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Full title:

Exploring the implications of different approaches to estimate centre-level adherence using objective adherence data in an adult cystic fibrosis centre – a retrospective observational study

Running title:

The impact of different adherence measures in CF

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ABSTRACT:

Background

Accurate centre-level medication adherence measurement allows identification of highly performing CF centres, drives shared learning and informs quality improvement. Self-reported adherence is unreliable but data-logging nebulisers can capture objective data. However, adherence levels in current literature are limited by the use of agreed prescriptions and convenience sampling. In this single-centre retrospective study, we quantified the differences in centre-level adherence with different methods of calculating adherence (unadjusted vs normative adherence) and different data sampling frames (convenience sampling vs including difficult to obtain data).

Methods

Adherence data were objectively captured using I-neb® from 2013-2016 in Sheffield Adult CF Centre. Adults on non data-logging devices, on ivacaftor or with previous lung transplantation were excluded. Adherence was calculated based on agreed regimen ('unadjusted adherence') or minimum required regimen ('normative adherence'). I-nebs® not brought to clinic were downloaded during home visits. Adults not on any inhaled therapy but with chronic *Pseudomonas aeruginosa* infection were included by counting their adherence as "0".

Results

Of the 131 included adults, 126 provided I-neb® data. Calculating unadjusted adherence from I-nebs® brought to clinics resulted in the highest centre-level adherence (median 41.8% in 2013). Median adherence reduced after sequentially accounting for minimum required regimen (40.0% in 2013), I-nebs® not brought to clinics (32.9% in 2013) and adults not on any inhaled therapy (31.0% in 2013).

