**Incorporating binary short-term endpoints in multi-stage phase II oncology trials**

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For ethical and economic reasons Phase II trials in oncology are conducted in several stages where at each stage only a small pre-specified number of patients is enrolled. At the end of each stage it is then decided whether the new treatment is effective enough to justify further enrolment of patients. If the treatment is deemed ineffective, the trial is stopped and no more patients are enrolled. Otherwise enrolment continues until the end of the trial is reached.

Previous published designs for multi-stage Phase II oncology trials are based on the assumption that at each stage of the trial all patients are entered at the same time and that outcome measurements are therefore available for all patients at the same time. In reality, this is never the case as patients are entered consecutively. Furthermore, the outcome of interest is often measured after a long follow-up time leading to so-called overrunning of the planned sample size; that is more patients than previously planned are entered in the trial leading to higher costs of the trial.

As the problem of overrunning arises from long follow-up times in conjunction with fast accrual rates, we developed new designs based on endpoints that can be measured after a much shorter follow-up time. Hence, the new designs will allow us to minimise the negative impact of overrunning. Computer simulations were used to model patient enrolment allowing us to quantify how large the expected overrun will be for the different designs.

Depending on the length of the follow-up time and the accrual rate, the new designs have lower expected sample sizes (ESS) when the recruitment rate is low, and have considerably lower ESS when the recruitment rate is high. However, the total sample size might be slightly larger.

**Adaptive three-stage phase II/III designs with endpoint and treatment selection**

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Adaptive seamless phase II/III designs with treatment selection at an interim analysis have become increasingly more attractive due to their potential to save development costs and to shorten time-to-market of a new treatment. Different methods have been proposed for selection of the treatment group that will continue along with the control group to the second stage of the trial. If the primary endpoint is observed only after long-term follow-up, relatively little data might be available for the long-term endpoint at the interim analysis leading to poor selection.

In some settings it may be possible to collect data on short-term endpoints that are correlated with the long-term endpoints of interest. These endpoints may be observed more rapidly, and hence will be available for a larger number of patients than the long-term primary endpoint at the time of any interim analyses. Including these additional data in the interim analysis improves the precision of estimates of treatment effects associated with the long-term endpoint and can therefore increase the quality of decision-making or adaptation based on these estimates.

We propose a three-stage design in the setting of a phase II/III trial in which a number of short-term endpoints are available. At the first stage of the trial one of the short-term endpoints will be chosen based on the correlation with the long-term endpoint. At the second stage of the trial the treatment selection will then be made using the chosen short-term endpoint together with the long-term endpoint. The design is shown to perform well compared to previously proposed designs that do not allow for selection of the short-term endpoint.