

Primer: Observational Studies in Clinical Research

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What is an observational study?

Observational studies and randomized controlled trials (RCTs) are the major study types to investigate the effect of exposures and treatments in clinical research. In observational studies, differences in the outcome are observed without making an intervention or manipulating the independent variable (non-experimental study). In contrast, RCTs assign patients to treatment and control arms by randomization (experimental study). It is well known that observational studies have a tendency to provide more biased treatment effects and show more heterogeneity in the effect estimates because of confounding ([Grimes and Schulz, 2002](#)).

As a result the pyramid of evidence ranks observational studies below randomized controlled trials (RCTs), but this simplified view has been challenged ([Vandenbroucke, 2008](#)). RCTs are designed to control for measured and unmeasured confounding (through randomization and blinding), but their quality critically depends on adequate design and implementation. When randomization is compromised, treatment effects can be inflated ([Ioannidis et al., 2001](#); [Kunz and Oxman, 1998](#)). Thus, the premise that RCTs provide higher-quality evidence than observational studies critically depends on their scientifically rigorous and robust methodology.

Indeed, not all RCTs are of the same quality and, unless adequately designed, conducted and reported, they may not provide better evidence to assess the efficacy and/or safety of medical therapies than observational studies ([Grossman and Mackenzie, 2005](#)). Deemed to provide the highest level of evidence in medical research and considered as the gold-standard in clinical decision making, RCTs are often conducted in highly selected populations and managed in tightly controlled settings. As such, RCTs may fail to reflect real-world clinical practice. Observational studies can provide additional evidence when including a more diverse patient population, a wider spectrum of treatment types and dosages, and should also be considered when conducting meta-analyses of interventions ([Shrier et al., 2007](#)). Furthermore, there are settings where RCTs would be impossible or unethical. Hence, observational studies that are based upon real data obtained from patient healthcare records, medical databases, and registries are considered complementary to RCTs in assisting clinical decision making.

The quality of evidence depends not only on study type

Sometimes results from observational studies and RCTs do not align and may even provide contradicting results. A number of interventions or exposures seemed effective in observational studies only to be later contradicted by evidence from RCTs ([Ioannidis, 2005](#)). Fortunately, contradicting results are more the exception than the rule.

In fact, observational studies and RCTs are more often in agreement than in disagreement ([Ross, 2014](#)). A 2014 Cochrane review found little evidence that results from observational studies and RCTs systematically disagreed ([Anglemyer et al., 2014](#)). Thus, factors other than study type need to be considered when exploring reasons for lack of agreement. Instead of ranking observational studies against RCTs, we should be open to all types of evidence that rely on rigorous clinical science and good research practice ([Faraoni and Schaefer, 2016](#)).

The danger from bias

In observational studies, the presence of bias can cause a systematic error in the effect estimate and compromise the validity of the results. A 2002 report established a link between measles, mumps,

and rubella (MMR) vaccines and autism, but subsequent studies showed no evidence of an association. The initial finding was likely due to recall bias in the survey data [Andrews et al. \(2002\)](#). Bias can compromise the truth and even cause patient harm.

Oxford's University's Catalogue of Bias¹ is a comprehensive guide on the various biases. It is important to reflect on potential bias in an observational study, but also RCTs at risk despite randomization and, therefore, bias is commonly assessed in Cochrane systematic reviews ([Higgins et al., 2011](#); [Sterne et al., 2019](#)). In an RCT, risk of bias can arise due to problems with randomization, deviations from the intended intervention, missing data, or selective reporting.

Although observational studies can have a higher risk of bias, statistical techniques (like validation of parameters, comparison of population characteristics, matching, propensity scores, etc.) can control for confounding, and, when correctly used, can provide more accurate risk estimates. It then becomes clear that, to correctly interpret the results, the quality and methods used for data analysis must be carefully assessed. The STRATOS initiative² provides accessible and accurate guidance in the design and analysis of observational studies. Moreover, field-specific methodological standards and guidelines should be consulted. For example, methodological considerations for the conduct of pharmacoepidemiological studies in COVID-19 were proposed recently ([Pottegård et al., 2020](#)). Another example is the EMS's guidelines for registry-based studies which are under development.³

The importance of using reporting guidelines

Reporting guidelines have been developed for various study types to improve the quality of published research. Most prominent is the CONSORT statement ([Schulz et al., 2010](#)) which has been widely adopted for the reporting of RCTs. Reporting guidelines for other study types are also available, but they are less known to clinical researchers and therefore less widely adopted. In particular, the STROBE statement for reporting observational studies ([von Elm et al., 2007](#)) is not used by or not even known to a considerable proportion of authors of observational studies ([Sharp et al., 2019](#)). Different checklists are available for cohort studies, case-control studies and cross-sectional studies. An overview of available reporting guidelines is provided by the EQUATOR network.⁴