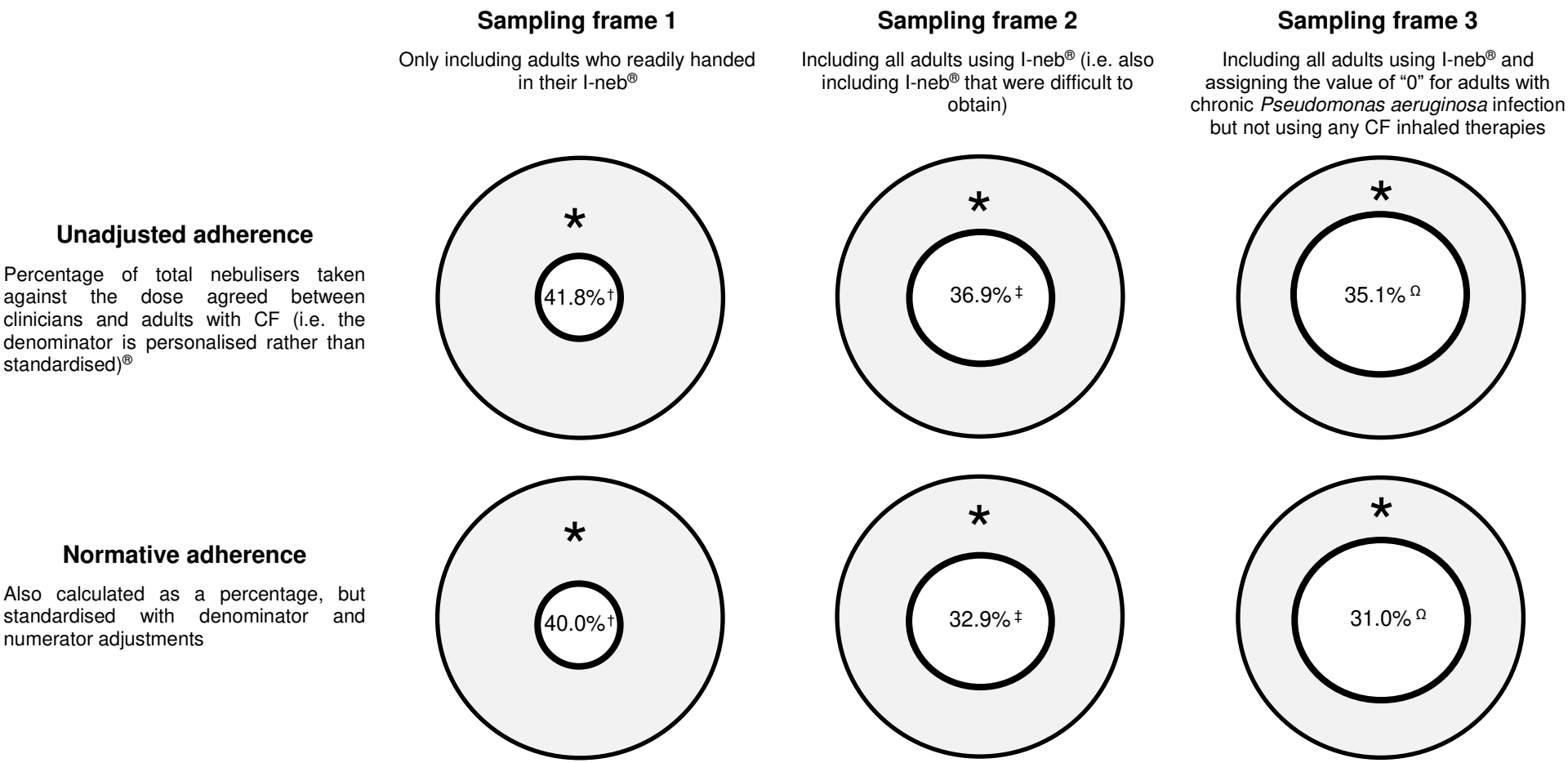
Conclusions

Different approaches of calculating adherence produced different adherence levels. Adherence levels based only on agreed regimen among adults who readily brought their nebulisers to clinics can over-estimate the effective adherence of CF centres.

KEYWORDS:

Cystic fibrosis; epidemiology; medication adherence; nebulizers and vaporizers

Graphical abstract: Illustrating the sequential reduction in centre-level median adherence as various aspects of adherence data processing and analysis are being implemented to reflect treatment effectiveness using data from 2013



* The total number of eligible population in 2013 was 166 adults, as represented by the area of the shaded circle.

† By only including adults who readily handed in their I-neb®, adherence would be calculated among 74 adults (the proportion of adults included are represented by the area of the white circle). The median unadjusted adherence was 41.8% and median normative adherence was 40.0%.

‡ By including all adults using I-neb®, adherence would be calculated among 89 adults (the proportion of adults included are represented by the area of the white circle). The median unadjusted adherence was 36.9% and median normative adherence was 32.9%.

Ω By including all adults using I-neb® and adults with chronic *Pseudomonas aeruginosa* infection not on any CF inhaled therapies, adherence would be calculated among 93 adults (the proportion of adults included are represented by the area of the white circle). The median unadjusted adherence was 35.1% and median normative adherence was 31.0%.

1. INTRODUCTION

Cystic fibrosis is a life-limiting genetic condition in which mortality is predominantly due to progressive lung damage driven by recurrent pulmonary exacerbations [1]. Inhaled therapies e.g. antibiotics and mucolytics are efficacious in preventing exacerbations and maintaining lung health [2]; but real-world median medication adherence of 35-50% among adults with CF is low [3, 4] especially in comparison to adherence of 80-100% in clinical trials [5]. The CF community is therefore unlikely to derive the optimal health benefits from inhaled therapies that were observed in clinical trials. Medication possession ratio of ~65% [6] in the presence of objectively measured adherence of ~35% [3] also highlights the possibility of significant waste. There are currently no effective adherence interventions for routine CF clinical use and the development of such interventions is a research priority [7].

Various quality improvement (QI) initiatives have transformed the delivery of CF healthcare [8]. The expertise of CF community in QI can potentially be harnessed to support adherence by creating a learning health system [9] in which objectively measured adherence using data-logging nebulisers such as I-neb® and eTrack® informs benchmarking and shared learning [10]. Benchmarking allows centre comparisons to highlight variation in care and the identification of highly performing centres to learn from [11]. Though data-logging devices are more costly than standard nebulisers, a health economics evaluation suggest these devices will more than justify their costs if they are used effectively to provide feedback and improve adherence [12]. In the UK, NHS England specialised commissioning have agreed to fund objective adherence data capture across most adult English CF centres via the national Commissioning for Quality and Innovation (CQUIN) programme. A learning health system among these centres has been established (ISRCTN14464661) and is currently recruiting adults with CF in 19 out of the 28 UK centres. Therefore, understanding how to use objective adherence data as a quality indicator is an important and timely issue.

Centre comparisons using adherence as a quality indicator rely on centres being confident that adherence measures are equally standardised, thus comparable between centres so that they accurately reflect the effective use of inhaled therapies within a centre. Though objective adherence data are accurate and reliable, robust comparison between centres also depends on how data are processed, analysed and reported. The ABC taxonomy for medication adherence recommends that adherence definitions should be clinically relevant and account for deviation that adversely influence the intended effects of medication regimen [13]. The Respiratory Effectiveness Group emphasises the importance of considering “successful medication adherence” holistically so that adherence levels reflect treatment effectiveness [14]. In general, inadequate prescription of efficacious treatment (“therapeutic inertia”) is the second biggest cause of ineffective treatment after low adherence [15]. Therapeutic inertia is pertinent in CF because “treatment burden” is widely perceived to be a major barrier to adherence [4]; with the result that treatment rationalisation or non-initiation of treatment can be one strategy that is adopted in the hope that a lowered treatment burden might

