322 | Using a single non-inferiority margin or a single preserved fraction for an entire pharmacological class may be invalid for the analysis of non-inferiority: A case study of statin non-inferiority trials

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Background: The use of a single non-inferiority margin or a single preserved fraction (PF) in non-inferiority trials for an entire pharmacological class will spare investigators from the extensive efforts required to define a new margin each time a member of this group is chosen as an active comparator (the recommended approach by regulators). However, the validity of this approach has not been assessed.

Objectives: To assess the validity of using a single margin or a single PF for all non-inferiority trials within a pharmacological class (statins).

Methods: A search in PubMed, EMBASE, and CENTRAL resulted in 7 active-controlled non-inferiority trials for treating hyperlipidemia. The impact of using a single margin (6% reduction of low-density lipoprotein cholesterol from the baseline) was assessed by evaluating how this margin corresponds to the PF for each comparator statin in the 7 trials. PF is the fraction of the effect of the comparator statin that was preserved by the test statin (the higher the PF the stricter the margin). The use of a single PF was assessed by re-analyzing non-inferiority in the included trials with new margins (based on the single PF) for each comparator statin and compare the new results with those of the original trials (in which a PF was assumed to be chosen for each comparator in each trial).

Results: The use of a single margin resulted in PFs that range between 81% and 89% for the different comparators. This means that the stringency of demonstrating non-inferiority, in terms of the PF, varies among the comparator statins. For example, non-inferiority of a test statin to 10 mg atorvastatin will be demonstrated if it at least preserved 84% of the effect of atorvastatin that was pooled from the historical placebo-controlled trials (both the test and comparator statins are equipotent). However, this PF may become higher or lower if another equipotent statin is chosen as a comparator instead of 10 mg atorvastatin. The use of single PF resulted in 4 of 9 (44%) different non-inferiority conclusions compared with the original analyses. This means that the new margins were either wider or narrower compared with the original ones.

Conclusions: The threshold of demonstrating non-inferiority with a single margin or single preserved fraction of the effect per pharmacological class may not be consistent with using a margin/PF for each comparator separately, which may also be invalid for the analysis of non-inferiority.

323 | Regulatory challenges in the design of non-inferiority trials: Evaluating scientific advice letters from the European Medicines Agency (EMA)

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Background: Non-inferiority trials are associated with methodological challenges. The European Medicines Agency (EMA) does not have a guideline on designing non-inferiority trials and recommend to define the non-inferiority margin based on clinical and statistical considerations. However, they do not recommend a specific method to determine the margin.

Objectives: To assess the challenges in designing non-inferiority trials for drugs intended to be marketed in Europe.

Methods: Using the database of the Dutch Medicines Evaluation Board (MEB), a search in recent (2014 and 2015) final EMA scientific advice letters was conducted to identify design proposals that were sent by pharmaceutical companies to the EMA about non-inferiority trials. Each scientific letter is for one drug, and it includes proposals for different aspects of the trial with a response from the EMA to each proposal. The proportion of the accepted proposals by the EMA was assessed taking into account the therapeutic class and the type of the drug application (orphan vs other drugs) using generalized estimating equations with an exchangeable correlation matrix to account for clustering of proposals within letters.

Results: The EMA accepted 142 of 232 (61%) of the total proposals. Almost 65% of the proposals were for three therapeutic classes: anti-infectives (most common), drugs for endocrine disorders (mainly anti-diabetics), and oncology drugs. The EMA acceptance did not differ between proposals for endocrine drugs vs anti-infectives (OR: 1.30, 95%CI 0.52 to 3.24) and between oncology drugs vs anti-infectives (OR: 0.54, 95%CI 0.12 to 2.47). The EMA acceptance also did not differ between orphan vs other drug applications (OR: 0.47; 95%CI 0.19 to 1.14). The non-inferiority margin was the main challenge, only 25 of 61 (41%) proposals for the choice of the margin were accepted. There was no common approach proposed by pharmaceutical companies to define the margin (the recommended approach by the EMA was proposed for only 18 of 61 margins) nor a common method of the recommended approach.

Conclusions: There are many questions about the design of non-inferiority trials with the choice of the inferiority margin as the main challenge. We did not find that the challenge was related to one of the three most common therapeutic classes or to a type of drug applications. This study shows that more explicit guidance from the EMA on the rationale for choosing different approaches to define the margin is needed.