Appendix 1

Sensitivity analysis for ACQ: missing value analysis by multiple imputation

A sensitivity analysis was carried out on the primary outcome measure (ACQ) using multiple imputation (MI). MI is a simulation-based approach for analysing incomplete data. Missing values are replaced with multiple sets of simulated values to the complete data. MI then applies standard statistical analyses, and adjusts the parameter estimates for missing data uncertainty [1]. The purpose of MI is not to predict missing values as close as possible to the true values, but to handle missing data in a way that allows valid statistical inference to be drawn [2]. MI assumes missing data are at random (I.e., the missing values do not carry any extra information about why they are missing other than what is already available in the raw data). MI is more efficient that imputing the median, mean or carrying the last observation forwards[3].

Sterne's guidelines were followed for presenting and analysing missing data[4]. The data was redefined as an imputation set using the Stata statistical software. Linear regression was used to impute missing values because of its simplicity[1]. We are aware that more complicated methods exist but these are outside the scope of this paper. To quote George Box "essentially, all models are wrong, but some are useful"[5]. Two MI analyses were carried out. The first looked at the difference between 12 months and baseline. The variable to be Imputed (ACQ 12 months - baseline) and those for calculating it (the imputing variables) were defined. The imputing variables (age, sex, randomized treatment, ACQ baseline, ACQ 12 months) were as broad as possible to minimise bias. Five imputation sets were generated. There is little statistical theory on how many imputation sets are required with a minimum of five recommended[6]. The relative variance increase was used to assess the

impact of missing values on the variance of the estimate. The closer the relative variance increase is to zero, the less effect missing values have on the variance. A second MI analysis imputed ACQ at 3,6,9 and 12 months allowing an imputed AUC to be drawn.

The pattern of missingness for ACQ is presented in Figure A1. ACQ scores were unavailable at 44/188 scheduled visit times (23%) in group A (intervention), and 41/168 (24%) in group B (control).

