From: Helle Kieler
Subject: PCIM/11/01 - Public Consultation on implementing measures for pharmacovigilance

Thank you for the opportunity to comment on the concept paper regarding framework, structure, terminology, logistics and audits of pharmacovigilance activities.

The Centre for Pharmacoepidemiology (CPE) at the Karolinska Institutet in Stockholm is an academic unit engaged in pharmacoepidemiological research and research training of Swedish and international PhD students and post-docs. CPE is also an ENCePP-partner .

We are currently engaged in a number of PASS and interact regularly with both authorities as well as pharmaceutical companies. Therefore, we will only comment on the section on PASS, i. e. Annex IV pp 27-34.

In general, the different sections harmonize with the routines we already work by, from study protocols via research ethic rules to the writing of reports, which follow the recommendations from the association of editors of medical journals.

In our experience, three important aspects are often overlooked or neglected in PASS and these may benefit from clarification:

1. Absolute benefits and risks need to be presented, preferably by measures like numbers needed to treat /harm (NNT, NNH). The number and proportions of patients who benefitted without adverse effects need to be presented, not only risk estimates. Also, the number of patients who experienced no effect but only adverse reactions need to be quantified. This may be included already on p 30, item 3. Abstract format, ad 9. Results but also in the final study report p 33 item 10.4 Main results.

2. The phenomenon of "channeling", i e that patients offered a new drug may be a very particular subgroup with a long disease history and experiencesof almost all other conventional drugs. The methods to address this may be highlighted
already in the abstract, p 30, item 5. Study design and in the final report, p 32, item 9.3 Subjects.

3. Immortal time bias, i e that the final results are often based only on survivors who had to survive to later experience both drug exposure and outcomes. Also, numbers of and reasons for dropout need to be explicitly reported. This may be stated both in the abstract, p 31 item 7. Subjects, and in the final report, p 32, item 9.3 Subjects and item 10.1 Participants.

Sincerely

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