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Florian Naudet, Chirag Patel, Nicholas Devito, Gérard Le Goff, Ioana Cristea,
Alain Braillon, Sabine Hoffmann

► **To cite this version:**

Florian Naudet, Chirag Patel, Nicholas Devito, Gérard Le Goff, Ioana Cristea, et al.. Improving the transparency and reliability of observational studies through registration. *BMJ - British Medical Journal*, 2024, 384, pp.e076123. 10.1136/bmj-2023-076123 . hal-04387187

HAL Id: hal-04387187

<https://univ-rennes.hal.science/hal-04387187v1>

Submitted on 11 Jan 2024

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Analysis

Improving the transparency, reliability and accountability of observational studies through registration

I

Florian Naudet [1,2], professor of therapeutics
Chirag J. Patel [3], associate professor of biomedical Informatics
Nicholas J. DeVito [4], postdoctoral researcher
G rard Le Goff [5], patient representative
Ioana A. Cristea [6], associate professor of clinical psychology
Alain Braillon [7], retired senior consultant
Sabine Hoffmann [8,9], postdoctoral researcher

[1] Univ Rennes, CHU Rennes, Inserm, Irset (Institut de recherche en sant , environnement et travail)-UMR_S 1085, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], Rennes, France.

[2] Institut Universitaire de France (IUF), Paris, France.

[3] Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts, United States of America.

[4] Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX2 6GG, UK.

[5] France Rein Bretagne, Laill , France.

[6] Department of General Psychology, University of Padova, Padova 35131, Italy.

[7] 80000, Amiens, France.

[8] Department of Statistics, Ludwig-Maximilians-Universit t M nchen, Munich, Germany.

[9] LMU Open Science Center, Ludwig-Maximilians-Universit t M nchen, Munich, Germany.

Correspondence to:

Pr Florian Naudet

CHU de Rennes, 2 rue Henri Le Guilloux, 35000 France

Email: floriannaudet@gmail.com

Phone: + 33 2 99 28 43 21

Word count: 2179

References: 41

KEY MESSAGES

- The increasing use of routinely collected data requires transparency and reliability.
- This could be done through registration, which needs to consider the level of detail and flexibility that observational research needs.
- A centralised repository may reduce redundancy, help users and increase accountability by informing participants about the use of personal data.

Contributors and sources

Following a correspondence calling for registration of observational data that was published in BMJ with Alain Braillon, Florian Naudet was commissioned by the BMJ (Juan Franco) to write this analysis piece. Florian, a meta-researcher, is a professor of therapeutics. He invited a team of co-authors with different locations and perspectives (Chirag Patel, Nicholas J. DeVito, Ioana A. Cristea and Sabine Hoffmann) as well as a patient representative (Gérard Le Goff). Florian (who serves as the guarantor) and Sabine wrote the first draft. All other authors contributed in revising it critically and agreed on the final content.

Acknowledgements

None

Patient involvement

One patient representative (Gérard Le Goff) has been involved in this paper since the article planning stage. He introduced certain ethical dimensions including the notion of altruism. He contributed to the paragraph about patient information by providing useful references. His contribution is substantial and warrants authorship.

Conflicts of Interest

We have read and understood [BMJ policy on declaration of interests](#) and have the following interests to declare:

FN received funding from the French National Research Agency (ANR-17-CE36-0010), the French ministry of health and the French ministry of research. He is a work package leader in the OSIRIS project (Open Science to Increase Reproducibility in Science). The OSIRIS project has received funding from the European Union's Horizon Europe research and innovation programme under the grant agreement No. 101094725. He is a work package leader for the doctoral network MSCA-DN SHARE-CTD (HORIZON-MSCA-2022-DN-01 101120360), funded by the EU. CJP received funding from NIH (NIEHS R01ES0324702 and NIA RF1AG074372). NJD has received funding from the European Union's Horizon Europe program, also via the OSIRIS project, the Naji Foundation, The German Federal Ministry of Education and Research (BMBF) and the Fetzer Franklin Memorial Fund and has been employed on grants from the Mohn-Westlake Foundation, Laura and John Arnold Foundation, Elsevier, and the Good Thinking Society in the last five years. SH has received funding from the European Union's Horizon Europe program, from the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) and from LMUExcellent. GLG, IAC and AB have no conflict of interests to disclose.

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Improving the transparency, reliability and accountability of observational studies through registration

Standfirst

Florian Naudet and colleagues argue that registration is essential to increase the transparency, reliability and accountability of observational research, but to achieve its full potential, it needs to be more comprehensive and more flexible than the processes and tools designed for clinical trials.

