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COMMENTARY

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Reuse of data sources to evaluate drug safety signals: When is it appropriate?

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1 | INTRODUCTION

When can the same data source that generated a safety hypothesis also be used to evaluate it? Regulators who oversee health products frequently turn to health insurance claims, electronic medical records, as well as registries of drugs, devices, and diseases to support their decision making. In addition to protocol-based studies, these "real-world" data can be used to identify adverse events associated with drug use.[1] Can the same data sources help us understand whether the events are an effect of the drug?

Some of us were members of a joint task force between the International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology, which produced a report whose fifth recommendation was to "*perform hypothesis evaluating treatment effectiveness (HETE) studies on a different data source and population than the one used to generate the hypotheses to be tested, unless it is not feasible*."[2] This recommendation highlighted the value of examining associations in different patient populations and consideration of the role of chance in initial hypothesis generating analyses. The report stated that when replicate analyses in an external data source is not feasible, reuse of the original data source may be considered, but because "*…many consider this practice to be a departure from good science, a publication should acknowledge the risks involved in acting upon the results*."[2]

The main arguments against reusing data sources are (1) that using the same data in a reanalysis leads to replication rather than confirmation and (2) that a bias which affects an initial finding will affect follow-on studies in a similar way. The concern is that data from comparisons made in the initial analysis may drive the results of more comprehensive analyses that make the same comparisons. No one argues for bulking up a new analysis with already-examined data. The warning in the International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology (ISPOR/ISPE) report's fifth recommendation was against replicating a potentially biased analysis with a similarly biased study.

The ISPOR/ISPE report was focused on effectiveness studies. Effectiveness studies have prespecified, biologically based hypotheses and evaluate *intended* effects of specific products on well-defined outcomes. In contrast, although safety studies may arise from a prior concern, they evaluate *unintended* drug effects and often do not have narrowly defined or prespecified hypotheses. Guarding against artifact and chance in the safety setting relies more heavily on biology than on prespecifiable design. The goal of follow on analyses is to examine more evidence. For example, information from different drugs of the same class may be relevant to an apparent discovered effect, as would the presence of different adverse effects in the treated, if those distinct effects resulted from the same hypothesized biological mechanism.

We believe that the recommendation against reuse of data sources in hypothesis-evaluating treatment effectiveness studies is inappropriate in settings of discovery. The report's broad injunction may discourage researchers from digging into worrisome safety signals. In drug safety research, there are many situations for which "reuse" of a data source is appropriate and we would recommend it.

2 | REFUTATION OF HYPOTHESES THROUGH DATA QUALITY CHECKS AND SENSITIVITY ANALYSES

It is often not possible to do data validation and full confounder-adjusted analyses when conducting safety surveillance with data mining, sequential analysis, or other methods to detect potential safety problems. It is therefore good research practice to conduct sensitivity analyses and reevaluate findings in the data source with variations in eligibility criteria,[3] additional confounding control,[4] calibration of findings with external data,[5] as well as other checks for the robustness of a finding.[6,7] Such analyses quantify the impact of biases that compete with biologic explanation for a safety signal. Applying greater confounding control or calibrating outcomes or covariates with validation studies could potentially explain associations observed in hypothesis generating surveillance activities. For example, in the Vaccine Safety Datalink (VSD), sequential surveillance activities led to a statistical signal for measles-mumps-rubella-varicella (MMRV) and ataxia.[7] This was refuted after chart review informed removal of various gait problems that had been miscoded as ataxia at 1 of the study sites. Similarly, an initial statistical signal for RotaTeq and gastrointestinal bleeding disappeared after careful adjustment for confounding by age, site, and week of vaccination.[7]

3 | INVESTIGATION OF BIOLOGICALLY BASED, "ORTHOGONAL" HYPOTHESES

An initial safety signal can be refuted or strengthened by reusing a data source to evaluate a biologically based orthogonal hypothesis, a hypothesis which makes a testable prediction that is not a restatement of the initial finding.[8] Hypotheses are orthogonal and statistically independent when they pertain to a different exposure, a different outcome, or a different population. For example, sequential surveillance in the VSD found more febrile seizures after vaccination with MMRV compared with the measles-mumps-rubella (MMR) vaccine. If the theorized biological pathway is that MMRV sometimes causes fever, and fever sometimes causes seizure, then this theory can be tested by assessing whether MMRV causes fever, apart from seizure. An elevation in risk of fever after MMRV could strengthen the evidence for the MMRV-seizure relationship whereas lack of an association with fever might increase skepticism. VSD data showed that fever without seizure was also elevated during the same time period for MMRV versus MMR.[9] The test was statistically independent because the observations were physically independent. Because of the biological relationship between fever and febrile seizures, this strengthened the evidence for a causal link.

In an exploration of linked data from the Danish Cancer and Prescription Registries, an association was found between receipt of an amiloride/hydrochlorothiazide combination product and the occurrence of lip cancer.[10] Using the same data source, the researchers next showed that exposure to hydrochlorothiazide in drug combinations other than amiloride/hydrochlorothiazide was also associated with an elevated risk for lip cancer[11] as well as nonmelanoma skin cancers.[12] The hypothesis generated and refined in the Danish data was that the use of hydrochlorothiazide predisposes patients to skin cancer. Follow-on studies tested hypotheses that were orthogonal from the initial signal, involving different exposed patients. These results strengthened evidence for a hypothesized causal relationship between hydrochlorothiazide and skin cancers.