promote greater engagement [16]. Another aspect of therapeutic inertia is appropriate inaction; such as treatment modifications due to medication intolerance, costs of medication, therapy being ineffective in the past and patient values/preference. Regardless of the reason(s) for excluding efficacious treatment(s) from an agreed prescription, there is the potential to reduce treatment effectiveness whilst inflating calculated adherence level unless there is standardisation against a normative adherence metric. For example, not initiating long-term inhaled antibiotics in a person with chronic *Pseudomonas aeruginosa* infection due to medication cost will result in a lowered denominator for calculating percent adherence and the resultant percent adherence is unlikely to reflect the effective utilisation of inhaled therapies (i.e. the denominator will be one daily dose instead of three daily doses assuming the person was already using dornase alfa and a twice daily inhaled antibiotic was not initiated). Adherence measures that incorporate treatment effectiveness are largely neglected in extant CF literature which tends to only report agreed adherence. Whilst agreed adherence is a valuable patient centred measure, its personalised nature undermines the standardisation required for centre comparison.

Another limitation in extant literature is the use of convenience samples that ignores the group of people who are unwilling to share their data or who are not using any medication. People with the lowest adherence levels may be least willing to share their data [17]; hence centre comparisons would be confounded by inconsistent sampling frames and differential missing data unless the entire cohort is accounted for, such that the denominator used to calculate centre-level adherence is defined by all the appropriate patients making up the population of interest. In many studies, difficult-to-reach patients would simply be missing and the missingness might well be unavoidably invisible for long-term conditions such as asthma. Yet CF is unique in that almost all people with CF in the UK are identified within the CF registry [18]. Registry data can identify the number of people who should actually feature as the centre denominator in centre-level adherence measurement and quantify the number of missing people in adherence levels calculated by each centre.

Understanding the properties of different approaches to calculate centre-level adherence data is an important first step towards robust comparison using adherence as a quality indicator. We therefore set out to quantify the differences in centre-level adherence with different methods of calculating adherence and different data sampling frames.

2. METHODS

This single-centre retrospective analysis included all eligible adults with CF in Sheffield aged ≥16 years diagnosed with the UK CF Trust criteria. Adults with lung transplantation or on ivacaftor were excluded because this dataset was originally compiled to evaluate the impact of adherence on health outcomes, and both treatments have transformative effects on lung health [19]. Adults using inhaled therapies via devices without data-logging capabilities were also excluded because only objective

adherence levels were evaluated (the clinical characteristics of these adults were tabulated in Appendix A). However, adults with chronic *Pseudomonas aeruginosa* infection not on any CF inhaled therapies were included since they should have been on inhaled therapies. This study was approved by NHS Health Research Authority (IRAS number 210313).

Inhaled therapy prescriptions and relevant demographic data (age, gender, genotype status [20], pancreatic status, CF related diabetes, *Pseudomonas aeruginosa* status as defined by the Leeds criteria [21], body mass index, $\%FEV_1$, intravenous antibiotics use) were extracted by two investigators independently reviewing paper notes and electronic records. Where extracted data differed, both investigators re-reviewed original data to arrive at a consensus. Nebuliser adherence data were downloaded from I-nebs®, which typically store 3,000-4,000 datapoints and provide date- and time-stamped data for every dose of nebulised medication [16].

'Unadjusted adherence' was calculated as the percentage of total nebulisers taken against the dose agreed between clinicians and adults with CF (i.e. the denominator is personalised rather than standardised). 'Normative adherence' was also calculated as a percentage, but included denominator adjustment (standardised to define the minimum required treatment regimen) according to a person's *Pseudomonas aeruginosa* status and numerator adjustments (capping daily maximum nebuliser use at 100%, accounting for doses taken after midnight and accounting for dose spacing for inhaled antibiotics) as previously described [22]. For example, those with chronic *Pseudomonas aeruginosa* infection should take at least a nebulised mucolytic and an antibiotic i.e. the denominator will be at least "3" (1x dornase alfa, 2x antibiotic). If that person only agreed to use dornase alfa once daily (i.e. 1 nebuliser/day), even if every dose was taken (giving 100% unadjusted adherence), the normative adherence would only be 33%. A detailed description for the calculation of normative adherence in a range of clinical scenarios is provided in Appendix B.

For each adherence calculation method, centre-level adherence was determined as the median for all adults (i.e. adherence was calculated for every adult and the median for all adults was determined to avoid potential bias by differences in data duration between individuals). For each adherence calculation method, three sampling frames were applied to determine the centre-level adherence. First, adherence was calculated using only data from I-nebs® that were downloaded in each calendar year during clinical reviews, i.e. among adults who readily handed in their devices. Second, all available I-neb® data were used, i.e. including elusive I-nebs® that were "difficult to obtain" which had to be chased via repeated requests and home visits. This refers to I-nebs® that were not downloaded within the calendar year but data became retrospectively available when downloaded in subsequent year(s). These I-nebs® would have been a source of missing data without concerted efforts to retrieve them and would have remained missing in many settings. Therefore, the difficult to obtain I-nebs® were used to approximate the effect of 'missing I-nebs® data'. Third, adherence levels also included adults with chronic *Pseudomonas aeruginosa* infection but not using any CF inhaled therapies throughout the calendar year by assigning their adherence as "0".

