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Author/s:

Platt, RW;Platt, R;Brown, JS;Henry, DA;Klungel, OH;Suissa, S

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How pharmacoepidemiology networks can manage distributed analyses to improve replicability and transparency and minimise bias

Platt RW^{1,2,3*}, Platt R⁴, Brown JS⁴, Henry DA^{5,6,7}, Klungel OH^{8,9}, Suijsa, S^{1,2}

¹ Department of Epidemiology, Biostatistics, and Occupational Health, McGill University

² Lady Davis Research Institute of the Jewish General Hospital, Montreal, Canada

³ Research Institute of the McGill University Health Centre, Montreal, Canada

⁴ Harvard Medical School and Harvard Pilgrim Health Care Institute

⁵ Centre for Research in Evidence-based practice, Bond University, Gold Coast, Australia

⁶ Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia

⁷ Institute for Clinical and Evaluative Sciences, Toronto, Canada

⁸ Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

⁹ Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

***Corresponding author:** RW Platt

Mailing address: Dept of Epidemiology, Biostatistics, and Occupational Health
McGill University
1020 Pine Ave W
Montreal, Quebec, Canada, H3A 1A2

Email: robert.platt@mcgill.ca

Phone: 514-340-8222 x 28683

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Running head: Non-methodological biases

Key words: pharmacoepidemiology, distributed networks, bias, protocol, common data model.

Abstract

Several pharmacoepidemiology networks have been developed over the past decade that use a distributed approach, implementing the same analysis at multiple data sites, to preserve privacy and minimize data sharing. The structure of these networks can also be leveraged to improve replicability, increase transparency, and reduce bias. We describe some features of distributed networks using, as examples, the Canadian Network for Observational Drug Effect Studies, the Sentinel System in the USA and the European Research Network of Pharmacovigilance and Pharmacoepidemiology. Common protocols, analysis plans, and data models, with policies on amendments and protocol violations, are key features. These tools ensure that studies can be audited and repeated as necessary. Blinding and strict conflict of interest policies reduce the potential for bias in analyses and interpretation. Distributed networks are efficient, by interrogating data on very large populations. These developments should improve the timeliness and accuracy of information used to support both clinical and regulatory decisions.

Introduction

Bias is the pervasive threat to observational pharmacoepidemiology. Confounding, selection bias, and measurement error can arise in any observational study, and confounding by indication and protopathic bias are common in studies of drug effectiveness and safety. This is one of the reasons why regulators favor randomized trials as the primary source of evidence for drug approval. But randomized trials are costly and their ability to quantify adverse effects is often limited by insufficient sample size and duration of follow-up. Consequently, observational studies have become a cornerstone of drug safety research. Considerable gains have been made in the development of design and analytical methods to minimize biases in pharmaco-epidemiological research (1). These developments are recognized by regulators; for example, 21st Century Cures Act in the United States supports the use of observational data to support new drug indications and post-marketing requirements (2), while the EMA scientific guide on post-authorisation studies clearly indicates openness to observational studies for investigating post-authorisation issues (3).

Timeliness, replicability, reproducibility, and transparency are important in ensuring confidence in decisions based on research studies (4,5). Replicability and transparency are particularly important in drug safety, where study results may lead directly to regulatory and public health

action. Divergence in study results can create significant uncertainty for patients, practitioners, drug manufacturers, and regulators (6). There are multiple examples of “one-off” studies, where the findings have not been replicated. Sometimes this indicates true variability, but more often it is attributable to methodological variation between studies (7) and lack of transparency. It is often not possible to discern the underlying cause of these differences. Observational studies have been increasingly used to investigate new indications for older drugs, including hormone replacement therapy to prevent cardiovascular disease, statins to treat chronic obstructive pulmonary disease (COPD) and metformin to treat cancer (8,9). These hypotheses were refuted in subsequent randomized trials and the observational studies were found to have important methodological weaknesses (10,11) further indicating the need for minimally biased and reproducible observational studies. While there are well-established procedures for Good Clinical Practice for the conduct of randomized trials, these procedures are less standardized for observational studies. For example, pharmacovigilance studies in the European Union should follow analogous Good Pharmacovigilance Practices, and may be subject to routine inspections.

