**Use of time-varying covariate in assessing disease remission in the early and late phases of a treatment with application to RITAZAREM trial**

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**Background**

In a randomised trial, we are interested in assessing whether overall improvement in relapse-free survival is sustained beyond a treatment period.

**Methods**

The RITAZAREM trial aim is to assess the efficacy of rituximab compared to the current standard of care (azathioprine or methotrexate and glucocorticoids) in the prevention of disease relapse in ANCA-associated vasculitis (AAV). Rituximab is an established induction agent in AAV, however the trial aims to demonstrate its efficacy as a maintenance agent given that a large majority of patients relapses within 2 years of a course of treatment.

Patients are recruited at the time of relapse and initiated on a 4 months induction regimen of rituximab. Those achieving disease control are then randomised to either maintenance treatment with rituximab lasting 20 months or standard therapy with azathioprine. Patients are followed up to between 36 and 48 months from enrollment. The primary outcome measure is time to disease relapse from randomisation. A secondary objective is to demonstrate disease remission beyond the 24 month treatment period. The primary intention-to-treat analysis will be based on a Cox proportional hazard model. Firstly we plan to test the null hypothesis for a hazard ratio of 1 at all time points. If rejected at a global level, we will employ time-varying covariates to investigate the two further sub-hypotheses of a hazard ratio of 1 pre- and post- 24 months. This will elucidate whether rituximab overall efficacy in maintaining disease remission is achieved during the active treatment phase of the trial and also sustained in the post treatment phase.

**Conclusions**

The RITAZAREM trial is ongoing. Simulations will investigate operational characteristics of our model under a variety of assumptions. Alternative methods of assessing efficacy at varying time points will also be considered.