Analysis were performed using SPSS v25 (IBM Corp) and R v3.3.0 (www.r-project.org). Data for 2013, 2014, 2015 and 2016 were analysed separately to determine the consistency of any observations. Appropriate descriptive statistics were generated. Where relevant, between-group comparisons were performed using non-parametric tests [23] (due to non-normal adherence data distribution and presence of outliers) whilst agreement between paired measurements were assessed with 'difference vs average' plots [24]. P-value <0.05 was considered statistically significant. The sample size was pragmatic, and all available data were included in this analysis.

3. RESULTS

This analysis included 131 adults, with 126 adults providing I-neb® data and five adults with chronic *Pseudomonas aeruginosa* infection but not on CF inhaled therapies. Year-by-year demographic data were stratified in Table 1 according to whether the adults used I-neb® or not. The number of adults with chronic *Pseudomonas aeruginosa* infection not on inhaled therapies was small. Around 1/3 of the adults in Sheffield used only non-data logging devices (31% in 2013, 28% in 2014, 30% in 2015 and 37% in 2016) and were excluded from this analysis. Results in Appendix A suggest that these adults shared broadly similar clinical characteristics compared to adults included in this analysis.

Although many of the unadjusted adherence values were similar to normative adherence, unadjusted values generally over-estimated adherence (see Figure 1 and Table 2). At a centre-level, the median paired differences were 2.6-5.1%. In those with low adherence (<5%), unadjusted and normative adherence differed little due to the floor effect of adherence (adherence level cannot be negative). However, in some adults with higher unadjusted adherence levels, the difference could be up to 40-100% especially in those with nebuliser over-use (unadjusted adherence >100%) because daily adherence was capped at 100% for normative adherence.

Despite the modest sample size, adherence levels for difficult to obtain I-nebs® (median normative adherence 8.4% in 2013, n=15; 9.8% in 2014, n=13; 6.1% in 2015, n=10; and 10.2% in 2016, n=8) were significantly lower than readily obtained I-nebs® (median normative adherence 40.0% in 2013, n=74; 45.2% in 2014, n=84; 49.6% in 2015, n=94; and 53.4% in 2016, n=94), Mann-Whitney p-value <0.001 for all four years. Thus measuring adherence using only readily obtained I-neb® over-estimated centre-level adherence. Since difficult to obtain I-nebs® typically had such low adherence levels, adopting the convention of assigning their adherence levels as "0" would only result in very slight under-estimation of centre-level adherence (the resultant median normative adherence would be 30.6% in 2013, 41.0% in 2014, 44.6% in 2015 and 50.8% in 2016). Despite the small number of adults with chronic *Pseudomonas aeruginosa* infection who were not on any CF inhaled therapy, centre-level median adherence fell further if they were included in the overall estimate of adherence (see Table 2).

4. DISCUSSION

Once randomised controlled trials have demonstrated the efficacy of a treatment, it is reasonable to consider the proportion of eligible patients in a centre who are prescribed that treatment by clinicians and objectively captured adherence of patients to the prescription as an indicator of care quality. That is to say that once an RCT establishes a relationship between a process and an outcome, it is reasonable to use a process measure as an indicator of care quality. Our analysis empirically demonstrates that different approaches to processing and analysing objective data are likely to influence centre-level medication adherence. Medians are typically more robust to the impact of outliers [25], yet there was sequential reduction in centre-level median adherence as the analysis methodology moved from unadjusted adherence among readily obtained I-nebs® to normative adherence which included difficult to obtain I-nebs® and adults not on inhaled therapies when they should. Therefore, the considerations of both treatment appropriateness (normative adherence) and missing data (sampled via difficult-to-reach I-nebs®) are important in accurately understanding objective adherence as a centre-level quality indicator.

In many long-term conditions, centre performance based on objective adherence and clinician prescribing patterns can be difficult to interpret, as the best centres might appear to have the worst adherence if therapeutic inertia is least prevalent and if they retain some engagement with difficult-to-reach patients with the lowest medication adherence. An adolescent diabetic clinic where the most rebellious teenagers refuse to attend might have excellent glycosylated haemoglobin data; but that data is potentially misleading as an indicator of care quality without an understanding of the population that should have been reached. CF is unique in that the UK CF registry has data on almost all people with CF, thus the number of patients within a centre eligible for care (the centre denominator) is known, allowing CF to provide a unique setting for the study of intervention reach in long-term conditions.

