creating standardised guidelines for all these aspects would help to improve the transparency of research and validate the findings

of observational studies. This would help to avoid the duplication of data and misinterpretation of results, and would contribute to the worldwide spread of knowledge.

- It is advantageous for researchers/sponsors to register their studies and consider ethical requirements because the ultimate aim is to improve patient healthcare and thereby benefit society.
- The ideal process for conducting and publishing an observational study is illustrated in Figure 2.

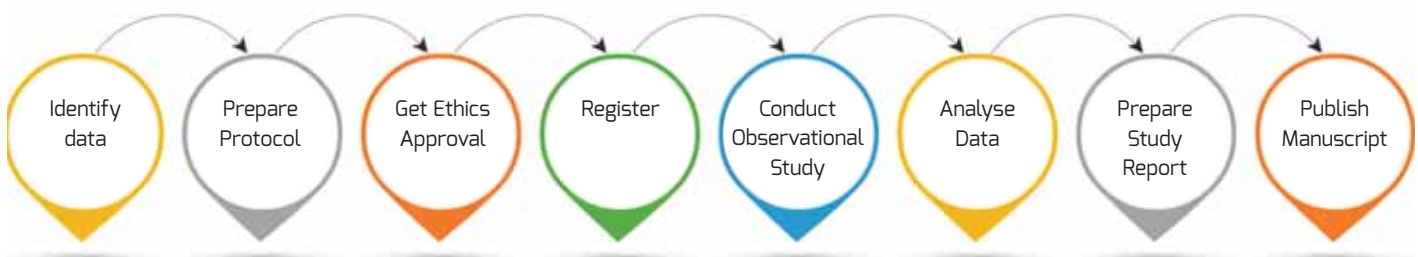


Figure 2. The ideal process for designing, conducting, and publishing an observational study.

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Conflicts of Interest and Disclaimers

The authors disclose no conflict of interest.

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