**Dose escalation due to suboptimal medication adherence in a clinical trial setting: An anonymised case study**

Daniel F.B. Wright1,2, Uni of Sydney1; St. Vincent’s Hospital2, Sydney, NSW.

**Introduction.** Suboptimal medication adherence in clinical trials can lead to unnecessary dose escalation and an overestimation of dosing requirements.

**Aims**. To determine the incidence of unnecessary dose escalation associated with suboptimal medication adherence in an anonymised randomised controlled trial. This case study is intended to provide a forum for discussion with workshop participants about the consequences of low medication adherence in clinical trials.

**Methods**. Data was retrospectively analysed from a 2-year randomised controlled clinical trial with monthly clinic visit. The study protocol included provision for dose escalation to achieve a target biomarker concentration. Target achievement was associated with the control of disease flares. Suboptimal adherence to medication was assumed if drug plasma concentrations were below a pre-defined individualised reference range. The criteria for defining an unnecessary dose-escalation decision at each clinic visit included: 1) the biomarker target was not achieved, 2) the participant was nonadherent to medication, and 3) the observed maintenance dose was equal to greater than a ‘reference dose’ predicted from a pharmacokinetic-pharmacodynamic model. The incidence of unnecessary dose-escalation, biomarker target achievement, disease flares, and observed doses ≥ reference doses were compared between participants adherent ≥ 80% of the time to those who were < 80% adherent. Statistical comparisons used Fishers Exact and Mann-Whitney U tests.

**Results**. Data from 175 individuals were available, including 1612 paired drug and biomarker measurements. Participants adherent at <80% of clinic visits (n=94) were less likely to achieve the biomarker target (52% vs 60%, p=0.0009), had more disease flares (0.56 /month vs 0.39, p<0.0001), had more unnecessary dose-escalations (45% vs 18%, p<0.0001) and were more likely to have a maintenance dose ≥ reference dose (39 vs 7%, p<0.0001) compared to participants adherent >80% of the time (n=81), respectively.

**Discussion**. Nearly half of the dose-escalation events in participants with low medication adherence were unnecessary based on the criteria defined in this study. Daily maintenance doses exceeded the reference dose in about 40% of those with low adherence resulting in an over-estimation of dose requirements in this cohort of about 30%.