The high prevalence of missing data in studies investigating adherence has been reported previously [17]. Data are seldom missing at random and analyses in other long-term conditions also demonstrate the potential for missing data to introduce bias [26]. In our analysis, we have chosen to account for people not on any CF inhaled therapies by assigning “0” as their adherence level. This adjustment may be crude, but people not using any CF inhaled therapies when they should (since long-term inhaled antibiotics are recommended for chronic *Pseudomonas aeruginosa* infection) do have zero adherence. We also justify our approach by exploring the data of people on data-logging nebulisers who did not readily share their data. If a centre was not engaged in chasing down these data and simply omit difficult-to-reach I-nebs® from the centre denominator, an inappropriately high estimate of centre performance would be obtained. Assigning “transiently missing” adherence levels as “0” for the calculation of centre-level adherence in real time would only result in very slight under-estimation since difficult-to-reach I-nebs® tended to have very low adherence levels.In addition to completely missing data, there is substantial variation in the prescription of inhaled therapies which

is too large to be explained by just case-mix and chance. UK data showed an almost 3-fold difference (86.8% vs 30.2%) in the prescription of dornase alfa between the adult CF centres with highest and lowest use [18]. US data showed that only two-thirds of people with CF were prescribed the recommended inhaled therapies [27]. Since some of this variation reflects therapeutic inertia, it is important that treatment appropriateness is captured by standardisation according to patient characteristics via normative adherence.

The extant CF literature tend to report unadjusted adherence levels from convenience samples without accounting for the appropriateness of treatment prescription or people with missing adherence data. This is likely to over-estimate centre-level adherence. In other words, although reported adherence levels among adults with CF in the literature are low at 35-50% [3, 4], the actual total cohort effective adherence levels are almost certainly even lower. This perspective is important in highlighting that the challenges of medication adherence may be even worse than published data suggest. With median centre-level objective adherence as low as 30%, centre comparisons and benchmarking within a learning health system that starts to drive improvement has the potential to make a major impact on the quality of care.

Our findings have implications for benchmarking in justifying a standardised approach that allows objective adherence data to be used as a centre-level process measure suitable for quality measurement. The use of standardised process measure is important since using health outcomes as a quality measure for benchmarking in CF is particularly problematic because a relatively small UK CF population is spread across many centres. FEV_1 is an important outcome measure in CF, but a recent sample size estimation suggests that 273 adults per centre are needed to detect a 5% FEV_1 difference at the 5% statistical significance level [28]. Yet only 6/28 (21.4%) of all UK adult CF centres have ≥273 adults [18]. CF QI initiatives focusing on process measures that allow rapid feedback to prompt improvement and subsequent reassessment have been reported,[8] but to date real time adherence data have not been exploited for this purpose. We hope that this study will lay the groundwork for such studies in the future. For any benchmarking exercises using adherence as a metric to be reliable, it is crucial to determine whether differences in the metric represents a genuine difference in effective adherence or whether it is merely an artefact of data issues (e.g. different prescribing practices between centres or differential missing data). The patient-centred unadjusted adherence measure based on personalised prescriptions reflecting individualised concordance is important when discussing adherence with individual patients but it is not a suitably standardised indicator for centre benchmarking. By using a standardised metric free from the vagaries of prescribing practices (normative adherence which is standardised in light of patients' clinical characteristics) and missing data (standardised using registry data to define the centre denominator) to reflect treatment effectiveness, centres involved in the benchmarking exercise can be more confident that apples are being compared to apples.

We acknowledge the uncertainty involved in deciding what inhaled therapies an adult with CF should be using based on their clinical characteristics. There are differing levels of evidence for inhaled therapies among people with differing lung disease severity and also for different treatment options. In our previous publication [22], we have taken the approach that perfect should not be the enemy of the good in attempting to specify an *a priori* method of processing adherence data which might be expected to ensure that a higher percentage adherence to the specified treatment regimen is associated with greater treatment effectiveness. The approach we have used will not capture all the subtleties involved in matching treatment regimens to complex patients; nevertheless the approach is pragmatic, can be applied in busy clinical setting, goes some way towards dealing with the issue of treatment effectiveness and goes much further in resolving issues around missing data. The Sheffield dataset was not large enough to definitively elucidate the relationship between health outcomes and different approaches of calculating adherence. Therefore, different adherence indices and methods of processing adherence data should be empirically tested in a suitably large dataset with objective adherence data and carefully measured key outcomes to determine the optimum method of calculating adherence levels. Nonetheless, different methods of adjusting for inadequate prescriptions would still find lower levels of adherence following the adjustments if efficacious treatments are under-prescribed. It is important to understand the direction of any bias. In this study, by only implementing denominator adjustments for adults with chronic *Pseudomonas aeruginosa* infection as defined by the Leeds criteria (which is known to lack sensitivity [29]), we are likely to under-adjust for required treatment prescription and hence our estimates of effective adherence is likely to be an over-estimation. Thus when adjustment lowers centre adherence, we can be confident that the revised figure is appropriately lowered and if anything, elimination of measurement bias (if technically possible) would merely lower it further. More thorough adjustments for other factors which influence treatment effectiveness would reveal even greater discrepancies between unadjusted and normative adherence. Another factor to consider in adjusting for treatment prescription is that not everyone would be able to tolerate inhaled therapies. It is uncertain whether the proportion of people with CF genuinely unable to tolerate any inhaled therapies will vary substantially from centre-to-centre. Accounting for this group consistently across all centres should help to improve the reliability of centre-comparison with adherence as the metric for improvement.