4 | INVESTIGATION OF TEMPORALITY

Another way to explore orthogonal hypotheses using the same data source is to evaluate the same exposure and outcome with a statistically independent hypothesis about timing. If a cohort study were to show an elevation in risk for an acute event over a broad time window, many plausible biological mechanisms could be ruled out because they would not result in risk being distributed uniformly across the window. For such mechanisms, temporal clusters in the timing of outcomes in relation to exposure initiation may provide evidence that supports a biologically driven increase in risk. In the VSD MMRV example, the original signal was based on seizure counts in the 1 to 42 days after vaccination. Conditioning on those detected cases, a statistically independent temporal scan statistic was used to identify a cluster 7 to 10 days post vaccination.[9]

5 | IMPLICATIONS OF A CAUSAL EFFECT

Analyses that investigate related hypotheses can refine understanding of potential biologic pathways for an initial signal. Randomized clinical trials and cohort studies that involve primary data collection (eg, Nurses' Health Study, Women's Health Initiative) frequently identify unexpected safety signals and follow up with evaluation of both orthogonal and nonorthogonal hypotheses. For example, evaluation of dose-response, subgroups, and related outcomes may provide insight into potential mechanisms behind exposure effects. These investigations of related hypotheses may or may not be statistically independent of the original finding, but they can contribute to the evidence base, with the caveat that investigators should be clear about overlap with prior analyses. For example, if an initial analysis compared drug A with drug B, a dose-response analysis that compared medium or high doses of drug A to low doses is statistically independent from the initial analysis. However, a dose-response analysis that included a category with zero exposure to drug A (eg, those exposed to drug B) would not be independent.

5.1 | Reusing data sources is permissible and can contribute to understanding of unintended effects of drugs

Researchers, readers, reviewers, and meta-analysts should always be on guard against representing recycled data as new observations. The thrust of this commentary is that reusing data sources is distinct from reusing data. The examples show how multiple analyses can be conducted within a single, multipurpose data resource to better understand a hypothesis. The approaches described address the primary concerns about data reuse—statistically correlated findings and systematic biases. Re-examination of data to find the appearance

of structure where none truly exists ("data dredging," "fishing," or "torturing the data until it confesses") is never helpful.[13,14] In contrast, conducting analyses to refine understanding, strengthen, or refute an initial hypothesis in the same data source that generated is, in the words of the ISPOR/ISPE Task Force, most definitely "good science."

CONFLICT OF INTEREST

SVW, MK, JJG, and SS have received salary support from the FDA Sentinel System. SVW has received salary support from investigator initiated grants to Brigham and Women's Hospital from Novartis, Bayer, and Boehringer Ingelheim for unrelated work and is a consultant to Aetion, Inc. JJG has received salary support from grants from Eli Lilly and Company and Novartis Pharmaceuticals Corporation to the Brigham and Women's Hospital and is a consultant to Aetion, Inc. and Optum, Inc., all for unrelated work. SS is a consultant to WHISCON, LLC and to Aetion, Inc., a software manufacturer of which he also owns equity. He is principal investigator of investigator-initiated grants to the Brigham and Women's Hospital from Bayer, Genentech and Boehringer Ingelheim unrelated to the topic of this essay.

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REFERENCES

1. Platt R, Carnahan RM, Brown JS, et al. The U.S. Food and Drug Administration's mini-sentinel program: Status and direction. *Pharmacoepidemiol Drug Saf*. Jan 2012;21(Suppl 1):1-8.
2. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE special task force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf*. Sep 2017;26(9):1033-1039.
3. Schneeweiss S, Patrick AR, Sturmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care*. Oct 2007;45(10 Supl 2):S131-S142.
4. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. Jul 2009;20(4):512-522.
5. Sturmer T, Schneeweiss S, Avorn J, Glynn RJ. Adjusting effect estimates for unmeasured confounding with validation data using propensity score calibration. *Am J Epidemiol*. Aug 1 2005;162(3):279-289.
6. Gagne JW, Wang SV; Fox, M; Lash, T; Eddings, W; Dublin, Sascha; Gerhard, T; Psaty, B; Maro, J; Rogers, C; Ouellet-Hellstrom, R; Pinheiro, S; Levenson, M; Forshee, R; Shoaibi, A; Schneeweiss, S. *Analytical methods to assess robustness of drug safety monitoring results*. September 14, 2015.
7. Yih WK, Kulldorff M, Fireman BH, et al. Active surveillance for adverse events: The experience of the vaccine safety datalink project. *Pediatrics*. May 2011;127(Suppl 1):S54-S64.
8. Walker AM. Orthogonal predictions: Follow-up questions for suggestive data. *Pharmacoepidemiol Drug Saf*. 2010;19(5):529-532.
9. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. Jul 2010;126(1):e1-e8.
10. Pottegard A, Friis S, Christensen R, Habel LA, Gagne JJ, Hallas J. Identification of associations between prescribed medications and Cancer: A nationwide screening study. *EBioMedicine*. May 2016;7:73-79.
11. Pottegard A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med*. Oct 2017;282(4):322-331.
12. Pederson SG, D; Schmidt, SAJ; Holmich LR; Friis, S; Pottegard, A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case control study from Denmark. *J Am Acad Dermatol*. 2017;9622(17)(S0190).
13. Pocock SJ, Collier TJ, Dandreo KJ, et al. Issues in the reporting of epidemiological studies: A survey of recent practice. *BMJ*. 2004;329(7471):883.
14. Strom BL, Kimmel SE, Hennessy S. *Pharmacoepidemiology*. *123Library*. 5th ed. Wiley-Blackwell; 2011.

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