A case for a checklist

In order to further support the quality of observational studies, we have compiled a checklist named "SHORT: a Simple cHecklist for Observational Research in clinical sTudies" (Table 1). The aim of this checklist is to guide clinical researchers to various good research practices in the design, conduct, analysis, and reporting of observational studies to ensure the highest standards of scientific quality, integrity, patient safety and investigator objectivity. The checklist reflects on good practices in observational studies and also includes more recent proposals (e.g., registration of observational studies). A recent review outlined the most important problems in medical research ([Bradley et al., 2020](#)). Study registration and a novel publishing scheme called registered reports can effectively address many of the problems, such as presenting exploratory results as confirmatory, known as HARKing⁵, or exploiting analytic flexibility to obtain the desired results (p-hacking). But also outcome switching and publication bias become less likely with a registered study.

Novel proposals aimed to improve observational research are inspired from best practice in RCTs. RCTs are much more regulated, for example, study registration is mandatory in RCTs, as well as reporting of results after study completion. Observational research would benefit from registration as well as hypotheses and methods are prespecified ([Loder et al., 2010](#)), and some have aries to also amend a statistical analysis plan ([Thomas and Peterson, 2012](#)). ClinicalTrials.gov permits to register

¹<https://catalogofbias.org>

²<https://www.stratos-initiative.org>

³<https://www.ema.europa.eu/en/guideline-registry-based-studies>

⁴<https://www.equator-network.org>

⁵Hypothesizing After the Results are Known

observational studies as well, and not only RCTs. Other platforms to register any type of study are available, for example the Open Science Framework (osf.io). However, registration of observational studies is not yet the standard, perhaps also because many journals do not require it.

In the current explosion of COVID-19 research output, it is more important than ever to generate reliable, reproducible, and transparent evidence. The European Medicines Agency (EMA) recently called for transparency in observational studies in COVID-19.⁶ According to EMA researchers should post all protocols and reports from observational COVID-19 studies in the EU PAS register⁷ to ensure transparency and scrutiny of study design and results.

Note

This primer is a summary of the preprint “SHORT: A simple checklist for observational research in clinical studies” (Schwab et al., 2021).

⁶<https://www.ema.europa.eu/en/news/ema-calls-high-quality-observational-research-context-covid-19>

⁷<http://www.encepp.eu/encepp/studiesDatabase.jsp>

Table 1: SHORT checklist for observational research in clinical studies

Category	No.	Items	Yes/No
Literature review	1	(a) Has a systematic literature review been conducted on the current state of the research?	<input type="checkbox"/>
Protocol registration	2	(a) Is a protocol or study plan available? (b) Was the protocol registered (e.g., on clinicaltrials.gov)? (Loder et al., 2010; Williams et al., 2010) (c) Was the protocol published or a “registered report” considered? (d) Is a statistical analysis plan (SAP) available? (Thomas and Peterson, 2012) Are the following items publicly available before acceptance for publication? (e) Study protocol (f) Statistical analysis plan (SAP) (g) Other relevant materials and documents (e.g., contracts)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Sources of bias	3	(a) Was potential sources of bias considered in the design of the study? (b) Were potential sources of bias critically discussed in the discussion section?	<input type="checkbox"/> <input type="checkbox"/>
Good statistical practice	4	(a) Was a trained statistician/biostatistician involved in the project? (b) Is one of the authors taking responsibility for the availability and integrity of the data? (c) Was a sample size calculation performed? (d) Were the grounds the anticipated effect size explained?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Study reporting	5	(a) Were STROBE (von Elm et al., 2007) guidelines (or any other relevant guidelines) followed? (b) Were all performed analyses reported? (c) Were exploratory analyses declared as exploratory?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Publication	6	(a) Were ICMJE authorship guidelines followed? (Ross, 2014) (b) Were contributor roles reported? (Anglemyer et al., 2014)	<input type="checkbox"/> <input type="checkbox"/>
Data and code sharing	7	(a) Was data shared with all authors, reviewers and editors throughout the publication process? (b) Was code shared with all authors, reviewers and editors throughout the publication (c) Can all results be reproduced? (d) Are there no contractual agreements that deny investigators and reviewers the right to examine the data independently? (e) Are de-identified raw data publicly available to scientists and reviewers for inspection?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Ethics	8	(a) Was ethical approval granted? All, even low-risk observational studies, require formal ethical approval.	<input type="checkbox"/>
Declaration of interests	9	Have the following conflicts of interest been declared? (a) Monetary interests (payments, benefits such as travel, hospitality and conference fees, etc.) (b) Non-monetary interests (memberships of committees, etc.) (c) Institutional conflict of interests (d) Do all investigators vouch to follow standards and procedures that ensure that the design, conduct, or reporting of research is not biased by any conflicting financial and/or academic and/or institutional interests?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

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