Data networks are highly efficient, and with distributed analyses they effectively implement the same study at multiple sites (12). Distributed analyses, using near-identical protocols, can assure methodological quality and transparency, and increase the likelihood that differences between

sites are due to true variation in effect size, rather than design or process-related problems. Moreover, study designs developed by teams help ensure that errors are not overlooked, and should be more likely to avoid known errors and minimize bias. Nevertheless, while study methods are the primary focus of efforts to minimise bias, network operations offer additional opportunities to improve study quality.

In this commentary we focus on management approaches to minimisation of bias in network analyses *other than* good study design and methods. We illustrate these principles in the context of work by three distributed pharmacoepidemiology networks: Sentinel, The Canadian Network for Observational Drug Effect Studies (CNODES), and the European Pharmacoepidemiology and Pharmacovigilance Research Network (formerly IMI-PROTECT).

Phased Common Protocol-driven Analyses

One of the strengths of the randomized trial paradigm is the requirement for detailed protocols and statistical analysis plans. These are typically followed carefully, across multiple sites, with documentation of any amendments and protocol deviations. This ensures that the study accomplishes what was intended, and that others can replicate the study setting and results if necessary.

Distributed networks enable similar protocol-driven analyses of observational data at multiple sites. As an example, CNODES conducts studies using a structured protocol, along with a very

detailed data management and statistical analysis plan, to ensure that processes are comparable (ideally, identical) in the various study sites, and that others can follow and validate these processes. The guiding principles of this process are reproducibility and bias minimization. The intent is that any potential biases or problems in the data are discovered before any decision is made on the drug-outcome association, and that any analyses done in one center could be reproduced if another analyst were given the same data and the statistical analysis plan. At CNODES protocols are developed in a collaborative way involving several researchers and stakeholders, to ensure that multiple inputs are considered, and no group or perspective dominates the discussion. CNODES protocols are registered with clinicaltrials.gov, with clearly specified outcomes and exposures (including description of codes and measures used to define them). Protocol amendments, deviations and outlying results are monitored and recorded and registered, increasing the likelihood that the process is reproducible. Similarly, all study protocols of the IMI-PROTECT network were registered at the European Union electronic Register of Post-Authorization Studies (EU-PAS Register), available at the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (www.encepp.eu).

The statistical analysis plan (SAP) is a key component of CNODES' process. This is a step-by-step guide that sets out how each CNODES site will design their study and analyze their data. It is usually written after the scientific protocol has been developed by the project team in consultation with site investigators and analysts, who must ensure the feasibility of the work at

the participating sites. The statistical analysis plan includes detailed descriptions, including SAS code for complex analyses of primary outcomes, as well as detailed sensitivity analysis.

The SAP is created and implemented in phases. The first phase describes cohort construction, including definitions of exposures, outcomes, and measures of confounding, and requires production of descriptive statistics. These descriptive statistics are reviewed before proceeding with further analyses, to ensure that the initial assumptions (e.g. outcome frequencies and distributions of potential confounders) on which the study was based were valid, and that data are roughly comparable across sites. For example, Renoux et al (13) detected a nine-fold difference between sites in the rate of coding of sudden cardiac death after reviewing initial data. These processes enable judgement on the feasibility of the study, and on appropriateness of confounding control at an early stage in the research. Importantly, they allow the research team to understand comparability of the data before any analyses of association are conducted. Any comparisons across sites after associations are computed may be subject to the biases mentioned above; comparing only baseline data preserves the statistical properties of the estimation process so that, for example, 95% confidence intervals have appropriate 95% coverage.

The second phase of the analysis includes models for the primary analysis as well as secondary and sensitivity analyses. These analyses are conducted only after review of initial results by the research team and by the query submitter. As above, any protocol deviations or amendments are recorded. The analyses are then deposited in a secure repository for review by the central team.

When site teams lodge results, they are unaware of the data that have been lodged by other sites (see section on Blinding).

