Supplementary material 2: Statistical Designs and Analysis Methods for Umbrella/Platform Trials

Three statistical methods related topics are covered in this supplemental material: 1. Study-wise Type I error control consideration; 2. Adaptation features in platform trials; 3. Usage of adaptive randomizations. Similar to the main text, we use the term platform trials here to cover features applicable to both umbrella and platform trials.

1. Considerations on platform trial level family-wise type I error (FWER) control. When multiple treatment arms are included in the same platform trial purely for operational efficiency, the platform trial level FWER control usually is not required (1-4). Though seem clear at a high level, it may not be a clean-cut decision when facing individual situations. Bretz and Koenig (5) had more deliberated argument on this topic. Indeed, the determination whether multiplicity adjustment is needed is based on "the degree of distinction between treatments". As pointed out by Bretz and Koenig, determination of multiplicity adjustment or not is not a purely methodological problem and requires the consensus of all stakeholders involved and should be carefully evaluated with respect to the consequences of their rejection. If the FWER control is deemed necessary in the platform trial or in some of the sub-studies within a platform trial, the general multiplicity adjustment approaches would also be applicable here. Some proposed using alternative metrics such as false discovery rate (FDR) when controlling type I error rates in multi-arm clinical trials (6, 7).

2. Considerations on adaption features in platform trials. Platform trials usually build in adaptation features to allow promising experimental treatments to stop the trial early and claim efficacy, move on to the next stage of the trial to collect more evidence, or to allow inefficacious treatments to exit the trial and claim futility. These decision rules can be based on pre-specified statistical measures such as p-value, posterior probability, or predictive probability. Like any adaptive designs, the criteria for graduation or futility should be pre-specified and carefully calibrated to maintain statistical properties prior to the study conduct.

Same as other trials with adaptive features, platform trials have pre-specified decision rules when an investigational treatment arm could exit the trial, either for lack of benefit or because sufficient evidence of

efficacy has accrued for the arm to "graduate" to the next stage of clinical development. The number of treatment arms that are active in the platform trial may expand or contract over time as some treatment arms exit the trial and new treatment arms are added. Depending on the availability of patient resources, assessments may be required to evaluate the feasibility of a maximum number of experimental arms the trial can support at any time.

3. Considerations on adaptive randomization. Adaptive randomization may be considered in an platform study with multiple treatment arms. Various researchers have conducted simulations to compare the performance of adaptive randomizations vs. fixed randomization ratio (8-12). Yuan and Yin (13) showed with theoretic derivations that outcome-adaptive randomization might not have substantial advantages over fixed-ratio randomization when the response rate of the experimental treatment is not substantially higher than that of the standard treatment. In the case of platform trials with multiple experimental arm and common control arm, if adaptive randomization is used, the randomization ratio to the control arm should be fixed to ensure the control allocation ratio is not reduced over the course of the trial and detailed simulations must be conducted with respect to type I error control, bias etc. prior to deciding on the choice adaptive randomization. Another consideration of using adaptive randomization is the concern of potential drift of treatment effect over the course the enrollment. Though covariate adjusted adaptive randomization could mitigate this concern at a certain level, it may not be preferred especially in confirmatory trials. In practice, we recommend starting the trial design process with fixed randomization, and conduct simulations to evaluate the benefit of adaptive randomization if there is a desire to do so to meet the trial's goals with considerations on other operational aspects including enrollment rate and sample size.

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