Appendix A: Further explanation and details regarding the study variables

Demographic and health outcomes data e.g. age, gender, $\%FEV_1$, IV antibiotics use and quality of life were collected as part of the pilot trial procedure. Baseline $\%FEV_1$ collected at the time of recruitment was measured during a period of clinical stability and calculated using the Global Lung Function Initiative (GLI) equation.[1] IV antibiotic days were recorded for the 1-year period prior to recruitment, and for 6 months during the pilot trial. Quality of life at baseline was self-reported using all six relevant statements from the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain,[2] e.g. 'Have you been coughing during the day?'; $\alpha = 0.90$. The CFQ-R scale ranged from 0 (lowest quality of life) to 100 (highest quality of life).

Adherence data were downloaded from chipped nebulisers (eTrack®) in the 3-month period following the point of recruitment; and calculated as was calculated as 'normative adherence'. 'Normative adherence takes into account a person's characteristics when defining the minimum required treatment regimen.[3] Calculation of 'normative adherence' involves adjusting the denominator based on the clinical characteristics of a person with CF, adjusting the numerator by capping daily maximum nebuliser use at 100% (also accounting for doses taken after midnight) and adjusting the numerator by accounting for dose spacing of inhaled antibiotics. For example, a person with chronic *Pseudomonas aeruginosa* infection should take at least a nebulised mucolytic and an antibiotic. Thus the denominator for a person with chronic *Pseudomonas aeruginosa* infection will be at least 3 (1x dornase alfa, 2x antibiotic). If a person with chronic *Pseudomonas aeruginosa* infection only agreed to use nebulised dornase alfa once daily (which is 1 nebuliser/day), even if they take every does of their dornase alfa, the 'normative adherence' is only 33%. This is because in the calculation of 'normative adherence', the denominator is at least 3 nebulisers/day for a person with chronic *Pseudomonas aeruginosa* infection. The detailed methods and worked examples of calculating 'normative adherence' are provided in the paper by Hoo et al.[3] 'Normative adherence' is a continuous scale that ranged from 0 (lowest possible adherence level) to 100 (highest possible adherence level, due to capping of daily adherence levels at 100%), with higher adherence being more desirable.

Severity of anxiety at baseline was self-reported using all seven statements from the General Anxiety Disorder 7-item anxiety scale (GAD),[4] e.g. 'Feeling nervous, anxious or on edge'; $\alpha = 0.83$. The GAD scale ranged from 0 (lowest anxiety severity) to 21 (most severe anxiety).

Severity of depressive disorder at baseline was self-reported using all eight statements from the Patient Health Questionnaire depression scale (PHQ-8),[5] e.g. 'Little interest or pleasure in doing things'; $\alpha = 0.84$. The PHQ-8 scale ranged from 0 (lowest depressive disorder severity) to 24 (most severe depressive disorder)

Intention at baseline was self-reported using a statement adapted from the Capability Opportunity Motivation Behaviour (COM-B) Self Evaluation Questionnaire.[6] The statement used was "I want to do all my prescribed nebuliser treatments in the next two weeks" with which participants rate agreement on a scale of 1-7, where 7 represents strongest intention.

Necessity at baseline was self-reported using all seven 'necessity statements' from the Beliefs about Medicines Questionnaire – specific (nebuliser adherence) (BMQ), e.g. 'My life would be impossible

without this nebuliser treatment'; α = 0.84. The necessity BMQ ranged from 1 (lowest perceived necessity) to 5 (highest perceived necessity). BMQ is a validated self-report tool [7] that was customised for the pilot trial to identify perceived necessities and concerns for nebuliser treatment.

Concerns at baseline was self-reported using all 14 'concern statements' from the Beliefs about Medicines Questionnaire – specific (nebuliser adherence) (BMQ), e.g. 'I sometimes worry about becoming too dependent on this nebuliser'; α = 0.84. The concern BMQ ranged from 1 (lowest perceived concern) to 5 (highest perceived concern). BMQ is a validated self-report tool [7] that was customised for the pilot trial to identify perceived necessities and concerns for nebuliser treatment. Necessity and concerns are components of conscious motivation.

Habit strength at baseline was self-reported using all four statements from the Self-Report Behavioural Automaticity Index (SRBAI),[8] e.g. 'deciding to use my nebuliser is something I do automatically'; α = 0.93. Each statement begins with 'Deciding to use my nebuliser …' to capture habitual instigation. Habit strength ranged from 4 (weakest habit) to 20 (strongest habit). Habit is a component of unconscious motivation.

