Author's response to reviews

Title: Adherence to treatment in children and adolescents with cystic fibrosis: a cross-sectional, multi-method study investigating the influence of beliefs about treatment and parental depressive symptoms

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Author's response to reviews: see over
Dear Editor,

RE: Research article 8305800721443991

The authors would like to thank the reviewers for taking the time to review this manuscript and providing their comments. Please see responses to the reviewers’ comments below.

Reviewer 1

Minor essential revisions

1. In line 88, a citation for the TIDES-CF study should be included since results have been presented.
   The TIDES-CF study has been referenced in the text.
2. Citation number 18 (Bucks et al., 2009) should be included in the background section since it seems directly relevant to this manuscript.
   The paper by Bucks et al., 2009 has been included in the introduction section of the manuscript.
3. Please provide statistical justification for considering a p value of <0.2 a trend.
   The wording in the text has been altered slightly to reflect that this was the method used to reduce the large number of variables investigated compared to the observations of adherence on which to conduct logistic regression analysis.
4. Line 243 includes an extra period after Figure 2.
   The extra period has been removed (now line 261).
5. Lines 337-340. The two sentences in these lines seem contradictory.
   This has been clarified in the text (lines 363-365).

Discretionary revisions

1. It would be helpful to make the title more description by including words such as “parent beliefs”.
   The title has been updated to be more descriptive.
2. For the background section, the authors may wish to review the recent publication by Sawicki, Heller, Demars, and Robinson (2014) in Pediatric Pulmonology which supports the role of beliefs about importance of treatments in medical regimen adherence.
   Thank you for highlighting this paper which has now been included in the background section.
3. There are many hypothesized barriers to medical adherence in cystic fibrosis (child resistance, time management etc.). Because of this, it would be helpful if the authors provided further rationale for choosing to study beliefs about treatments and parental depression since these two variables do not intuitively fit together.

Parental depression and treatment beliefs have been identified to play a role in adherence to treatment in other chronic diseases, however, there was limited information about whether these factors played a role in adherence to treatment in children/adolescents with cystic fibrosis.

4. In the methods section under the review of the BMQ, it would be helpful to explain what “successfully piloted in 10 parents and their children” means. It may be more useful to include the internal consistency information here to support the modifications made to the instrument.

The MARS and BMQ-specific were altered through discussion with the authors and clinicians. When piloting these amended questionnaires parents and children requested no further changes, this has been clarified in the text and the internal consistency information has been moved to the methods section.

5. Please explain how the CES-D prevents “underestimation of depressive symptoms present in parents of children with cystic fibrosis”.

A previous study by Driscoll, Montag-Leifling, Acton, Modi (as referenced) showed that rates of depressive symptoms varied depending on which instrument was used: CES-D vs Hospital Anxiety Depression Scale. It was believed that instruments that included somatic items, such as the CES-D, should therefore be used to prevent underestimation of depressive symptoms.

6. In the discussion of adherence in the results section, it would be beneficial to know how many children were non-adherent across all treatments (vitamins, chest PT, and enzymes). These data have been inserted into the text (line 263-265).

7. It may be worth rechecking the odds ratios for the apparent necessity of enzymes and chest PT since it is interesting that they are exactly the same. This was rechecked and the same results were produced.

8. Consider providing justification or noting in the conclusions why such a large age range was used (0.2 years to over 18 years) since age was so strongly associated with adherence, and it would be expected that parents would play a very different role in adherence across this age range.

Very few studies have investigated that factors affecting adherence in children with cystic fibrosis at very young ages and the authors felt it was important to investigate potential parental factors affecting children’s adherence at this age and through adolescence.

Reviewer 2

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. The title has been updated to reflect this.

2. The introduction is well written. The authors should propose more specific hypotheses and/or research questions at the end of the introduction. Specific hypotheses have now been stated 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 rationale 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?

There are many differences in healthcare provision across the world and many different factors contribute to depressive symptoms. It could reasonably be argued that pressures associated with payment for treatment, different treatment regimens (more vs less aggressive treatments) and the fact that children in the UK have poorer lung function than their counterparts in the US could affect parents’ mental health to different degrees according to their country of origin.

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.

Thank you for this observation.

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.

A number of factors (age, gender, BMI percentile, P. aeruginosa colonisation status and FEV\textsubscript{1} % predicted) were investigated across participants and non-participants to get an idea of group differences as stated in the article. Non-participants have the potential to be less adherent to treatment, however, and as such this has been highlighted in the limitations section of the article.