Introduction

From the use of booster doses against covid-19¹ to approval of novel cancer therapies,² health authorities and health technology assessment bodies are increasingly relying on non-randomized trials and observational studies. Beyond methodological issues that are difficult to resolve, such as the existence of residual confounding (e.g.³), there are additional issues concerning the transparency, reliability, and accountability of observational studies that can be addressed by adopting a new approach to the registration of these studies. Registration is an open science practice that consists in the pre-specification of research hypotheses, elements of study design, and planned statistical analyses, preferably in a centralised repository. Registration has been the norm for clinical trials (i.e. interventional studies)⁴ and some have called for systemic adoption of registration for observational studies,^{5 6} but others object to this because it would be unrealistic, unnecessary^{7 8} and too complex.⁹ Some have even argued that it may cause more harm than good as it might force researchers into scientific dishonesty⁹ and provide stakeholders with vested interests the possibility to weaponize deviations to the initial protocol in order to discredit inconvenient findings.¹⁰

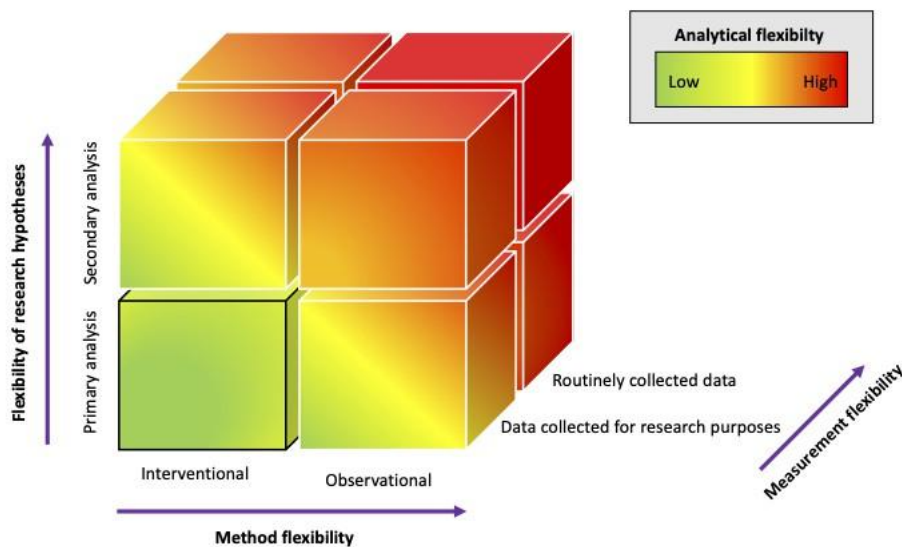
However, unreliable research findings may be just as misleading as unjustified criticism of valid evidence. These are often two sides of the same coin, as illustrated by nutritional research¹¹ or the marketing of doubt by the tobacco industry.¹² Given the stakes, if observational studies are to be used in regulatory or public policy decisions, they should be required to meet the same basic quality standards as interventional studies, which includes registration. This already happens for certain studies, e.g. non-interventional post-authorisation safety studies in Europe, but it can be further expanded to any observational studies.

New types of observational studies require a renewed discussion

Various accelerated approval pathways have given rise to conditional approvals of medicinal products based on non-randomised and sometimes uncontrolled pivotal trials. In this context, the use of routinely collected datasets, as primary or complementary source of data, can be used to address remaining uncertainties.¹³ Observational research aiming to emulate clinical trial design has also increasingly been seen as a complement, and even as a substitute, to evidence from randomised controlled trials (RCTs).¹⁴ Exponential advancements in the field of data science and computational power alongside the increased availability of data sets (e.g. routinely collected data, data sharing, etc.) make secondary use of data easier to perform, at relatively low cost. Interventional studies are indeed heavily standardised and regulated (e.g. ICH guidelines, national regulations), within a relatively simple statistical paradigm which also helps to combat bias from major financial conflicts of interest inherent in the evaluation of pharmaceuticals. As illustrated in **Figure 1**, observational studies offer far greater analytical flexibility. Paradoxically, journals mandate registration only for primary analyses of clinical trials, precisely the situation in which analytical flexibility is often the lowest.

