Reviewer's report

**Title:** Adherence to treatment in children with cystic fibrosis: a cross-sectional, multi-method study

**Version:** 2  
**Date:** 28 October 2014

**Reviewer:** Lutz Goldbeck

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Adherence to treatment for CF is considered a major area for increased research. The authors report on the results of a study with 100 Irish patients 0-18 years and their parents. In line with the literature, they found differences between parent- and self-reported adherence, between objective and subjective adherence measures, and between adherence to different treatment components. Increasing age of the child was significantly associated with low adherence, as were parental necessity beliefs with high adherence.

The strengths of the study are the multi-method approach to assess adherence, and the relatively large sample size. Weaknesses comprise the mono-centre approach, the selectivity of the sample within the centre, and the use of an arbitrary dichotomous definition of adherence vs. non-adherence. I have some concerns regarding the data analyses and interpretation of the results.

**Major comments:**

1. **Title:** Although some developmental delays may occur in patients with CF, the age range of this study comprises children and adolescents. Please change the title accordingly.

2. The introduction is well written. The authors should propose more specific hypotheses and/or research questions at the end of the introduction.

3. In the introduction, the authors repeatedly mention possible country-specific findings, and therefore they propose the need for UK-specific studies. It would be interesting to provide a rational for this proposal. Which “significant differences in healthcare provision and culture” (lines 101-104) might impact upon adherence to treatment? Why should the effect of parental depression on adherence to treatment be different in the UK compared to other countries?

4. The authors made a good job in improving the internal consistency of several psychometric scales which had been reported to be low in previous studies.

5. According to figure 1, n=46 patients were not approached and n=30 declined to participate. It can be assumed that these non-participating patients were less adherent to their treatment than the participants. The authors might consider this potential selection bias when interpreting their results.

6. Please provide information, how the individual reference value of 100% adherence was determined. Did the patients receive written treatment plans, indicating dosage of enzymes, vitamins and number or chest physiotherapy
procedures?

7. My main concern with the statistical procedure relates to the artificial dichotomy of adherence vs. non-adherence, and the definition of these two categories as provided by the authors. Adherence is a continuous and not a categorical variable. To categorize a patient "non-adherent" when adhering to less than 80% of the prescribed treatments in any of the three measures appears arbitrary. This definition generates artificially high non-adherence rates. The subsequent analyses of determinants of (non-)adherence suffer from this methodical bias. The authors might reconsider their dichotomous approach. The terms "high" or "low" adherence might be rather appropriate, instead of labeling patients "adherent" or "non-adherent".

8. As an alternative analysis, I would suggest to analyse adherence as it is - a continuous variable and to use appropriate statistical tests to determine factors impacting on this continuous variable. If these alternative analyses would replicate the findings as reported by the authors based on dichotomous categories, this would clearly strengthen the evidence of the main findings.

9. How many cases were included in the multivariate regression analyses? This information should be provided in the methods section and in tables 5 and 6. When interpreting the findings of the regression models, the low stability of results with small samples has to be considered. The amount of variance explained by the model should be reported.

10. Please provide information which independent variables were included in the regression analyses before stepwise backward inclusion. Was parental depression included? If not, the analyses might be repeated with parental depression due to the previous findings in the literature. Were self-reported necessity and concerns included?

11. Due to the findings of very high rates of parental depression in the international TIDES study (please report more recent references from TIDES), the impact of parental depression on adherence to treatment and medical outcomes (and vice versa) is an important issue. Therefore, I would recommend to invest some more effort to analyse potential associations of parental depression and adherence in the current study. The authors report that n=10 parents had high levels of symptoms indicating major depression. Could the authors compare adherence rates broken down by families without significant depression (CES-D < 16) and with high depression (CES-D >27)? So, does depression really make no difference as suggested by the authors, or is this null-finding only an artifact of the method (see 7.)?

12. The effects of predictors of adherence are quite small, and only few predictors survived the multivariate analyses. Only age seems to have a relevant effect size, as indicated by the OR, whereas the effect of parental health beliefs appears very small (OR 1.01-1.09 and 1.02-1.09) and should therefore not be over-interpreted. Again, I would encourage the authors to test whether their results hold true when treating the dependent variables as dimensions (see 8.).

13. The major predictor of non-adherence according to many studies including this one is being an adolescent. This result should be emphasized and discussed
more extensively. Possible reasons for non-adherent behavior among adolescents might be discussed, such as competing interests, developmental tasks, good health condition of average adolescent patients with CF, lack of anticipated late effects, etc.

14. It is an important finding that adolescents reported less necessity for treatment compared to their parents. Please elaborate some more in-depth explanations for this finding.

Minor comments:

15. When reporting descriptive analyses, please provide raw score ranges (min-max) instead of interquartile ranges, or additionally.

16. Tables/figures should be self-explanatory. Please spell out table headings and explain abbreviations.

17. Table 1 is redundant with the methods section and can be omitted.

18. Table 3: The difference between necessity and concerns was not used in the analyses, this information is redundant as well.

19. Figure 2: please include indicators of variance (SD or SE).

20. Figure 3: better use block design, lines would rather indicate multiple assessments across different time points in the same population. Clarify which statistical test the p-values refer to.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.