300 word limit

Robust, value-based sample size determination for cluster randomised trials when nuisance parameters are unknown

Duncan T. Wilson

Background: The power of a cluster randomised controlled trial (cRCT) is partly determined by the value of nuisance parameters, such as the intracluster correlation coefficient (ICC). The conventional method of sample size determination, based around attaining a nominal power level (typically 80% or 90%), is highly sensitive to these parameters. However, they are generally not known at the design stage, and as a result the choice of sample size can be far from optimal. Although sample size re-estimation methods can be used to adjust the sample size based on interim estimates, they can lead to considerable variability in the final sample size and do not formally account for the associated costs of increased sampling.

Methods: We present an alternative method for cRCT sample size determination, introducing a value function based on the costs of sampling and the benefits of power. We show how the function’s parameters can be determined, and propose two maximin-type optimality criteria which can be used to determine sample size in face of uncertainty in the nuisance parameters.

Results: We use the method to determine the sample size of a parallel group cRTC with a continuous primary endpoint with unknown total variance and ICC, and where there are costs to sampling at the patient and cluster levels. We show the proposed method is significantly less sensitive to nuisance parameters than the conventional approach, and that a fixed design with no interim sample size adjustment can be near-optimal for large deviations of the nuisance parameters from their initial estimates.

Discussion: By explicitly incorporating the cost of sampling into the sample size determination problem, we can find simple fixed cRCT designs which are robust to variation in the nuisance parameters. This may be particularly useful when the ICC is unknown and difficult to estimate precisely at an interim analysis.