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Foreword to 8th Revision: ENCePP Guide supports strong observational research for the COVID-19 pandemic

The rapid progression of the COVID-19 pandemic has generated several hypotheses on the safety and effectiveness of therapeutic interventions, such as repurposed medicines. The need for quick answers triggered the initiation of observational studies carried-out with fast data collection, analysis and reporting. In a pandemic situation, the same methodological standards as those applied in any other circumstance should nevertheless be used to provide valid and reliable evidence supporting rapid treatment decisions by clinicians and regulators. Adherence to existing guidance on the appropriate design and conduct of pharmacoepidemiologic studies is therefore of utmost importance. ENCePP believes that this 8th Revision of the Guide on Methodological Standards in Pharmacoepidemiology should be the backdrop against which observational studies related to the COVID-19 pandemic should be conducted.

Pottegård et al. provide methodological considerations for the conduct of pharmacoepidemiological studies in relation to the COVID-19 pandemic across eight domains. The ENCePP Guide addresses each of these domains: (1) timeliness of evidence generation, including the need to prioritise some questions over others in the acute phase of the pandemic (addressed in Chapter 2); (2) the need to align observational and interventional research on efficacy (Chapter 10.1); (3) the specific challenges related to "real-time epidemiology" during an ongoing pandemic (Chapters 4.1, 4.2 and 4.3); (4) what design to use to answer a specific question (Chapter 5); (5) considerations on the definition of exposures (Chapter 5.1); (6) what covariates to collect (Chapter 5.1); (7) considerations on the definition of outcomes (Chapter 5.1); and (8) the need for transparent reporting (Chapter 8).

The methodological challenges described by Pottegård et al. are illustrated by studies that examined the differences in the incidence and severity of the SARS-CoV -2 virus infection between patients receiving angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and those not receiving ACEi/ARB, which may help to inform hypertension treatment decisions. In these studies, the subset of patients being tested was not a random and unbiased sample of the total population, which may lead to the selection bias described in Chapter 5.2. Patients with symptoms and with comorbidities, including hypertension, may have been more likely to be tested, therefore influencing the testing probability of patients exposed to ACEi/ARB. Although some of these studies have adjusted for relevant comorbidities and other potential confounding variables, some factors that may have affected the testing probability and the risk of being tested positive may have been

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unmeasured or uncontrolled for. Amongst the studies referenced in an EMA Press Release (June 2020), five large and well-conducted studies were considered adequate to assess this risk (de Abajo et al., Gnavi et al., Mancia et al., Mehta et al. and Reynolds et al.).

The risk of a severe outcome of infection in patients exposed to ACEi/ARB has been measured in several studies by mortality, admission to intensive care unit (ICU) or need for respiratory ventilation in hospitalised patients. A common issue in these studies is the potential for selection bias, due to factors associated with hospitalisation or admission to ICU, and for time-related bias due to misclassification of the observation time in different treatment groups. Another frequent limitation is the presence of unmeasured or unadjusted confounding factors, for example factors associated to the prescription of ACEi or ARB, or to higher risk of patient hospitalisation or patient treatment with ventilation. Several studies attempted to adjust for confounding by indication but potential issues have included the limited number of variables introduced in the model and the timing of the assessment of the relevant variables. Chapters 5.2 on bias and 5.3 on methods to address bias offer guidance to identify and address these sources of errors in observational studies. The study by Yung et al. is considered to be a good example of a study providing valid results between ACEi/ARB and the risk of mortality in patients hospitalised with SARS-CoV -2 virus infection.

In the context of a pandemic where rapid answers to research questions are needed, combining data across different databases affords insight into the generalisability of the results and may improve precision if outcomes or exposure of interest are rare or when there is interest in subgroup effects. It may also inform on specific patterns of drug utilisation. Chapter 4.6. on research networks for multi-database studies describes the different models that can be applied for combining data or results from multiple databases. An example of a collaboration in the context of the COVID-19 pandemic is the study published by Lane et al. using data from 14 multinational sources of claims data or electronic medical records. This study followed the model of a general common data model (CDM) described in Chapter 4.6.2.5.

During the COVID-19 pandemic, many studies were published on the effects of a specific drug or drug class. Systematic reviews and meta-analyses were subsequently performed to provide summaries of their results but some of them lacked the methodological rigor needed for the selection and review of studies and the appropriate statistical methods to pool estimates from individual studies if a meta-analysis was conducted. Annex 1 of this Guide provides a Guidance on conducting systematic reviews and meta-analyses of completed comparative pharmacoepidemiologic studies of safety outcomes, and it may serve as a helpful tool to generate valid conclusions from systematic reviews and meta-analyses.

The impact of the COVID-19 pandemic has accelerated the development of vaccines. By June 2020, the first COVID-19 vaccine candidates have entered human clinical testing and might be available rapidly with potentially remaining questions and the need for close monitoring. Chapter 10.2. on vaccine safety and effectiveness helps developing such studies.

As stated by Watson et al.in relation to one of the published studies, lack of transparency and uncertainties about research standards applied raise doubts about published results. Morales et al. supported the reproducibility of their study by publishing the study protocol in the EU PAS Register ahead of time, providing a start-to-finish executable code, facilitating the sharing and exploration of the complete result set with an interactive web application and asking clinicians and epidemiologists to perform a blinded evaluation of propensity score diagnostics for the treatment comparisons.

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