This study has other limitations. Objective adherence to dry powder inhalers (used by <10 adults each year in this single-centre cohort) and non-data logging nebulisers (e.g. eFlow®) could not be measured and were therefore excluded. However, the characteristics associated with adherence e.g. age and socioeconomic deprivation were broadly similar between the adults excluded because they were solely using devices without data-logging capabilities and adults using I-nebs®. Hence this exclusion may not necessarily bias the results and our analysis could still provide an insight into what data might be available if adherence were measured across the whole centre. Our sample size is pragmatic and single-centre studies may lack generalisability. Nonetheless, our dataset is currently the largest electronic data capture adherence dataset in CF with 18,303 weeks of adherence data

from 126 adults. The consistency of our findings from 2013-2016 also provide some reassurance that the results are unlikely to occur just by chance.

5. CONCLUSIONS

We have demonstrated that objective adherence levels are influenced by the different approaches of sampling, processing and analysing adherence data. We have also proposed pragmatic methods to account for between-centre variation in treatment prescriptions and potential differential adherence data missingness, so that the resultant adherence metric better reflects the centre-level effectiveness of medication use. Standardising the approach of calculating adherence is an important first step towards robust centre-comparison to identify the relevant differences in structure and care processes that can stimulate improvement. After ensuring that adherence data between centres are comparable, understanding the case-mix factors which influence centre-level adherence is the next important step to make sense of the variation in adherence according to the 'pyramid of investigation' model [30]. Case-mix factors that influence adherence level will be the subject of our next paper. It has also not escaped our notice that the results in Table 2 suggest a consistent improvement in our centre's adherence levels from 2013 to 2016, regardless of the metric used to report objective adherence. More detailed longitudinal analyses of our adherence data will be the subject of another paper.

COMPETING INTERESTS

None declared.

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CONTRIBUTORS

Each author had full access to the data and takes responsibility for the integrity and accuracy of this study. All authors contributed to and approved of the final submitted manuscript. HZH and MJW were responsible for the study design, data analysis and interpretation, and the writing of the manuscript.

HZH and RC were responsible for acquisition of data. RC, SJW and MJC contributed substantially to the data analysis and interpretation, and the writing of the manuscript.

ETHICS APPROVAL

Regulatory approval for this study was obtained from NHS Health Research Authority (IRAS number 210313).

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Table 1: Clinical characteristics of study subjects[ϕ] for 2013 to 2016

Clinical characteristics	2013		2014		2015		2016	
	Used I-neb® *(n = 89)*	**No nebuliser†** *(n = 4)*	**Used I-neb®** *(n = 97)*	**No nebuliser†** *(n = 3)*	**Used I-neb®** *(n = 104)*	**No nebuliser†** *(n = 3)*	**Used I-neb®** *(n = 102)*	**No nebuliser†** *(n = 0)*
Age in years, median (IQR)	25 (19 – 30)	28 (26 – 31)	25 (19 – 31)	29 (29 – 31)	26 (20 – 32)	43 (39 – 46)	26 (19 – 32)	N/A
Female, n (%)	37 (41.6)	2 (50.0)	39 (40.2)	2 (66.7)	43 (41.3)	2 (66.7)	42 (41.2)	N/A
Homozygous class I-III,[‡] n (%)	80 (89.9)	4 (100.0)	88 (90.7)	3 (100.0)	91 (87.5)	2 (66.7)	91 (89.2)	N/A
Pancreatic insufficient, n (%)	85 (95.5)	4 (100.0)	91 (93.8)	3 (100.0)	96 (92.3)	2 (66.7)	95 (93.1)	N/A
CF related diabetes, n (%)	23 (25.8)	1 (25.0)	25 (25.8)	2 (66.7)	25 (24.0)	1 (33.3)	32 (31.4)	N/A
Chronic *P. aeruginosa*,[¶] n (%)	47 (52.8)	4 (100.0)	52 (53.6)	3 (100.0)	51 (49.0)	3 (100.0)	49 (48.0)	N/A
BMI, median (IQR)	21.5 (19.7 – 24.3)	19.9 (16.7 – 20.8)	22.2 (20.1 – 24.3)	19.4 (17.1 – 19.9)	23.0 (20.7 – 24.9)	30.2 (25.7 – 30.5)	23.2 (20.6 – 25.4)	N/A
Best %FEV_1,[§] median (IQR)	75.9 (52.9 – 90.0)	60.8 (20.4 – 92.0)	74.0 (55.0 – 87.5)	37.8 (25.8 – 64.5)	76.0 (58.5 – 87.6)	89.9 (85.1 – 92.7)	76.4 (62.1 – 87.0)	N/A
IV antibiotic days, median (IQR)	14 (0 – 41)	63 (21 – 95)	14 (0 – 31)	28 (21 – 56)	20 (2 – 36)	21 (11 – 46)	18 (0 – 42)	N/A
On inadequate prescription,[Ω] n (%)	12 (13.5)	4 (100.0)	12 (12.4)	3 (100.0)	16 (15.4)	3 (100.0)	16 (15.7)	N/A