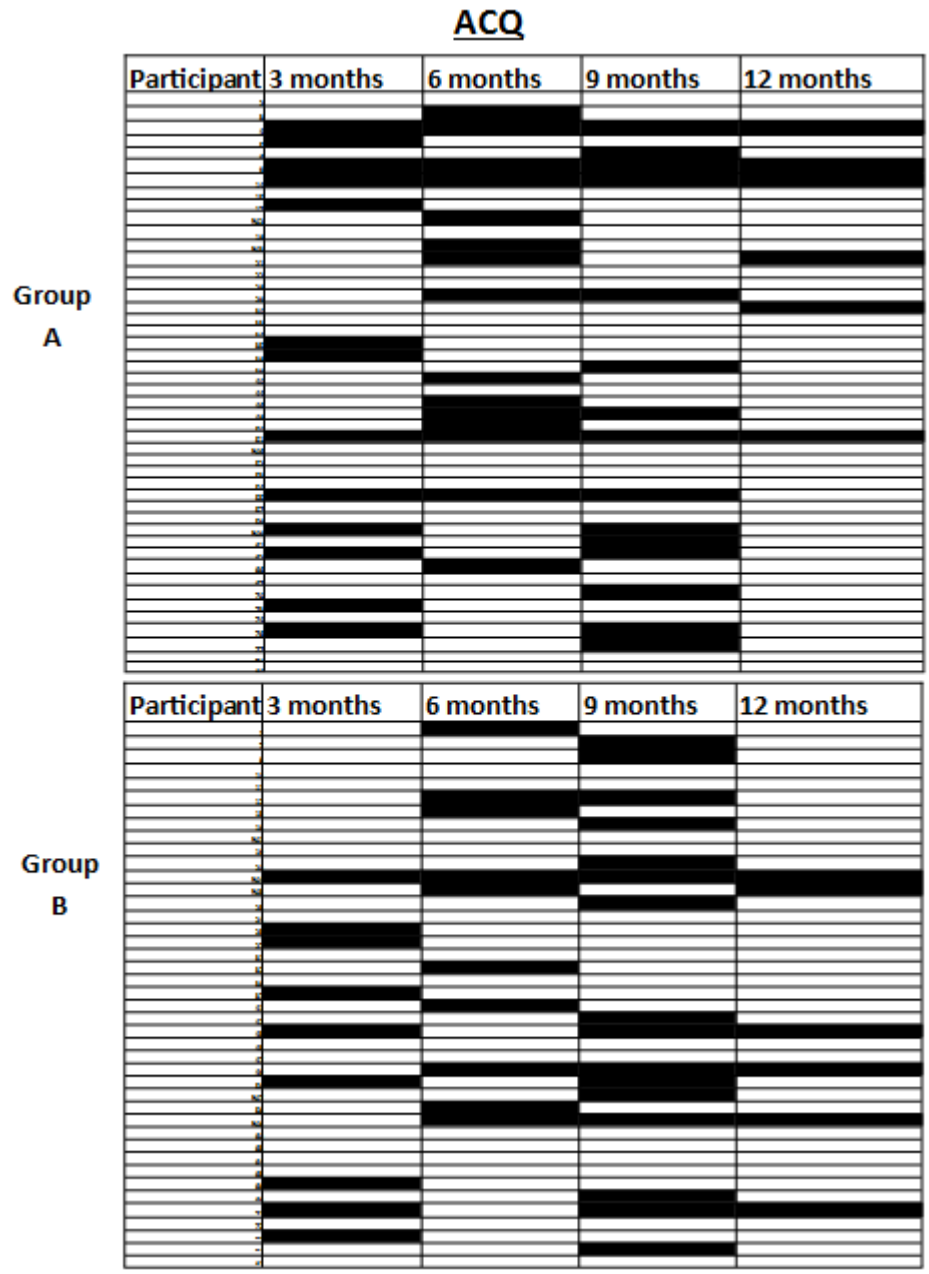


Figure A1 – Patterns of missing ACQ data for group A (intervention) and B (control). Black boxes indicate a study visit time with no ACQ score available.

Missing values analysis: results

The five imputed means for ACQ 12 months-baseline ranged from 1.02 to 1.21. There was no significant difference between randomised treatment and the primary outcome measure

on the imputed values mean difference =-0.16 (95% CI=-0.76, 0.43), p=0.57. The relative variance increase was 0.21. Figure A2 shows the imputed AUC graphically. There was no significant difference between treatments (p=0.27).

