Futility interim analyses in Phase III registration trials

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In clinical trials terminology, the term 'futility' is used to refer to lack of efficacy, i.e. inability of a clinical trial to achieve its objectives. Futility interim analyses are increasingly utilized in clinical trial design both due to ethical motivations (not exposing patients to inefficacious treatment) and due to potentially significant savings (resources, time, money).

There is a variety of statistical approaches used to define a futility rule in a group sequential design: beta spending function, conditional power and predictive power (predictive probability). Those different approaches can be also viewed as different scales on which we express the futility rule. All those methodologies have been extensively discussed in literature.

Decision on whether a futility interim analysis should be included in the study design represents a complex and multifactorial issue. There is no 'one size fits all' solution available. Eventually, motivations and criteria for futility interim analysis require case-by-case considerations. What is, in particular, a complex and challenging task is how to choose the right level of futility rule aggressiveness and how to choose the right timing of futility analysis. This presentation primarily focuses on those two aspects and provides examples (generated by East® software or by SAS® simulations) illustrating 'behaviour' of various futility rules and inherent trade-offs.

With regard to the aggressivity of the futility rule (influenced e.g. by the choice gamma function parameter when defining beta-spending in East®), there is always and inherent conflict: Aggressive futility rule will increase chances of 'correct' stopping under H0 (no effect) but also increase chances of 'false' stopping under H1 (potentially successful study) while cautious futility rule will decrease chances of stopping under H0 but also increase chances of continuing under H1. Similarly, choice of timing in terms of information fraction is a trade-off due to the conflict between the following: Stopping earlier yields potentially greater savings, however, an early interim analysis is associated with high variability, therefore less ability to distinguish between scenarios which should and should not justify study continuing.

The above described issues and trade-offs are illustrated by several examples of studies that include one or more futility analyses and general recommendations on the level of aggressiveness and timing are provided along with operating characteristics and probabilistic assessments.

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