Biomarker-guided clinical trial designs: Sample size calculations with survival endpoints

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Biomarker-guided treatment is a rapidly developing area of medicine, where treatment choice is personalised according to one or more of an individual’s biomarker measurements. A number of biomarker-guided trial designs have been proposed in the past decade, including both adaptive and non-adaptive trial designs which test the effectiveness of a biomarker-guided approach to treatment with the aim of improving patient health. A better understanding of them is needed as challenges occur in terms of trial design, analysis and practical application, including the control of the false-positive rate, power of the study, prevalence of the biomarker, treatment effect estimation and the potential increases in cost and time. We have undertaken a comprehensive literature review based on an in-depth search strategy with a view to providing the research community with clarity in definition, methodology and terminology of the various reported biomarker-guided trial designs from a total of 211 included papers. Of these 211 included papers, 107 papers related to biomarker-guided adaptive trial designs were reviewed in our published paper Antoniou et al. (2016) [1]; biomarker-guided non-adaptive trial designs were referred to in 100 papers and are reviewed in our more recent paper to be published shortly.

Navigating the literature to gain an understanding of which trial design to implement in a given situation, and the practical implications of doing so is difficult as our reviews revealed. Hence, in order to improve the understanding of the biomarker-guided trial designs and provide valuable and much-needed guidance on their implementation we are developing a user-friendly online tool (www.BiGTeD.org) informed by our literature review. BiGTeD will provide an easily accessible resource to inform on the most optimal design when embarking on a biomarker-guided trial including easy to navigate graphical displays of the various trial designs. Knowledge on how to design, implement and analyse these trials is essential for testing the effectiveness of a biomarker-guided approach to treatment. Hence, in this study, we focus on key statistical aspects of several of the identified trial designs with particular focus on examining the sample size requirement under different settings where outcome is time-to-event. To achieve this, we applied statistical simulation methods and here we report on our findings.