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

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Background: The conventional approach to clinical trial sample size determination is to choose the smallest value such that the power of the trial is above some nominal threshold. The sensitivity of this sample size to nuisance parameters has led to sample size re-estimation methods which allow parameters to be estimated at an interim analysis and the sample size adjusted accordingly. However, these methods do not formally account for the associated costs of increased sampling, and as a result can lead to incoherent decisions.

Methods: We present an alternative model for sample size determination which explicitly balances costs and benefits by introducing a value function to be maximised. We show the method is significantly less sensitive than the conventional approach to nuisance parameters, to the point where a fixed design with no interim sample size adjustment can be near-optimal for large regions of the nuisance parameter space. We propose a criterion for choosing an optimal fixed sample size, considering the range of nuisance parameter values for which the value of the fixed design is within a tolerable distance of the value of the best possible design.

Results: We illustrate our approach by applying it to two sample size problems: a parallel group trial comparing overall survival with unknown median survival time in the control arm; and a cluster randomised trial with unknown variance components at both individual and cluster levels.

Conclusion: Fixed sample size designs can be highly robust to nuisance parameter uncertainty when accounting for the costs of sampling.