ASCOT ADAPT Statistics Summary

July 2020

In ASCOT ADAPT, each trial participant is assigned to receive a treatment regimen which consists of one treatment from each of a number of domains for which that participant is eligible. Each viable treatment regimen is an available arm in the trial. Initially, all interventions within each domain are assigned at random with equal probability.

Sequential statistical analyses using Bayesian inference for pre-specified models of the primary outcome are undertaken as the trial progresses. These analyses use the accumulating trial information for estimating the relative efficacy of the interventions being considered and assessing how probable it is that each intervention is superior (best within a domain), inferior (not best within a domain), effective (better than the standard of care), or futile (no better than the standard of care).

Statistical decisions are then based on comparing the probability of each hypothesis with predefined evidence thresholds which when exceeded trigger a decision of superiority, inferiority, effectiveness, or futility of each intervention. If an intervention is found superior then randomisation to all other interventions within that domain may cease. If an intervention is found futile or inferior then randomisation to that intervention may cease. This allows for elimination of ineffective treatments as soon as there is sufficient evidence available.

In addition to informing trial decisions, the updated model is used to update the allocation probabilities to each of the regimens still active in the trial via response adaptive randomisation. The allocation probabilities of each intervention within a domain are revised in proportion to the modelled probability that each regimen is best in terms of the primary outcome. This allows for trial participants to potentially benefit in light of the information being generated from the trial itself.

The statistical models consist of structured parameters representing intervention effects. To account for variation in the primary outcome the models are also adjusted for each participants domain eligibility, region, site, and time of enrolment. Additional prognostic factors, such as age or baseline severity, may also be included as model terms to increase the precision of treatment effect parameters. Subgroup effects can be investigated within an expanded model which allows for varying treatment effects across selected baseline factors.