Figure 1: An idealised version of analytical flexibility across the research landscape

Analytical flexibility increases for observational research as the research question no longer shapes the design of the experiment (methods flexibility). Using data not primarily collected for research purposes adds the dimension of measurement flexibility: While in a trial one has to declare primary and secondary outcomes, timepoints and instruments, in the analysis of routinely collected data, one rather has to choose among many imperfectly measured variables which may have to be curated, combined, cleaned, and derived with each step adding opportunities for analytic choices. Examining existing data, on the other hand, presents the opportunity to analyse relationships between many variables, testing multiple hypotheses with ease (flexibility in research hypotheses). The black line delimits the studies for which the ICMJE requires a priori registration.



Registration can help to produce more reliable and transparent results

Since the analysis of observational data is highly flexible, there are often many possible analysis strategies that may produce very different results.^{15 16} If researchers are under the pressure to publish a “clear and convincing” story or invested in a given hypothesis, they may selectively report an analysis strategy, potentially arrived at *post hoc*, that yields the most convincing or impressive results while implicitly giving the impression that this analysis strategy was chosen in advance. This behaviour, also referred to as fishing for significance, or p-hacking, increases the probability of false positive and therefore spurious research findings that would likely not independently replicate.¹⁷ Registration does not eliminate analytical flexibility, but it avoids result dependent selective reporting or at least increases transparency by informing readers about the analytical decisions that were prespecified, compared to those that came later ideally with justification.¹⁸ In some instances, researchers could register a post hoc selected analysis of data they already have access to and have analyzed, however ideally registration would be done prior to data access or include disclosure of the research team’s familiarity with the dataset however there is no perfect solution to motivated dishonesty and fraud.

Prespecification can vary from minimal to maximal depending on whether the research question adopts an exploratory or a confirmatory approach.¹⁸ Ideally, this issue can be addressed by peer review prior to data analysis e.g. via the “registered reports” publication format.¹⁹ In this format, the decision to publish is taken before the research is carried out on

the basis of the quality of the question and proposed methods. Thereby, it is possible to gauge the level of pre-specification with regard to the question posed and guarantee publication independent of the findings.²⁰

Registration is therefore expected to reduce the likelihood of false positive results and increase the publication of findings no matter the direction of results. Registered clinical trials are more likely to have negative results than those that were unregistered,²¹ although the magnitude of the difference remains variable across surveys.^{22 23} Likewise, a recent study in psychology found a far greater percentage of negative results for registered reports than for studies without registration²⁴ and there is evidence suggesting high replication rates associated with registration in social and behavioural sciences.²⁵ In addition, without consistent registration we cannot know how many analyses remain unpublished.²⁶ For instance, we know that only 40% of observational studies evaluating an intervention with safety outcome(s) registered at ClinicalTrials.gov were published at least 30 months after study completion²⁷ but it is impossible to estimate this proportion for the vast majority of non-registered observational studies.

Registration also allows for checks of pre-registered outcomes against those presented in final reports, although issues remain with ensuring these checks routinely occur. For instance, discrepancies between registered and published outcomes of clinical trials are very common with estimated rates that are around 30%.²⁸ Such transparency is currently lacking for observational studies and the extent of biases resulting from result dependent selective reporting remains largely unknown and difficult to appraise: registration rarely occurs and when it occurs, it is usually after studies have started, with no specification of statistical analysis plans; around 30% do not even register a primary outcome.²⁶ European legislation requires the publication of study protocols of non-interventional post-authorisation safety studies²⁹ but statistical analysis plans are rarely if ever registered.

Existing registration tools need to be adapted to observational research

Registration of observational data should be as detailed as possible and as flexible as necessary, allowing for discussion of the knowns and unknowns. Of course, many observational studies do not involve interventions and instead aim to explore aetiological research questions around the causes and correlates of human disease.³⁰ Since many of these studies require a variety of analytical approaches, in which some flexibility is warranted, one cannot simply apply processes made for RCTs. Trial registries such as clinicaltrials.gov already offer registration of observational studies but their templates cannot,

and should not, be expected to work without modification for observational research³¹ since they lack the ability to specify detailed and nuanced analytical and statistical elements that are key sources of analytical flexibility in observational research. A non-exhaustive list of information to include in registration of observational studies is provided in **Box 1**. Some of these items are difficult to include in current registration formats, e.g. causal models often have a graphical display. Moreover, many routine procedures like exact methods for data cleaning and standardisation cannot be prespecified as they require interacting with the real data.

Box 1: Important information to be included in the registration of observational studies. Some of those characteristics may also be applicable to better reporting of plans for interventional studies, which are not currently detailed in registration.