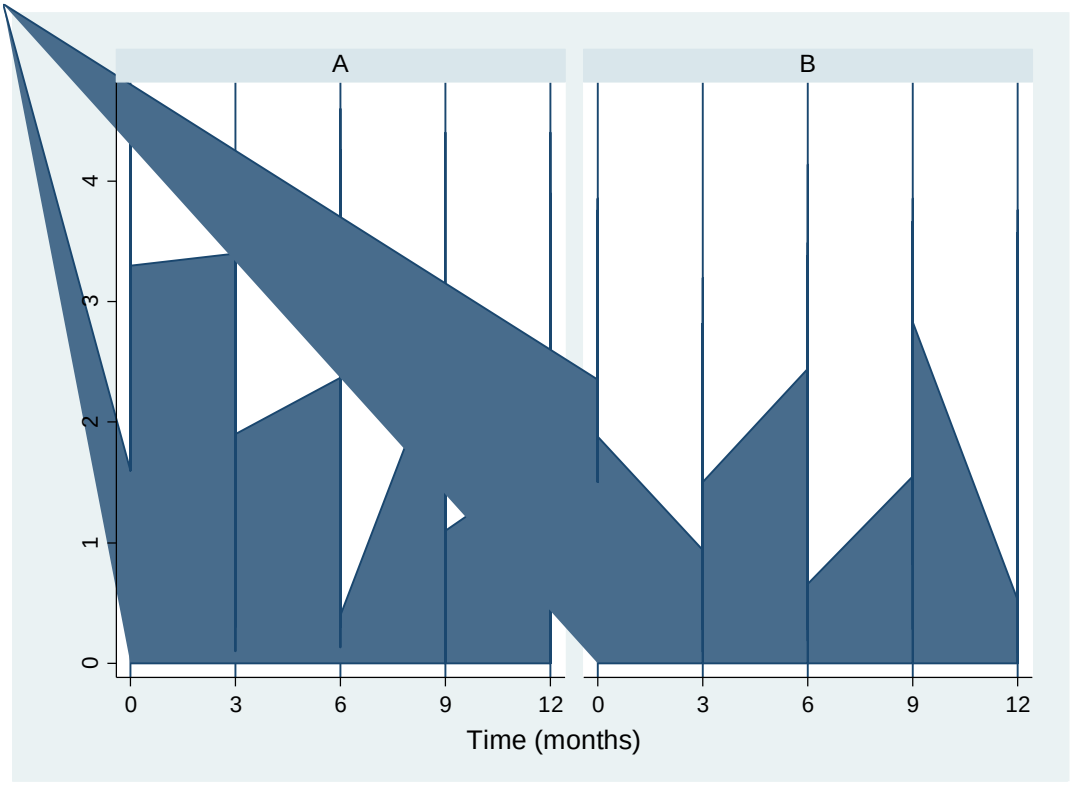
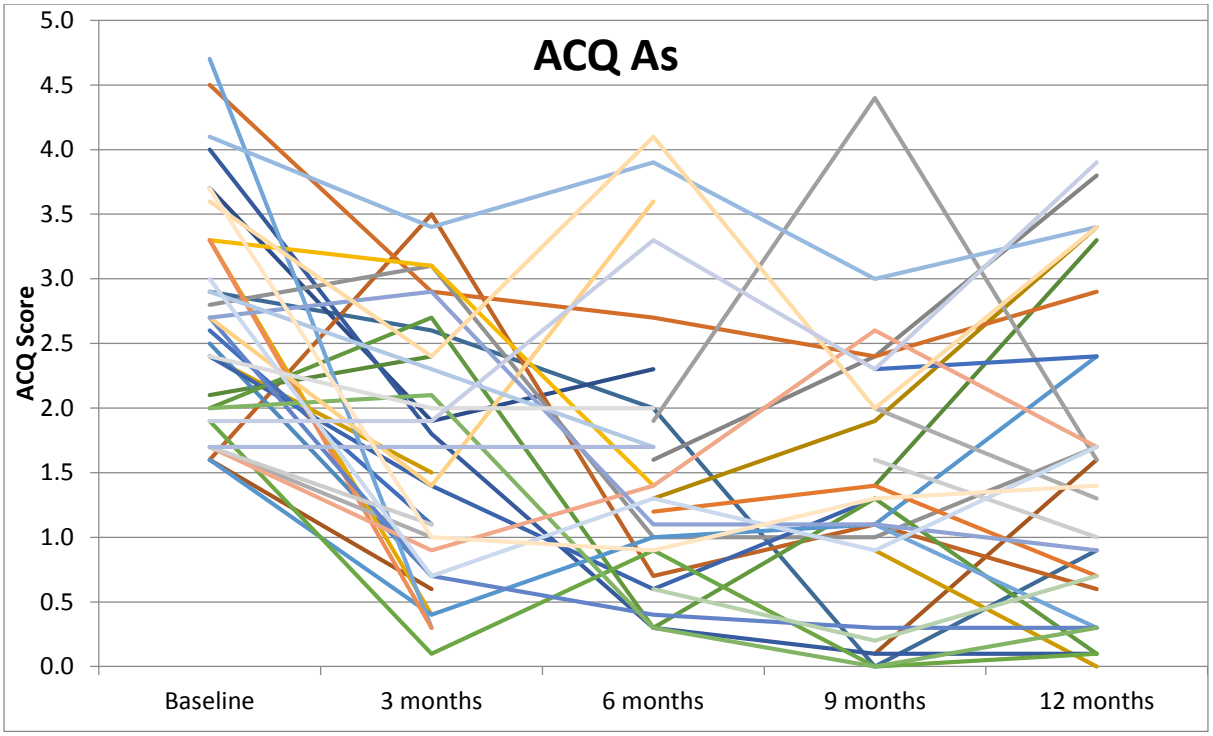


Figure A2 - AUC (trapezoid method) following imputation. Group A = Intervention, Group B = Control.

