February 18, 2012.

European Commission

Post-authorisation efficacy studies (PAES)

This is to respond to the Commission's request for feedback on the PAES Delegated Act. I would like to make the following comments:

Consultation item 2:

The core problem with the PAES document is that various key definitions are inconsistent with literature. The Commission defines a controlled clinical trial as a study that is randomised and uses a control group (either placebo or established intervention). This is correct. PAES also correctly states that effectiveness measures the effects of an intervention under *real-life* conditions. But is then incorrectly defines efficacy as the *measurement of a benefit in controlled clinical trials*. Efficacy is the measurement of benefit in studies that apply strict eligibility criteria and strict monitoring procedures in carefully selected patient groups conducted by well-trained investigators. In other words, efficacy studies measures the benefits in *ideal* conditions. Both effectiveness and efficacy studies (that measure the effects in *real-life* and *ideal* circumstances, respectively) can be done using (randomised) controlled clinical trials, in contrast what is stated in the PAES. These two types of trials are also known as pragmatic and explanatory clinical trials. The PAES statement that pragmatic trials are non-interventional is simply wrong and also inconsistent with the Trial Directive, which clearly defines pragmatic trials as interventional studies. The PAES statement that pragmatic trials have often been considered inappropriate for the measurement of *efficacy* is like saying that a car is inappropriate for cycling. Pragmatic trials measure effectiveness and explanatory trials efficacy. It is important that the definitions in the PAES are consistent with the scientific literature.

The PAES states that pragmatic trials have limitations, being 'less perfect' experiments, 'sacrificing internal validity to achieve generalisability' and the 'non-randomised' design. Pragmatic trials are randomised trials. It is incorrect to make the generalisation that pragmatic trials are always 'less perfect' experiments. A pragmatic trial that does not blind investigator and patients to treatment allocation clearly is less perfect than a explanatory trial that blinds clinicians and patients in the measurement of subjective outcomes (such as quality of life). However, the measurement of mortality is not affected by the lack of blinding as the clinician's diagnosis of corpus mortis is generally unaffected by knowledge of treatment allocation. The Commission wonders whether pragmatic trials would be capable of addressing the regulatory needs. But does the current trial system, with its undue focus on explanatory trials, provide the answers the healthcare system needs? A recent analysis by John Ioannidis found that only one of the 24 "blockbuster" medicines (with annual sales exceeding $1 billion) had been studied in a trial with more than 10,000 participants. This is an important deficiency because large trials are needed to evaluate effects on major clinical

outcomes. Few of the trials with blockbuster medicines included death as outcome, so we currently do not know whether these widely used medicines prevent death or may increase it due to side-effects. Five of the blockbuster medicines are used long-term to treat patients with mental-health problems yet the use by millions of patients is based on trials of short-term duration (3-4 months) enrolling only a few hundred patients [JAMA 2013;309(3):239-40]. Simple pragmatic trials could address these uncertainties at low cost: patients would be randomised after consent and e.g. the electronic health records would be used to record death unobtrusively. The analysis by John Ioannidis (and other studies) should lead the Commission to reconsider the statement that pragmatic trials should be the exception rather than the rule. We need many more pragmatic trials to complement the often limited evidence base of explanatory trials.

Consultation item 3:

The PAES describes seven different scenarios in which post-authorisation studies should be considered. It is unclear why the PAES does not approach this from the perspective of public health needs. Explanatory trials are often conducted using strict eligibility criteria with many inclusion and exclusion criteria and with close monitoring of study patients and instructions of how to use the medications. They also often exclude patients based on age, gender, co-morbidity and geographical accessibility and may just measure proxy outcomes rather than major clinical outcomes or death. Patients in routine clinical practice are diverse, with varying disease histories and co-medications and they do not always comply with instructions and persist with treatment over time. The question of when post-authorisation trials should be conducted is dependent on how well the existing trial evidence has established the beneficial and adverse effects of the medicinal product in these diverse real-life populations rather than on a set of very limited scenarios.

The very limited scenarios, as described the PAES, do not cover some important examples in which pragmatic trials are needed. One example is that of the relative effectiveness. An example is the relative effects of different types of statins. While the effects of statins are well established, there is only very limited evidence on whether one type of statin is better than another in reducing cardiovascular events. The vast majority of trials concerned comparisons of statins versus placebo rather than direct comparisons of different types of statins. If one type statin would be moderately better than another, it could mean thousands of lives saved due to their widespread use. Relative effectiveness trials are important for public health (and cost-effectiveness) but PAES does not mention these. Pragmatic trials may be preferable over explanatory trials in establishing relative effectivessness given the importance of compliance and persistence. The enhanced monitoring and patients instructions in explanatory trials may mask real differences in actual clinical practices.

An important omission in the PAES document is that of the need for post-authorisation trials for unlicensed indications. A recent Canadian study evaluated the treatment indications for 253 347 electronic prescriptions. It found that the prevalence of off-label use was 11.0%; of the off-label prescriptions, 79.0% lacked strong scientific evidence.

Off-label use was highest for central nervous system drugs (26.3%), including anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%) [Arch Intern Med 2012;172(10):781-8]. These results indicate the major need for post-authorisation trials for unlicensed indications.

Consultation item 4:

The PAES document optimistically states that propensity score methods and instrumental variables could provide unbiased analysis of data from non-randomised observational settings. However, there is no strong evidence that these advanced statistical techniques will overcome confounding. All statistical techniques suffer from the same limitation that they cannot overcome unquantifiable or poorly recorded confounders [Lancet 2004;363:1728-31]. Instrumental variables may potentially control for unobserved confounding, though the strong assumptions underlying this method are often limiting its widespread application [Epidemiology. 2006 May;17(3):260-7]. The eminent epidemiologist Vandenbroucke has argued that observational studies should be restricted to questions that meet the underlying assumption that exposure allocation is unrelated to the outcome [Lancet 2004;363:1728-31].

It is recommend that the Commission consults experts on pragmatic trials so that their advantages and disadvantages can be considered in a balanced manner. Also, the Commission should conduct a systematic review of the limitations of the current trials system so this can inform the question on when post-authorisation studies should be conducted. It should not be based on the more subjective 'current regulatory experience' (as stated in the PAES) given the widespread criticism of the current trial system.

Yours sincerely

TP van Staa
Chair of Pharmacoepidemiology
London School of Hygiene & Tropical Medicine