Wednesday 24 July 2024

14:00-15:30 Invited Session 7 (Main Room)

Regulators' view of randomized and non-randomized evidence in drug development (Chairs: Adbel Babiker, Giota Touloumi)

The magic of randomization versus the myth of Real-World Evidence

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Non-randomized observational analyses of large electronic patient databases are being promoted as an alternative to randomized clinical trials as a source of "real-world evidence" about the efficacy and safety of treatments. For drugs or procedures that are already being used widely, such observational studies may involve exposure of large numbers of patients. Consequently, they have the potential to detect rare adverse effects that cannot plausibly be attributed to bias, generally because the relative risk is large (e.g. rhabdomyolysis associated with the use of statin therapy). Non-randomized clinical observation may also suffice to detect sudden beneficial effects when good outcomes would not otherwise be expected (eg, control of diabetic ketoacidosis with insulin, or sudden tumour shrinkage).

However, because of the potential biases inherent in observational studies, they cannot generally be trusted when — as is often the case — the effects of the treatment are actually null, or only moderate (ie, less than a twofold difference in the incidence of the health outcome between using and not using the treatment). In those circumstances, large observational studies may yield misleading associations of a treatment with health outcomes that are statistically significant but non-causal, or that are mistakenly null when the treatment really does have clinically important effects. Instead, randomized, controlled trials of adequate size are generally required to ensure that realistically *moderate* benefits or *moderate* harms of a treatment are assessed reliably enough to guide patient care appropriately.

The solution to the problems caused by the bureaucratic burdens that have been increasingly imposed on randomized trials during the past 25 years is not to replace randomization with unreliable non-randomized database analyses. Instead, unnecessary obstacles to the reliable assessment of the efficacy and safety of treatments in randomized trials of appropriate size need to be removed.

Terminology: It has unfortunately become common usage for "real-world evidence" to mean non-randomised evidence, and that is the usage in this abstract. The term "real-world data" has been used in recent guidelines merely to mean data not specifically collected for research (eg, from electronic health records); with this usage, *both* randomised *and* non-randomised studies use "real-world data".

Reference: Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. NEJM 2020; 382: 674-8. Acknowledgement: This abstract was drafted by R Collins.