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**Statistical Analysis Plan (SAP)**

**Handling of Missing Data**

There are two types of missing data, at the respondent level (unit non-response) and at the specific question level (item non-response). At the respondent level, missing data occurred because of patient death, withdrawal from study, or inability to be reached via phone for an interview. For the SGRQ, values of 100 (worst QOL) were substituted for an assessment in which a patient was not available because of death. Comparisons of missingness of change in SGRQ score (from baseline to 6 months) by several patient characteristics were performed with Fisher’s exact or Chi-Square tests to evaluate potential bias on the treatment effect. A sensitivity analysis was performed using a mixed-effects generalized linear model with all available SGRQ data (baseline, 3 months and 6 months post-discharge) for each patient. This analysis compared the baseline to 6-month change with robust variance estimates, clustering by hospital unit, patient as random effect, and treatment arm as fixed effect.

For counts of rehospitalizations and ED visits, visits within a measurement period when a death occurred were neither counted nor imputed. Visits for some patients took place at non-Hopkins sites. Information on these visits could not always be confirmed adequately for inclusion in the cumulative counts. To evaluate the potential effect of missing events, patients with no non-Hopkins COPD-related events were compared to patients with at least 1 non-Hopkins event by age, hospital unit, and prior hospitalization (within last year).

At the item level, efforts were made to ensure that no or very limited amounts of missing data existed on all data, and especially on primary study outcomes and patient characteristics from the baseline assessment considered as covariates for analysis. No data were missing for the covariates such as age, gender, home oxygen use, and prior hospitalization. Missing data for

30 other patient characteristics were minimal. Since they were not critical to the current analyses,  
31 imputation was not considered.

32 In preparing the outcomes that were based on items as part of a scale or domain statistic, the  
33 handling of missing items was consistent with the outcome's literature to determine if, and  
34 how, the outcome could be calculated or if it was to be considered missing. For example, the  
35 SGRQ scores were prepared in spreadsheet calculators, provided by the instrument's authors,  
36 and accounted for any assignments of missing scores based on the availability of item  
37 responses.

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### 39 **Statistical Analysis**

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41 Statistical summaries and distributions of patient characteristics were reviewed across hospital  
42 enrollment units. Statistical summaries and distributions of patient and clinical characteristics  
43 were also reviewed across study arms. Such periodic assessments of the data provided  
44 opportunities to evaluate missing data and provided input for additional data review and  
45 quality assurance. Randomization of the patients to the study arms expects that on average the  
46 arms were balanced on characteristics that might affect the study results, such as socio-  
47 demographic and health status. Thus, no statistical tests to compare the arms on patient  
48 characteristics were performed (Assmann et al 2000).

49

50 Exploratory analyses were performed cross-sectionally at baseline, 1-week, 1, 3 and 6 months  
51 post-discharge for each of the outcomes across the study arms. This provided an assessment of  
52 the outcomes' distributions, missingness patterns and the need for additional data review and  
53 quality assurance.

54

55 The main analysis approach consisted of performing unadjusted analyses of the treatment  
56 effect under intention to treat (ITT), followed by analyses adjusted for at least hospital  
57 enrollment unit. The type of general linear model analysis performed depended on the  
58 distribution of the outcome variable, and included gaussian, logistic, poisson and negative

59 binomial with robust estimators of variance and accounting for within hospital-unit correlation.  
60 The outcomes were either point-in-time, change from baseline, or cumulative counts. Analyses  
61 of change score outcomes also included the outcome's baseline score as a covariate. With  
62 respect to SGRQ change from baseline to 6 months, two types of treatment effect analyses  
63 were performed. One analysis used a general linear model to evaluate change in SGRQ score  
64 (1-100), adjusted by the baseline score. A second sensitivity analysis was based on a 3-category  
65 outcome of SGRQ change – better:  $\leq -4$ , worse:  $\geq 4$ , or no change:  $> -4$  and  $< 4$ . The  
66 distribution of the three categories was compared between the arms with a Chi-square test.

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68 Analyses of cumulative rehospitalizations and ED visits, separate or combined, were analyzed as  
69 all-cause and COPD-related. Estimates of means and incidence rates with 95% confidence  
70 intervals (CIs) for the two arms were calculated based on the analysis models. Adjusted models  
71 included age category, home oxygen use, prior hospitalization and hospital unit. Distributions of  
72 each type of cumulative count were plotted for the two arms and compared by Fisher's exact  
73 test. A further evaluation of the treatment effect for each type of cumulative count, where  
74 there are a large number of zeroes, was performed. The visit count was dichotomized to zero  
75 visits and at least one visit, and unadjusted and adjusted logistic regressions were performed.  
76 Between arm comparisons for questions or measures taken at one-time point, or number of  
77 deaths were performed using Fisher's exact test, Chi-square test, t-test or Mann-Whitney test  
78 as appropriate. Unadjusted survival analyses using Kaplan-Meier and log rank tests were  
79 performed for 'time to death or first COPD-related hospitalization or ED visit'. Analyses of  
80 caregiver outcomes were performed with nonparametric tests for correlated measures.  
81 Statistical significance was considered for  $p < 0.05$ .

## 82 **References:**

83 Assmann SF, Pocock SJ, Enos LE, Kasten LE (2000), "Subgroup Analysis and Other (Mis)Uses of  
84 Baseline Data in Clinical Trials", *Lancet*, 355, 1064-1069

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