Methodological Data Supplement

Who was included and why were there repeat enrollments in RAMPART? At least five minutes of convulsive seizures or intermittent seizures for at least five minutes without return of consciousness were required prior to treatment. Given the urgent need to provide treatment for status epilepticus, paramedics were not able to check for prior enrollments before providing study medications. Sites attempted to prevent repeated enrollments of the same subject by briefing participating paramedics about "frequent flyers," and by offering the subjects do-not-enroll bracelets after each enrollment.

What were the hypotheses tested in the primary analysis of RAMPART? The specific null and alternative hypotheses were: H_0: $p_{IV} - p_{IM} = \delta_o$ (probability of seizure cessation by the time of ED arrival for patients receiving IV lorazepam minus the probability for patients receiving IM midazolam) and H_A: $p_{IV} - p_{IM} < \delta_o$ (non-inferior) where $\delta_o = 0.10$ is the pre-defined non-inferiority margin.

How is the treatment effect estimated? Let Y=1 when a subject has seizure cessation by ED arrival and Y=0 if he or she did not. The treatment effect is modeled as follows:

Logit(Prob(Y=1)) = $\beta_0 + \beta_1$*IM with IM being an indicator variable equal to 1 if patient receives IM midazolam and 0 if receives IV lorazepam.

What is Crossover? A crossover occurs when a subject first receives one treatment and in his or her subsequent enrollment receives a different one. This introduces a different correlation structure as there are potentially between treatment effects within individual (e.g. a subject may respond very reliably to the IV agent and more variably to the IM agent). As the RAMPART trial had a limited number of these crossovers, there was little statistical power to more completely explore the possibility of these more complex relationships.

How is the ICC calculated? The ICC is estimated for models 2 and 3 using the covariance parameter estimate (using the standard logistic regression distribution variance of $\pi/3$).[1] The ICC can range from 0 to 1. The smaller the value, the larger the variance within a cluster relative to the variance between clusters. For example, if the ICC was 0 then there is no correlation between responses from repeat enrollments and each enrollment can be treated as an independent outcome. Conversely, if the ICC was 1 then there is perfect correlation and repeat enrollments only provide as much information as one single enrollment.

Reference

1. Rodrıguez G, Elo I. Intra-class correlation in random-effects models for binary data. Stata J 2003;3(1):32-46.