Improving the efficiency of rare disease trials using composite endpoints

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Suggested talk duration (15-60 minutes)
20 minutes

Summary (max. 500 words)
Composite endpoints combining continuous and binary measures into a single endpoint are common in clinical development, particularly in autoimmune diseases and solid tumour oncology. It is well acknowledged in the literature that these endpoints can be useful for trials in rare diseases. By allowing more than one event to indicate effectiveness of a treatment, we ensure the complexity of many rare disease manifestations are captured. Furthermore, the higher event rates that result from combining single measures often translate to the requirement for smaller samples.
Standard practice when assessing the performance of a treatment in these settings is to dichotomise the information recorded on the continuous scale and combine this with the binary measures. This provides a single binary outcome based upon whether patients reach a predefined goal, i.e. are 'responders'. Dichotomising continuous variables is highly statistically inefficient. This is particularly problematic in disease areas with few patients, such as Lupus Nephritis, which struggle to recruit the required sample size for a clinical trial. An alternative, originally proposed by (Wason & Seaman 2013), is the augmented binary method. It employs joint modelling techniques which retain information on how close patients are to being 'responders'. It has been demonstrated to result in substantial efficiency gains when applied to phase II cancer trials and in OSKIRA-1, a phase III trial in rheumatoid arthritis. However, in these cases, the sample sizes considered were much larger than would be possible in many rare diseases.
We aim to determine whether these gains are also experienced in smaller samples. Previous work suggested there may be problems with the augmented binary method in small samples due to an increased number of parameters. We evaluate the behaviour of the augmented binary method in terms of type I error rate, power and coverage when we have few available patients ($n<100$), by resampling from the OSKIRA-1 trial. We identify finite sample corrections and implement these in the augmented binary method to improve its small sample properties. We compare this with the operating characteristics of the standard binary method and show that the augmented binary method with small sample corrections maintains nominal type I error rate (5%) whilst still offering much higher power. We make recommendations for future evaluations of treatments in rare diseases that utilise these endpoints.

Relevance to conference theme
The methodology proposed offers a more efficient way to analyse composite endpoints, which feature frequently in rare disease studies. By retaining more of the information in the trial the method can provide much higher power than methods currently in use and may allow for randomised trials to proceed successfully in areas where they may otherwise not have been possible.

Keywords (max. 3)
rare diseases; composite endpoints; augmented binary method.