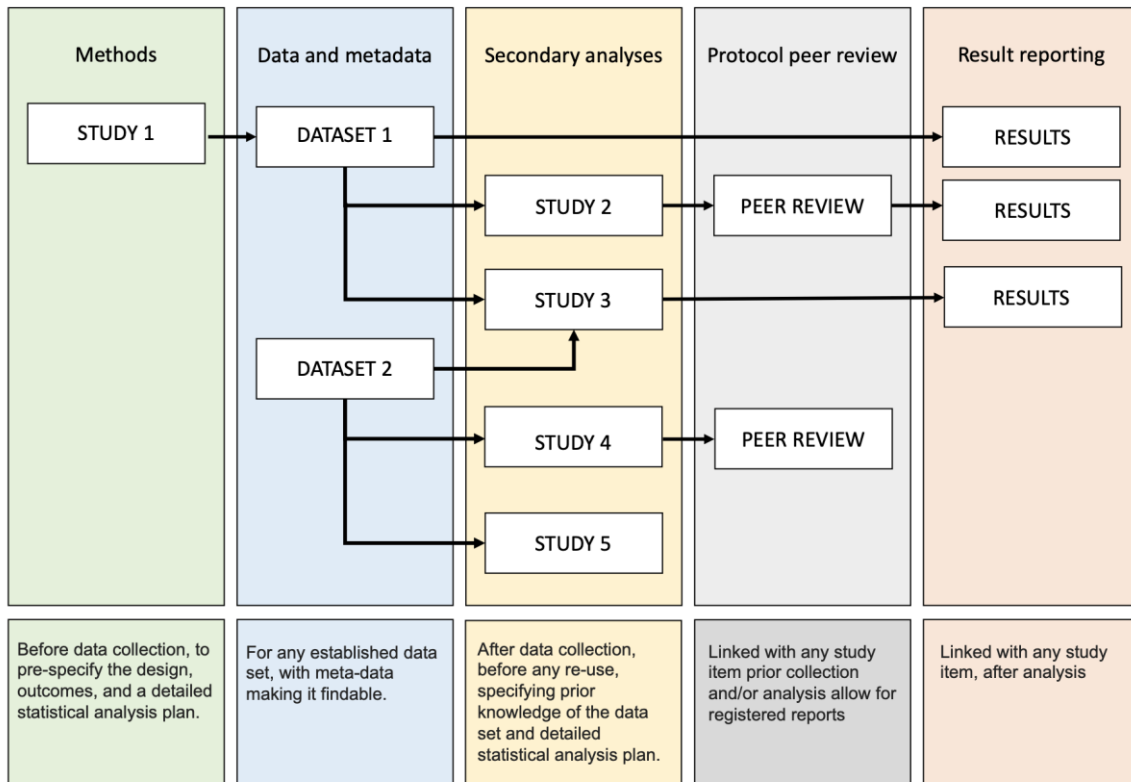
- . Approach (exploratory and/or confirmatory aspects)
- . Hypotheses to test
- . Causal model (e.g. exposures, outcomes, covariates, modelling approach and hypothesised association size)
- . Precise definition of variables to be used in the analysis
- . Strategies to handle challenges that may be encountered during data collection and analysis (e.g., missing values, outliers, deviations from modelling assumptions)
- . Approaches considered for control of multiple hypotheses (e.g., Bonferroni, false discovery rate)
- . Prior knowledge of the dataset (prior use of the dataset by others and degrees of bias control in case of prior access to the dataset by the authors)³²

At the same time, developments in observational study methods and analysis allow for better standardisation and sharing of protocols. The RCT-DUPLICATE project³³ used routinely collected data to replicate RCTs and demonstrated that registration is possible for these studies, with a time stamped national clinical trial (NCT) entry accompanied by both detailed protocols and statistical analysis plans drafted after feasibility analyses but before analysis of exposure-outcome relationships. These documents were much more detailed than the template offered by the registry and had to be provided as attachments. Registration can also complement and enhance applications for data access. When applying for access to many observational cohort datasets, such as the UK Biobank or publicly funded cohorts (e.g., BioLINCC), investigators are obliged to provide high-level hypotheses and analytic plans. Collecting and publicly archiving these applications, alongside descriptive

documentation such as codebooks, would result in a data-centric living repository of the existing and planned analyses of a given dataset that can influence and inform future research. Innovative ideas such as the UKRN octopus platform³⁴ can create a unified, streamlined and centralised approach to observational research registration. Octopus allows for publishing a wide range of interconnected building blocks throughout the lifecycle of a project including protocols, data, analyses, and peer review. **Figure 2** indicates how such a model fits with the research landscape we describe in this piece.