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 of chest physiotherapy procedures?

Patients were prescribed individual enzyme regimens by a cystic fibrosis dietician. These notes were reviewed for all of the participants throughout the year prior to entry into the study. Similarly, vitamins were prescribed as per physician prescriptions. Chest physiotherapy adherence was measured using self-reported non-adherence through the MARS questionnaire.

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 categorise a patient ‘non-adherent’ when adhering to less than 80% of the prescribed treatments in any of the 3 measures appears arbitrary. This definition generates artificially high non-adherence rates. The subsequent analyses of determinants of (non-)adherence suffer from this methodological bias. The authors might reconsider their dichotomous approach. The terms “high” or “low” adherence might be rather appropriate, instead of labelling patients “adherent” or “non-adherent”.

The terms “high” and “low” adherers has been adopted in the article. The dichotomous approach was employed to triangulate the four different measurement methods of adherence. Analysing adherence as a dichotomous variable and the threshold of
80% has been used previously in a range of research articles, including a recent article in BMC Pulmonary Medicine 2014, 14:107.

8. As an alternative analysis, I would suggest to analyse adherence as it is- a continuous variable. If these alternative analyses would replicate the findings as reported by the authors based on dichotomous categories, this would strengthen the evidence of the main findings. While adherence could be considered a continuous variable the outcomes of adherence are not. There is always a cut point under which adherence has a direct impact on patient outcomes. The generally accepted lower limit for adherence is 80% (see item 7 above) we have therefore reported adherence using this criterion throughout the manuscript.

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. The number of cases the regression analysis relates to for enzyme supplements and chest physiotherapy and the variance has been added to the methods section and appropriate tables. The amount of variance explained by the models has been added to the tables.

10. Please provide information which independent variables were included in the regression analyses before stepwise and 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?
   The preliminary effects models have been added to the results section (lines 288-294).
   The preliminary effects model for enzyme supplements included; increasing age, increasing parental BMQ necessity score and increasing parental BMQ concern score.
   The preliminary effects model for vitamins included; increasing age, presence of concurrent medical condition, increasing parental BMQ concern score, increasing CES-D score.
   The preliminary effects model for chest physiotherapy included; increasing age, number of medications, presence of concurrent medical condition, increasing parental BMQ necessity score and increasing parental BMQ concern score.

11. Due to the findings of very high rates of 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 depressions (CES-D < 16) and with high depression (CES-D > 27)? So, does depression really make no difference as suggested by authors, or is this null-finding only an artefact of the method (see 7)?
   See response to points 7 and 8 above. The authors feel that a dichotomous approach is more appropriate and is in line with the published literature on adherence.

12. The effects of predictors of adherence are quite small, and only a 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).
While the odds ratios regarding the effects of parental health beliefs appear small, an odds ratio of 1.09 reflects that a 9% change in adherence can be observed for every percentage point change in beliefs.

13. The major predictor of non-adherence according to many studies including this one is being an adolescent. This result should be emphasised and discussed more extensively. Possible reasons for non-adherent behaviour among adolescents might be discussed, such as competing interests, developmental tasks, good health condition of average adolescent patients with CF, lack of anticipates late effects, etc. More information on specific barriers facing adolescents with cystic fibrosis has been added to the discussion (lines 376-378).

14. It is an important finding that adolescents reported less necessity for treatment compared to their parents. Please elaborate some more in-depth explanation for this finding. A possible explanation for this finding has been added to the discussion (lines 346-347).

Minor comments

15. When reporting descriptive analyses, please provide raw score ranges (min-max) instead of interquartile ranges, or additionally. The authors considered this but in the end decided against it in view of the table to ‘cluttered’.

16. Tables/figures should be self-explanatory. Please spell out table-headings and explain abbreviations. Tables and figures have been updated as applicable.

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

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

19. Figure 2: please include indicators of variance (SD or SE) As adherence was analysed as a dichotomous variable there is no variance for Figure 2.

20. Figure 3: better use block design, lines would rather indicate multiple assessments across different time point in the same population. Clarify which statistical test the p-values refer to. The p-values refer to Mann-Whitney U tests, this has been added to Figure 3.

We hope that with these amendments that the paper can now be considered suitable for publication.

Yours sincerely,

Professor J.C. McElney
Professor of Pharmacy Practice