[ϕ] Complete clinical characteristics data were available for all study subjects.

[†] These are adults who should be on preventative inhaled therapies since they have chronic *Pseudomonas aeruginosa* infection but were not on any preventative inhaled therapies.

[‡] Genotype status was defined by international consensus [20]. Homozygous class I-III mutations indicate 'severe genotype'.

[¶] The Leeds criteria were used to define *Pseudomonas aeruginosa* status [21].

[§] This represents the highest %FEV_1 reading (calculated with GLI equations) in the calendar year period.

[Ω] A person with chronic *Pseudomonas aeruginosa* infection was deemed to be on inadequate prescription if he/she was not on at least once daily dose of mucolytic and at least twice daily doses of inhaled antibiotic (taking into account on/off long-term antibiotic regimens). In this group of people, denominator adjustment was required to calculate normative adherence. Everyone with chronic *Pseudomonas aeruginosa* infection not on any inhaled therapies was deemed to be on inadequate prescription.

Table 2: The impact of different data analysis and processing methods on adherence levels for 2013 to 2016

Year	**2013**	**2014**	**2015**	**2016**
Method 1: **% unadjusted adherence**, median (IQR)				
Sampling frame 1 †	41.8 (25.8 – 70.0) *n = 74*	52.6 (29.1 – 82.8) *n = 84*	57.7 (28.4 – 85.5) *n = 94*	59.1 (28.6 – 88.9) *n = 94*
Sampling frame 2 ‡	36.9 (19.1 – 64.7) *n = 89*	44.9 (19.3 – 77.1) *n = 97*	51.4 (23.8 – 80.7) *n = 104*	52.8 (24.3 – 88.0) *n = 102*
Sampling frame 3 Ω	35.1 (16.9 – 64.3) *n = 93*	44.7 (16.3 – 76.6) *n = 100*	50.8 (22.0 – 80.2) *n = 107*	52.8 (24.3 – 88.0) *n = 102*
Method 2: **% normative adherence**, median (IQR)				
Sampling frame 1 †	40.0 (20.4 – 67.2) *n = 74*	45.2 (28.4 – 75.2) *n = 84*	49.6 (23.1 – 80.1) *n = 94*	53.4 (27.7 – 77.4) *n = 94*
Sampling frame 2 ‡	32.9 (16.4 – 59.9) *n = 89*	41.0 (17.2 – 65.4) *n = 97*	45.4 (19.4 – 73.8) *n = 104*	50.8 (23.8 – 71.6) *n = 102*
Sampling frame 3 Ω	31.0 (15.1 – 58.1) *n = 93*	39.7 (16.1 – 64.8) *n = 100*	44.2 (18.8 – 69.6) *n = 107*	50.8 (23.8 – 71.6) *n = 102*

† Including adults who readily handed in their I-neb®

‡ Including all adults using I-neb® (i.e. including I-neb® that were difficult to obtain)

Ω Including all adults using I-neb® and assigning the value of "0" for adults with chronic *Pseudomonas aeruginosa* infection but not using any CF inhaled therapies

Appendix A: Clinical characteristics of adults included in the analysis vs adults excluded due to the use of inhaled therapies via devices without data-logging capabilities

In total, 84 adults were excluded from this analysis because they were only using CF inhaled therapies via devices without data-logging capabilities (e.g. eFlow® nebuliser or dry powder inhaler), i.e. their objective adherence were not measured. Their clinical characteristics were detailed in Table 1A.

