

6 November 2019

ICH Secretariat
Route de Pré-Bois, 20
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1215 Geneva
Switzerland

Dear Members of the ICH E8(R1) Expert Working Group,

For the last 15 years, I have evaluated drug safety and effectiveness in observational settings, largely using secondary data. I have also studied the methods and study designs that we use to do so. With that background, I would like to address the important contribution that these guidelines might make toward setting expectations for the use of modern pharmacoepidemiologic study designs as we increasingly draw on non-interventional, or observational, research to characterize drug effects.

Randomized, placebo-controlled trials provide evidence of efficacy when specific assumptions are met, and the features of study design that enable a reasonable chance at meeting those assumptions have been well established. Most would agree that two critical features are 1) randomization and 2) blinding (or masking) patients and providers to the assigned treatment. These design features do not guarantee unbiased estimates of treatment effects, but adherence to these standards makes it less likely that systematic bias has been introduced.

Evidence of efficacy can also be based on findings from non-randomized (or non-interventional) studies under a specific set of assumptions. Moreover, in the last 15 years, the field of pharmacoepidemiology has identified key features of study designs in non-interventional settings that can tip the scales in favor of meeting these assumptions. There are three of particular importance: use of an active treatment for the comparator; anchoring the start of follow-up up at the time of treatment initiation; and avoiding looking into the future to select patients. I would like to briefly elaborate on each of these.

The use of an appropriate **active comparator** can often balance the treatment groups on major drivers of the outcomes such as the indication for treatment and disease severity, health care seeking and frailty. For example, we have shown that patients with gestational diabetes who are initially treated with metformin are substantially similar to those who receive insulin; women treated with ondansetron are more like those who receive other anti-emetics in early pregnancy than those who receive no prescriptions for nausea and vomiting in pregnancy; and adults who receive glargine are much like those who receive NPH insulin. In contrast, non-user comparison groups include an unhelpful mix of patients who are 'too healthy' by virtue of not being sick enough to require treatment and those who are 'too frail' to tolerate treatment despite being indicated for it. Focusing on patients who are receiving active treatment greatly reduces this bias by design.



The second key design feature is the identification of **new users**, or treatment initiation, which effectively anchors the start of follow-up at a common point. Like in a randomized trial, this design feature ensures that the capture of outcomes includes similar windows of time for both treatment groups. This is particularly important when those patients who are vulnerable to an adverse outcome or who fail to have sufficient therapeutic response discontinue the medication early on. The pool of prevalent users has already eliminated both of these groups and therefore no longer represents the risks and benefits of treatment for all those who initiated it but rather is enriched with those who receive benefit and did not experience any harms. Anchoring time at treatment initiation also ensures that confounders measured at baseline have not already been affected by the treatment itself.

The third key development of modern observational pharmacoepidemiology is a recognition that we cannot use omniscient powers derived from access to secondary healthcare data to select patients. Physicians are not able to selectively treat patients based on events that will occur months or years in the future, and therefore neither can we. Eliminating patients from treatment groups up front based on failure to adhere to the treatment or failure to survive for some time into the future introduces bias, just as it would in a randomized trial.

Let me conclude by acknowledging that there are some settings in which deviations from these 'best practices' (as I am calling them) are necessary just as there are times when blinding in a randomized trial is not feasible. Likewise, these three features of modern pharmacoepidemiology studies are not exhaustive. Given the variety of research questions, diversity of data sources and complexity of clinical contexts, robust study design requires expertise and insight from pharmacoepidemiology.

Quality by design is essential to the development of reliable real-world evidence. And yet, at present there seems to be little official guidance from ICH regarding the design of these studies. In the absence of clear statements, some investigators will continue to rely on outdated approaches (such as comparisons of ever vs. never users) simply due to a lack of awareness rather than well-founded necessity. The revision of ICH E8 is an opportunity to increase the quality and decrease uncertainty around non-interventional studies at a time when both are needed by communicating clear expectations for the design features that are known to reduce common sources of systematic bias.

Respectfully submitted,

A handwritten signature in blue ink that reads "Michele Jonsson Funk". The signature is fluid and cursive, with a long horizontal flourish extending to the right.

Michele Jonsson Funk, PhD, FISPE

On behalf of the International Society for Pharmacoepidemiology