PLANNING FOR CLINICAL TRIALS FROM PHASE II TO PHASE III: COMBINE OR NOT TO COMBINE

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Traditionally, phase II trials are relatively small and can be expected to result in a large degree of uncertainty in the estimates based on which Phase III trials are planned. Phase II trials are also to explore dose regimens with high probability of showing effectiveness, appropriate primary efficacy endpoint(s) or patient populations. When the biology of the disease and pathophysiology of disease progression are well understood, the phase II and phase III studies may be performed in the same patient population with the same primary endpoint and the selected dose. In disease areas where the clinical outcome endpoint may not be observed in a short-term study, e.g., mortality in cancer, or the molecular pathways may not be well established, the treatment effect may be measured through an intermediate surrogate endpoint in phase II trials. Generally, the ability to fully evaluate the clinical endpoint in the phase II trial is limited whether it is a surrogate endpoint or not. In this presentation, we will investigate the impact of using various phase II effect size estimates on the sample size planning for phase III trials versus planning of combined phases II and III. An intuitive approach for non-adaptive planning will be discussed and contrasted it with the combined design strategy.