Both Sentinel and CNODES separate the work done by the analysis teams (conducting analyses at individual sites) and the group that conducts the summary analyses and meta-analyses. The independent scrutiny of site-specific results sometimes identifies outliers. CNODES uses a structured process for investigating these. A series of structured quality checks are initiated by the analysis team to determine whether there were any errors in coding, and further follow up is done to assess whether population or formulary differences may account for the results. This has occurred in few CNODES studies to date. In one study, an outlier was identified, but re-analysis and follow-up determined that the analyses were done correctly and that there were no obvious reasons for the outlier (14); in a second study, an outlier was identified and was eventually ascribed to differences in formulary restrictions across provinces (15).

Common Data Model-based Methods

Sentinel uses a similar process to CNODES but focuses on a common data model (16) and standardized analytic programs (17,18). The Sentinel common data model (SCDM) is a framework in which data are converted to a standardized data structure with common table formats, meanings, and variable names across data partners. The SCDM primarily preserves original data values, such as diagnosis or procedure codes, whenever possible, so that few values are mapped, combined or manipulated in the conversion process to minimize information is lost;

in principle the data could be converted back to the original dataset. The data model transformations are subjected to rigorous review and data are only used when each dataset has passed the Sentinel data quality review process (19)

Some Sentinel system studies begin with a detailed protocol that serves as the basis for a single team to developing analytic programs. A set of standardized SAS programs is then distributed to the sites, who run the analyses without modification and return only summary results to the coordinating center via a secure portal. Full protocols are publicly posted (20). Full reports are also publicly posted (21) and published when appropriate (22).

Increasingly, Sentinel employs reusable “modular” programs in place of custom written programs to perform commonly needed analyses, such as propensity score matched new user comparative cohort studies and self-controlled risk interval studies. These programs have the advantage of much faster development time, execute more efficiently than one off programs, and they obviate the need for detailed review at each site. These modular programs form the basis for FDA’s Active Risk Identification and Analysis (ARIA) program. When an ARIA analysis study is initiated, a study concept brief is used to develop a set of query specifications that are used by the standardized SAS tools to implement the specific query. Several aspects of Sentinel processes minimize the potential for bias. Most of the processes are like those used by

CNODES. In addition, since the distributed programs require that data structures and software are identical across sites, inter-analyst discrepancies are effectively eliminated.

Other networks have used variations on each of these systems. The Observational Health Data Sciences and Informatics (OHDSI) network uses the Observational Medical Outcomes Partnership (OMOP) common data model, which has aspects like the SCDM but with some key differences. The major difference is that the OMOP CDM maps the raw data to concepts; drugs, conditions, and outcomes are defined using summary concepts rather than the individual data elements; these concepts are the basis of the analyses. OMOP is also an open-source framework (23), so that quality checks are the responsibility of the individual sites rather than based on a centralized and standardized approach that determines acceptable levels of data quality, data model conformance to value sets, format, and meaning before use. The AsPEN network (24) has implemented the OMOP CDM. In contrast, the IMI-PROTECT network used a common-protocol method similar to CNODES (25).

Which of these strategies is better or more useful? It depends on the question and the setting. Common data model and protocol-based methods are clearly more likely to be replicated across network sites, because they reduce the amount of variation between datasets and data analysts. The Sentinel CDM standardizes data structures and is actively curated; data must be reviewed and approved before use in any analyses. The OMOP CDM takes one step further by mapping standard coding terminologies to standardize definitions. Both methods require significant up-

front development work, which pays off based on economies of scale. Further, the use of standardized programs potentially limits the kinds of analyses that could be done quickly using the tools, but may increase transparency of results by reducing ambiguity about the methods. The combination of a CDM and standardized tools enables transparent representation of the analysis, including sharing the detailed standardized specifications and even the executable code. Each Sentinel report is posted to the Sentinel website (<https://www.sentinelinitiative.org/>) and includes the detailed study specifications used by the standardized SAS tools, thereby allowing full transparency and greatly facilitating reproducibility.

Blinding

In clinical studies, in particular randomized controlled trials, it is standard practice to blind evaluators to the treatment status of the patient so as to avoid bias in the evaluation of patient outcomes (26). Sentinel, by using distributed SAS code, and centralized result collection, ensures that data partner-specific results are not seen by other data partners or any other stakeholders prior to final reporting of results. Only the central team sees all results before aggregation and final analysis. Further, because the results are aggregated based on the pre-determined study specifications, the potential for post hoc analyses is greatly reduced and often impossible given the data available to the central team.