Figure A3 shows the individual trajectories for each participant for ACQ across the time points in the study.



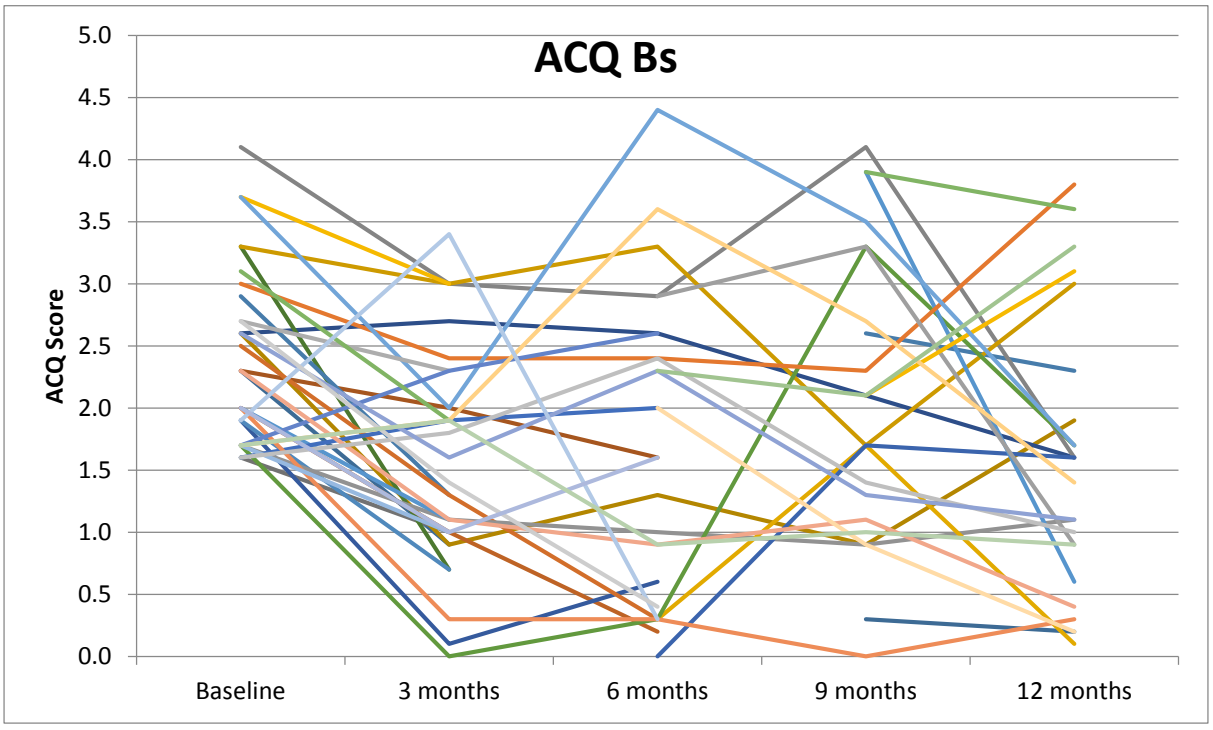


Figure A3 – Individual participant trajectories for ACQ in group A (intervention) and group B (control).

Figure A4 shows the patterns of missing adherence data for group A and group B.

Adherence data was unavailable at 49/188 scheduled visit times (26%) in group A (intervention), and 41/168 (24%) in group B (control).

