What's the rule for the pool? *Background*

- Some disease areas/circumstances: *two-study convention* not commonly enforced
  - Oncology
  - Cardiovascular diseases
  - Rare diseases
- Occasionally, two pivotal trials are conducted, however, these may
  - have a substantial lag time between their anticipated read-out dates
  - enroll populations that differ to some extent (indication, geographic footprint, inclusion/exclusion criteria, ...)
  - embed a different testing strategy, e.g., order of endpoints in testing hierarchy
- For endpoints with low power (e.g., mortality), pooling data across two studies highly attractive
  - questions arise around type I error control

What's the rule for the pool?
Selected perspectives

FDA's draft version[#] Multiple Endpoints in Clinical Trials Guidance for Industry (fda.gov) *(text removed in final version of guidance)*	*Moreover, the Type I error rate should be controlled for any preplanned analysis of pooled results across studies; pooled analyses are rarely conducted for the planned primary endpoint, but are sometimes used to assess lower frequency events, such as cardiovascular deaths, where the individual trials used a composite endpoint, such as death plus hospitalization.*
FDA's draft guidance Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products	General considerations
EMAs Points to consider on application with 1. meta-analyses; 2. one pivotal study	*There are, however, a number of accepted regulatory purposes for meta-analysis. These include:* *[...]* • *To evaluate an additional efficacy outcome that requires more power than the individual trials can provide.*
Bretz, Maurer, Xi. Replicability, Reproducibility, and Multiplicity in Drug Development. *CHANCE* 32:4, 4-11, 2019	Formal approach controlling type I error "at submission level" • well tailored for "two-study convention case" • more challenging in the situation discussed here

What's the rule for the pool? *Question(s)*

- Consider a (pre-specified) secondary endpoint that is not statistically significant in either study since power is low and it is usually logistically difficult to power this endpoint in a trial (e.g., CV death in the cardiovascular area)

  – Would the pooled data be considered as robust and strong evidence of the treatment effectiveness for this endpoint, potentially resulting in a labelling statement, if consistent positive trends are observed from both studies and statistical significance is reached in the pooled data at the nominal level of significance?

  – Would it be recommended to have a separate protocol for the meta-analysis (as suggested in the EMA guidance) with a protocol-specific alpha or should a meta-analysis be included in one (or both) study protocol(s) with type 1 error allocation from within the study?

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