Blinding is particularly relevant when there are differential delays in analyses across sites. Typically, these are due to the timing of approval by different data custodians. If one site in the

network is delayed, and other sites have already submitted results, the analyst could feel some obligation to make decisions leading to a result that is consistent with those already lodged. To prevent this possibility, CNODES analysts are advised not to discuss results amongst themselves prior to discussion of the complete pooled results. Analyses are deposited in a centralized repository, such that site researchers can only see their own results, and only the central analysis team has access to all sites' results. These blinding steps ensure that analysts don't have the opportunity to "chase" results, i.e., to try to manipulate their own results to resemble other sites, and that each analysis is done in compliance with the protocol. The IMI-PROTECT network applies a similar approach. Analysts in participating centres are blinded to the results of the other centres and results are stored at the coordinating centre. After completion of analyses by all centres, results are shared and discussed (27).

Conflicts of Interest

In studies of drug safety, conflict of interest (COI) is a potential source of bias. COI can arise when interests of a personal, financial, or other nature (e.g., ownership of, or consulting for, a pharmaceutical company that manufactures a treatment under consideration) may impact impartiality with respect to a particular study. Complete avoidance of COI is hard to achieve across a network comprising researchers with expertise in clinical sciences, epidemiology and biostatistics. Thus, large teams conducting network analyses must manage potential conflicts. The CNODES executive committee conducts an annual review of disclosures provided by all steering committee members and analysts; in addition, a study-specific disclosure is required

from each study team member. The CNODES policy (28) specifies conflicts of interest that preclude participation in CNODES studies, and provides principles for managing other, less serious, conflicts. Briefly, a researcher with a significant conflicting interest relating to a specific drug, or topic, cannot lead or provide substantial input into a CNODES study. If a conflicted researcher has relevant knowledge or skills (e.g. clinical content), input may be sought, but a management strategy is implemented. For instance, the researcher may be involved in the design phase, and qualify as co-author, but is not involved directly in the analysis or reporting of the study. Sentinel has a similar detailed policy to manage conflicts of interest. It requires that individuals who are in decision-making roles regarding analyses not have conflicts of interest. The IMI-PROTECT project was a public-private partnership and the initial studies were methodological case-studies on relevant drug safety issues that were known. In the EU Pharmacoepidemiology & Pharmacovigilance Research Network the public partners have continued their collaboration via a framework contract with the European Medicines Agency (EMA) (29) All studies are conducted according to the ENCePP Code of Conduct in which a set of rules and principles for pharmacoepidemiology and pharmacovigilance studies are provided to promote transparency and scientific independence throughout the research process (30).

Table 1 summarizes the three networks' approaches to each of these issues.

Conclusion

Bias and lack of replicability are constant threats to drug safety research. Best practices in study design and analysis, particularly when developed in a team environment, can avoid known errors, minimize bias, and increase replicability of findings across individually conducted studies. Moreover, distributed data networks are uniquely positioned to address these problems through procedures and processes such as those outlined here. Strict procedures for collaborative design, and careful attention to protocol development and implementation can help minimize bias; the use of distributed networks inherently ensures replicability, given that studies are conducted concurrently at multiple sites.

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Table 1:

Network	Protocol-driven analysis	Common data model	Blinding	Conflict of Interest
CNODES	Analyses follow registered, pre-specified protocol Detailed statistical analysis plan Interim analyses	None for most studies. Implementing Sentinel CDM (pilot) To be used for simple queries	All analysts blinded to others' results until central review complete	COI managed following pre-specified policy Study-specific and annual COI declarations.
Sentinel	Sentinel common data model projects follow pre-specified protocols. Analyses use standardized algorithms	Uses Sentinel CDM and distributed analyses	Only central site sees all results	COI managed following pre-specified policy
IMI-PROTECT/EnCEPP	Analyses follow registered, pre-specified protocol. Protocols registered at	No common data model	All analysts blinded to others' results until central review complete	Follows EU-ADR framework.

	EU-PAS Registry			
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