The missed adherence data was therefore 4410 days (mean 93) in group A, and 3690 days (mean 85) in group B.

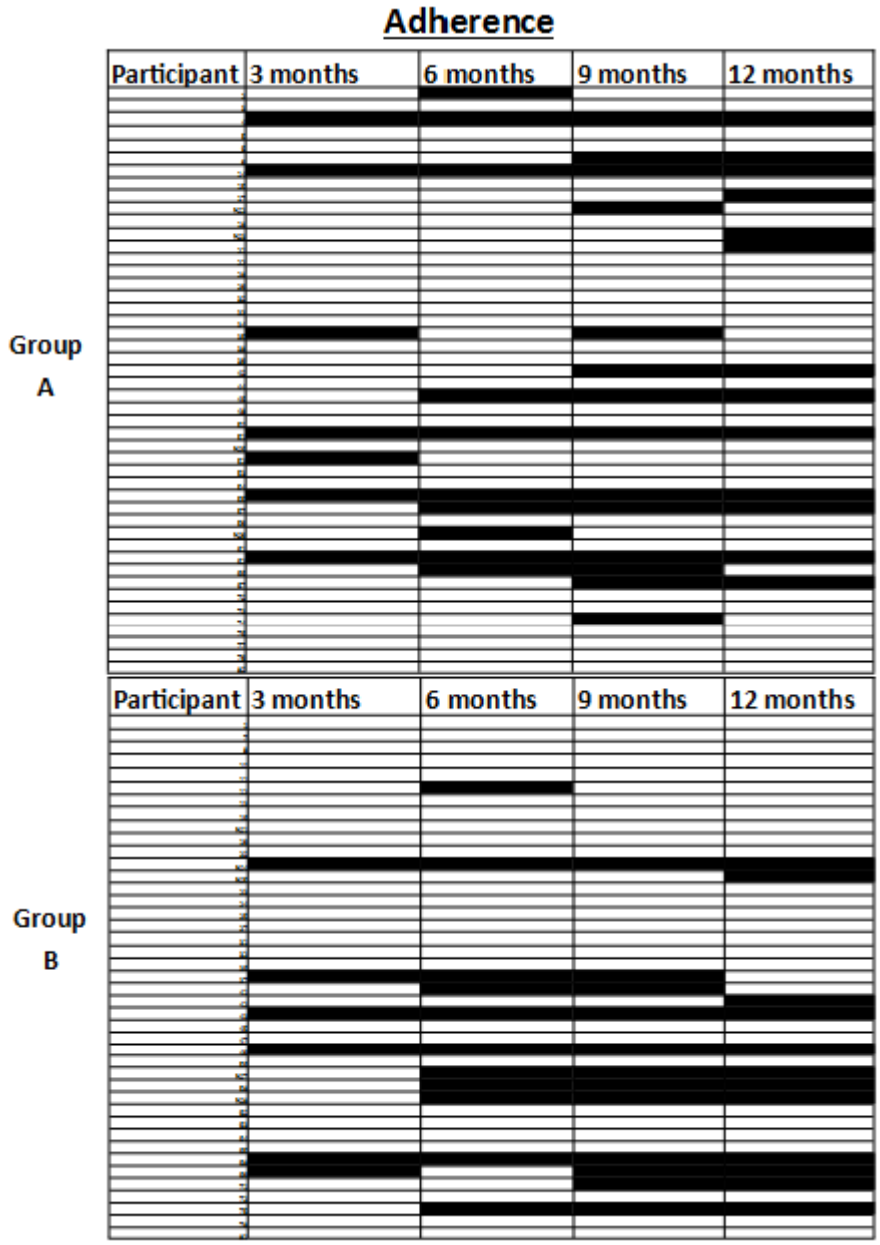


Figure A4 – Patterns of missing adherence data for group A (intervention) and group B (control). Black boxes indicate a study visit where no adherence data was available.

References

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