Figure 2: Fictional example of a comprehensive registration system suitable to address the flexibility of observational research, inspired by the UKRN Octopus³⁴

Study 1 is a prospective cohort study exploring the effect of deep brain stimulation (DBS) in a cohort of patients suffering from Parkinson disease in which registration occurs before data collection. Study 1 is linked to the registration of its dataset (dataset 1) and to the reporting of its results. Study 2 is a secondary analysis of study 1 exploring the effect of DBS in a subgroup of participants of study 1 with cognitive impairment. Study 2 underwent an a priori peer review of its analysis plan as part of a registered report process and has published some results. Data set 2 is an existing database of routinely collected data of patients with Parkinson disease and treated with various treatments that has been analysed in 3 distinct studies: study 3, a pooled analysis of datasets 1 and 2 that focuses on participants with deep brain stimulation and has some published results, study 4 (exploring the impact of various dopaminergic medications) and study 5 (emulating a randomised controlled trial that compares drugs versus DBS) that are ongoing studies (study 4 is a registered report) with no results available yet.



Registration can be used to inform patients

Centralised repositories on existing and planned analyses of a given dataset are not only essential for researchers to reduce redundancy in research efforts, but also possibly for patients and practitioners trying to navigate the potential multiplicity of results. Moreover, with the increasing availability of datasets, actors with vested interests can conduct their own re-analysis, adding to the confusion about which results to trust and how to interpret them.

Researchers need to be held accountable when reusing sensitive patient data for research. Several surveys support the altruistic wishes of patients to have their health data responsibly used and/or reused.^{35 36} However, any use of data with personal information, even if pseudonymised, carries risks such as reidentification. These risks bring with them an obligation to maximise the scientific value and benefit of research out of respect for the people whose sensitive personal data make these studies possible. Registration increases rigor and accountability and makes it possible to monitor the appropriate implementation of ethical principles and processes.³⁷ Furthermore patients have a right to be informed about, and to oppose, any use of their personal data. There is a unique opportunity to articulate registration of observational studies within existing and forthcoming mandates regarding data protection such as the European General Data Protection Regulation. This aspect could appear controversial and in stark contrast to current practice but it can be achieved by designing registration tools that can be easily searched by users including clinicians and patients, a feature that is currently lacking from the most comprehensive registration tools such as the Open Science Framework though this is improving.

Misconceptions and barriers must be overcome to make registration a new norm

A common concern around the registration of observational studies is that it will stifle exploration and discovery.³⁸ It is easy to conceive of registration as a bureaucratic exercise in which every single decision is rigidly pre-recorded without the opportunity for adaptation and adjustment for unexpected conditions.⁹ However, if we accept the idea that there can be no such thing as a perfect and exhaustive description of all possible analytic choices prior to data collection and analysis, registration becomes a flexible tool to enhance transparency without precluding authors from performing exploratory analyses or from changing analysis plans if they are duly justified and disclosed. Registration does not impede exploration or discovery, nor does it put the scientific value of exploratory analyses into question. It simply labels them as such allowing end-users to gauge their confidence when interpreting the study results.¹⁸ Authors should simply state whether there were deviations to the initial

analysis plan and report the initial and the final statistical analysis plan as well as the rationale for the deviations.

A second concern is that registration could create additional guidelines and bureaucracy that will ultimately hinder the scientific process more than help it advance.³⁹ Researchers with registration experience reported that registered studies are more time-consuming and increase work-related stress compared to non-preregistered work.⁴⁰ However, thinking carefully about your research plan, before it has begun, has the potential of increasing the methodological quality of the conducted research and making the actual data collection and analysis more efficient, for instance by including statisticians earlier in questions concerning research design and data extraction.

A final common fear of registration is that a research idea may be “scooped” by sharing it prior to conducting the study. While evidence for this fear is thin, some registration platforms such as the Open Science Framework offer an opportunity to embargo the public release of a registration until an analysis is ready to publish. In addition, with registration, the timestamped description of an idea is recorded, so it is possible to trace the provenance of an idea.

Stakeholders from throughout the research landscape should be consulted to create flexible and broadly acceptable standards for observational research registrations through organisations like the World Health Organization, the International Committee of Medical Journal Editors, and the EQUATOR network. These efforts should align with emerging priorities to promote research integrity and trustworthy science and to incentivise open science practices including registration of hypotheses, design and analyses.⁴¹ These are becoming the new standards by which science is judged. Observational research will not be exempted from these emerging expectations.

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