Implementation of a control arm into the Wages and Tait adaptive phase I/II trial design.

Wages and Tait developed an adaptive phase I / II trial design which considers information

on both toxicity and efficacy whilst recommending doses in a dose-finding clinical trial. The design aims to find the optimal biological dose (OBD). It assess toxicity in a similar way to the continual reassessment method (CRM) to determine doses with dose limiting toxicity (DLT) probabilities less than a threshold level. From this tolerable subset of doses, the model then selects the most efficacious of the doses, optionally using adaptive randomisation.

We propose an extension to this design, which would allow patients to be randomly allocated to a zero dose / control arm. During initial stages of the design adaptive randomisation is used to seek the OBD. At this point, it would be possible to randomly allocate some patients to the zero dose, thus creating a control group for the comparison of efficacy and toxicity outcomes. The performance of this modification will be assessed using simulations to determine impact upon operating characteristics.

We present methods for a fixed size of control group and consider methods that attempt to match the control group size with the cohort size at the OBD. We also discuss the ethical issues surrounding this approach and present situations in which it could be ethical.