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LETTER TO THE EDITOR

Authors' Reply to Harpaz et al. Comment on: "Zoo or Savannah? Choice of Training Ground for Evidence-Based Pharmacovigilance"

G. Niklas Norén · Ola Caster · Kristina Juhlin · Marie Lindquist

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Harpaz et al. [1] have provided a thoughtful response to our recently published commentary on the choice of reference set in pharmacovigilance methods development and evaluation [2]. Their letter offers important complementary perspectives. We share their view that the development and maintenance of reference sets of emerging adverse drug reactions are challenging, and will benefit from a concerted effort.

Harpaz et al. draw attention to the risk that backdated analyses may lack external validity for the context in which signal detection is performed today, and argue that efforts must be made to establish reference sets of more recently emerging adverse drug reactions. We agree: in some cases, changes in the properties of the underlying data could render conclusions based on historical data invalid, and this must be carefully considered on a case by case basis; in other cases, such changes will be inconsequential. Harpaz et al. note that more recently emerging adverse drug reactions may eventually be refuted. However, from a practical perspective this may not be a major limitation. Statistical signal detection is used to focus the attention of the pharmacovigilance assessors on those suspected adverse drug reactions that merit closer review, and this should include some that are eventually dismissed.

Harpaz et al. emphasize that some post-approval adverse drug reactions emerge soon after marketing, before much evidence has gathered in a particular data set. Indeed, this reflects the reality of pharmacovigilance where no single source of information is capable of detecting all emerging adverse drug reactions early, and highly sensitive methods are sometimes required for timely discovery. Boosting difficult positive controls with post-detection data would be counterproductive and disguise the limitations of a data set or analysis method at hand.

We agree that time-to-detection can be an important dimension for performance evaluation. Examples of its previous use include the comparison between regression and disproportionality analysis by Caster et al. [3] and the comparison between statistical and traditional signal detection by Alvarez et al. [4]. Time-to-detection is also one of the core metrics in the ongoing performance evaluations across multiple spontaneous reporting systems, within the European public-private partnership PROTECT (http://www.imi-protect.eu/). However, consideration of timeliness does not eliminate the need to distinguish between emerging and established adverse drug reactions; we would not recommend a comparison of statistical signal detection methods based on how early in the post-marketing phase they signalled adverse drug reactions that were known already from pre-marketing clinical trials.

We commend Harpaz et al. for developing a reference set of recently emerging adverse drug reactions and making it openly available. This should enable more relevant pharmacovigilance performance evaluation, and provide a first building block of an open access test bed for statistical signal detection methods in pharmacovigilance.

G. N. Norén (✉) · O. Caster · K. Juhlin · M. Lindquist
The Uppsala Monitoring Centre, SE, Uppsala, Sweden
e-mail: niklas.noren@who-umc.org

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