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Appendix B: Further discussion regarding the strengths and limitations of this study

One of the strengths of this study is that medication adherence was objectively measured using an intelligent nebuliser device (eTrack®) that provides time-stamped data on how every dose of nebulised medication is being used. We chose to analyse the adherence data over a 3-month post recruitment period because baseline objective adherence data (i.e. prior to adherence intervention) was unavailable, sampling adherence over shorter periods is an unreliable measure of stable behaviour [1] and adherence were similar in both arms of the pilot for the first three months (median 38.5%, IQR 8.7 – 71.8% for intervention; median 37.9%, IQR 5.5 – 54.6% for usual care). Sampling adherence over a 6-month post recruitment period would be complicated by the divergence in adherence at month 4–6 (median 33.7%, IQR 7.2 – 75.0% for intervention; median 21.2%, IQR 7.0 – 55.9% for usual care).

Due to the cross-sectional nature of the analysis, the directionality of the association between habit and adherence cannot be established. The relationship between adherence and habit over time is complex; initial adherence episodes (undertaken in consistent settings) cause habit to form, and as habit forms, it acquires the potential to direct subsequent adherence.[2] While the habit scores analysed were collected at baseline, prior to the delivery of any intervention during the pilot trial, we did not have detailed data on participants' adherence (or intervention) histories. It is possible that some of the participants to have been "successfully intervened upon" in the past, and so may have achieved higher adherence prior to entering the study, and maintained these throughout the study. Assuming stability of adherence and habit over time, high adherence prior to entering the study may have caused higher habit scores at baseline, which then subsequently predicted (in a statistical sense) higher adherence over the following three months.

The habit measure used in this study is the Self-Report Behavioural Automaticity Index (SRBAI),[3] which is an automaticity subscale of the Self-Report Habit Index (SRHI).[4] Unlike SRHI, SRBAI does not enquire about behaviour frequency.[3] That means it is perhaps less likely for SRBAI scores to be just acting as a proxy measure for behaviour frequency. Although changing adherence could potentially change habit (since habit is strengthened through consistent repetition of a specific action in a specific context, i.e. content-dependent repetition),[2] it is important to note that habit is not synonymous with behaviour (e.g. adherence). It is possible that someone using his or her nebuliser frequently to have weak habit if he or she does not use the nebuliser in a consistent setting, and instead rely on consciously remembering to use the nebuliser. It is also, in theory, possible to strengthen habit without directly increasing the frequency of nebuliser use, by instead encouraging more consistent performance.[5] For example, adults with CF might be encouraged to identify cues that they encounter reliably and regularly in everyday routines, in the presence of which they should use their nebuliser.[6] Such habit-based advice would therefore focus on harnessing potential contextual cues, not increasing the frequency of nebuliser use per se.

Although habit was found to be the only independent factor that is associated with nebuliser adherence in this study, this is not to say that other factors are irrelevant. Due to modest sample size, the pilot trial could only detect differences if the effect size is sufficiently large.[7] For example, a 1 unit decrease in concerns score (concerns score could vary from 1, lowest perceived concern to 5, highest perceived concern) was associated with a 65% increase in the odds of being in the next-higher adherence category (e.g. from <50% to 50–79.9%, or 50– 79.9% to ≥80%) but the pilot trial was not sufficiently powered to detect that effect with a conventional α level of 0.05.

It is likely that both reflective (e.g. treatment beliefs) and automatic (e.g. habit) processes are associated with adherence levels, which would be detected with larger sample sizes. Nonetheless, we have replicated the Sheffield findings in an independent cohort. Replication of results reduces the uncertainty of evidence, hence these exploratory studies provide tentative evidence for the role of habit in the health behaviour of using nebuliser among adults with CF. The modest sample size for both studies is a limitation, but studies with larger sample sizes could still find that habit is more strongly associated with nebuliser adherence compared to other factors.

There is only one previous study examining the association between respiratory medication adherence and habit strength. The study among 139 asthma patients also found that medication adherence was most strongly associated with habit strength compared to other psychological factors such as self-efficacy and attitude.[8] In other long-term conditions, habit has been shown to better predict medication adherence compared to conscious motivational factors.[9] A recent meta-analysis of 771 medication adherence intervention studies identified habit as a promising target for intervention.[10] Therefore, further studies of habit as an adherence determinant and the investigation of habit-formation as a potential intervention to support adherence should be seen as a priority within cystic fibrosis and other areas of respiratory medicine.

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