Reviewer’s report

Title: Biological quality control for cardiopulmonary exercise testing in multicenter clinical trials

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Reviewer: RA Evans

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The topic of this manuscript is the use of biological quality control testing to ensure the data accuracy of cardiopulmonary exercise testing within and between laboratories (essential for multi-centre studies). This is often an overlooked subject yet is essential for the accuracy of a commonly used outcome measure. As an important aside, the results highlight the high frequency of problems with equipment failure due to routine laboratory procedures not being adhered to (24%). Without rigorous biological quality control testing these errors could easily go unchecked and it's important that this data is available from any authors that publish CPET data.

The authors describe and compare three different methodologies to assess the data - the central reader (probably the most commonly used currently), z score, and criterion method. To my knowledge this is novel data and the aim of the manuscript is well justified i.e to be able to have precise and accurate data with the lowest number of research participants. The central reader method led to within centre variability of around 10% but there was even more between centre variability (up to 12.5%) and therefore the authors recommend the 'z score' method as this improved CV% with the compromise that more data were excluded (than the central method). The criterion method meant too many tests were excluded (including ones that were within the normal distribution).

The major limitations are covered by the authors in the discussion and include the error inherent in assessing mechanical power on a treadmill. The authors have tried to improve upon previous studies by accounting for people's weight. There are situations where data on a treadmill is desirable rather than a cycle ergometer so it is a reasonable approach.

Although this is a technical report, the paper is still rather long and distracting in places so suggest that some of the methods and results should be put in a supplementary file (eg. summarise the staff training, equipment calibration etc in the methods and put the detail in the supplementary file - currently 2 pages, remove Table 1 and the trouble shooting log to supplementary file). Anything to keep the reader focused on the three statistical methods being used would be helpful as the other information (although necessary to be documented somewhere) is distracting.

As the analysis was performed retrospectively on the participating centres, were any centres excluded from originally taking part in the trial because of quality control issues? Please include the details if 'yes' as this adds a limitation/bias.
Add 'biological' quality control to title if word count allows for accuracy

Some centres use more than two stages for a QC (up to five) - how might this effect the results?

Is the W statistic on the axis in Figure 1 described anywhere? If not please add to the statistics paragraph.

Pg 4 2nd line add comma 'discriminatory power, and minimising laboratory burden and participant risk'

Pg 4 Rephrase line 9 to avoid starting the sentence 'Because'

Pg 9 suggest removing first sentence line 197 - repeated from pg 7 line 159

Pg 9 line 207 is 'bin average' a standard phrase?

Pg 11 line 236-38 - remove the sentence which are results and not needed here.

Pg 11 line 240 - rephrase to avoid starting the sentence with 'Because'

Pg 12 probably more relevant to know BMI rather than height and weight of the participants?

Pg 13 line 281-286 contains a description of the trouble shooting that took place this should be in methods/supplementary file and referred to in the results not described.

Pg 13 line 287 what does 'a busy clinic' day really infer as far as a justifiable reason for variation? Was an error in protocol made? Were too many tests conducted leading to error? Suggest rephrasing to include specifics.

Pg 13 line 292 'an acceptable ...' suggest move to methods if not already covered there - remove from results

Pg 13 line 296 'In most cases ...' move to discussion and remove from methods

Pg 17 line 380 suggest change to 'ventilation measurements from 9.2% to 5.8%'

**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 am able to assess the statistics

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

Acceptable

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