Reviewer’s report

Title: Design for A Multicenter, Randomized, Sham-controlled Study to Evaluate Safety and Efficacy After Treatment with the Nuvaira® Lung Denervation System in Subjects with Chronic Obstructive Pulmonary Disease (AIRFLOW-3)

Version: 0 Date: 27 Dec 2019

Reviewer: Anant Mohan

Reviewer's report:

The authors have presented the study design of a double blind, RCT of a bronchoscopic procedure for moderate to severe COPD. This includes a sham group as control with a 12-month follow up. I have the following comments / queries for the authors:

Introduction:

Last sentence: "The primary objective......:" Is the main objective to compare the number of acute exacerbations in one year or to compare the "time to first exacerbation"? The primary outcome mentions the latter. Both are different and need to be clarified.

Methods:

"Randomization will be stratified ......:" How is it proposed to stratify based on prior PR? We understand that patients need to fulfil criteria for optimum medical treatment before getting the planned intervention, however, the protocol requirement assumes that all participating sites have a structured PR program running. The authors should justify why this is required. Similarly, the reason for stratification based on ICS use should be justified as to why multiple parameters are being used for randomization? Any impact of such a strategy on sample size and power of study should be clearly mentioned. If this has been already been considered then it should be mentioned.

Patient recall and recruitment: "Phone visit follow-ups ......:" Authors should discuss whether this can be a source of recall bias. The frequency of phone calls should be mentioned. Memory aids should be described in more details; are these similar to symptom diary cards?
Blinding and group allocations:

At each site, the first three participants......" if the first three participants in each site are going to be analyzed separately, will this not deplete the total patient pool and compromise the calculated sample size? Or will they be also included in the ITT analysis? Please clarify.

Table 3: Exclusion criteria point No 19:

Authors need to explain the genesis of these contraindications, whether they were adapted from a previous study, or have been specifically kept to allow patients to be considered for Bronchoscopic lung volume reduction procedures?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
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