Author's response to reviews

Title: Efficacy of a Physical Exercise Training Programme COPD in primary care: study protocol of a randomised controlled trial

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Author's response to reviews: see over
Description of our revisions

The revision is only applicable to the data analysis part of the Methods section, because of advanced insight.

**Data analysis**

The descriptive characteristics will be presented quantitatively as means (± standard deviation) for continuous variables and as number (%) for categorical variables. The longitudinal difference in primary and secondary outcomes between the groups (intervention versus control) will be assessed by using linear mixed models, since these models account for the correlation between repeated measures (at baseline, after 4 and 6 months) within the same patient, correct for baseline differences to gain efficiency, and use all available data, also for patients who have missing data (assuming missing at random (MAR)). Time (baseline, 4 and 6 months) and group*time will be included as fixed factors, where an unstructured covariance structure will be assumed for the repeated measures and restricted maximum likelihood will be used to obtain unbiased estimates.

Next to this effect-evaluation, we will also assess which variables influence the intervention effect, i.e. effect-modifiers. To obtain this goal, we will include the potential effect-modifier $X$ in the abovementioned linear mixed model as main effect and add the interaction terms group*time*$X$, group*$X$, and time*$X$. The following potential effect-modifiers will be considered: the outcome at baseline, MRC dyspnoea score, walking distance, peripheral muscle strength, level of daily physical activities and compliance with the training programme [60-62]. All analyses will be performed using IBM SPSS Statistics version 21.0. A two-sided $p$-value $\leq 0.05$ will be considered as statistically significant.