Table 1A: Clinical characteristics of adults included in the analysis vs adults using devices without data-logging capabilities for 2013 to 2016

Clinical characteristics	2013		2014		2015		2016	
	Adults included in the analysis *(n = 93)*	**Adults on non-data logging devices** *(n = 42)*	**Adults included in the analysis** *(n = 100)*	**Adults on non-data logging devices** *(n = 39)*	**Adults included in the analysis** *(n = 107)*	**Adults on non-data logging devices** *(n = 46)*	**Adults included in the analysis** *(n = 102)*	**Adults on non-data logging devices** *(n = 61)*
Age in years, median (IQR)	25 (19 – 30)	24 (20 – 30)	26 (19 – 31)	26 (21 – 33)	26 (20 – 32)	27 (23 – 34)	26 (20 – 32)	28 (23 – 35)
Female, n (%)	39 (41.9)	19 (45.2)	41 (41.0)	21 (53.8)	45 (42.1)	27 (58.7)	42 (41.2)	37 (60.7)
Homozygous class I-III,‡ n (%)	84 (90.3)	36 (85.7)	91 (91.0)	34 (87.2)	93 (86.9)	38 (82.6)	91 (89.2)	45 (73.8)
Pancreatic insufficient, n (%)	89 (95.7)	37 (88.1)	94 (94.0)	34 (87.2)	98 (91.6)	38 (82.6)	95 (93.1)	45 (73.8)
CF related diabetes, n (%)	24 (25.8)	12 (28.6)	27 (27.0)	13 (33.3)	26 (24.3)	15 (32.6)	32 (31.4)	21 (34.4)
Chronic *P. aeruginosa*,¶ n (%)	51 (54.8)	18 (42.9)	55 (55.0)	22 (56.4)	54 (50.5)	26 (56.5)	49 (48.0)	30 (49.2)
Deprivation quintile†								
1 i.e. most affluent, n (%)	11 (11.8)	5 (11.9)	13 (13.0)	6 (15.4)	15 (14.0)	5 (10.9)	14 (13.7)	8 (13.1)
2, n (%)	8 (8.6)	4 (9.5)	10 (10.0)	3 (7.7)	10 (9.3)	5 (10.9)	11 (10.8)	9 (14.8)
3, n (%)	26 (28.0)	7 (16.7)	28 (28.0)	7 (17.9)	30 (28.0)	9 (19.6)	27 (26.5)	12 (19.7)
4, n (%)	21 (22.6)	12 (28.6)	25 (25.0)	8 (20.5)	26 (24.3)	12 (26.1)	24 (23.5)	16 (26.2)
5 i.e. most deprived, n (%)	27 (29.0)	14 (33.3)	24 (24.0)	15 (38.5)	26 (24.3)	15 (32.6)	26 (25.5)	16 (26.2)
BMI, median (IQR)	21.3 (19.7 – 24.3)	21.5 (19.3 – 23.8)	22.1 (19.9 – 24.2)	22.1 (19.4 – 24.5)	23.0 (20.8 – 24.9)	21.5 (19.7 – 24.3)	23.2 (20.6 – 25.4)	22.0 (19.5 – 26.1)
Best %FEV_1,§ median (IQR)	75.9 (52.7 – 90.0)	65.7 (46.8 – 92.3)	73.9 (54.2 – 87.5)	66.5 (34.9 – 89.8)	77.2 (59.1 – 87.7)	65.6 (41.9 – 86.1)	76.4 (62.1 – 87.0)	73.2 (47.0 – 87.5)
IV antibiotic days, median (IQR)	14 (4 – 42)	14 (0 – 42)	14 (2 – 32)	14 (0 – 42)	21 (2 – 36)	17 (0 – 44)	18 (0 – 42)	14 (3 – 43)

‡ Genotype status was defined by international consensus [1]. Homozygous class I-III mutations indicate 'severe genotype'.

¶ The Leeds criteria [2] were used to define *Pseudomonas aeruginosa* status.

† These are Index of Multiple Deprivation (IMD) quintiles, which were derived from postcodes [3].

§ This represents the highest %FEV1 reading (calculated with GLI equations) in the calendar year period. One of the adults using non-data logging device did not provide any %FEV_1 readings from 2013 to 2016 due to the inability to perform spirometry. There is otherwise no missing data.

For each year between 2013 and 2016, many more adults in Sheffield were using I-neb® compared to non-data logging devices because the Sheffield Adult CF Centre concentrated on finding ways to objectively quantify nebuliser use. There were no clear differences in terms of genotype, pancreatic status, CF related diabetes status and *P. aeruginosa* status between those on inhaled therapies via non-data logging devices and I-neb® users. However, $\%FEV_1$ was lower among non-data logging device users, in part because I-neb® (which is an adaptive aerosol device that only releases aerosol with an inhalation of sufficient quality [4]) can be a struggle to use among people with FEV_1 <40%.

For clinical characteristics that are associated with treatment adherence e.g. age [5] and socioeconomic status [6], there were broad similarities between non-data logging device users and I-neb® users. Majority of the adults in Sheffield were in the 19-25 years age range and <25% of the adults were in two most affluent socioeconomic quintiles. Though nebuliser adherence could not be objectively measured among non-data logging device users, it seems unlikely for them to have much higher adherence levels compared to I-neb® users since the clinical team in Sheffield paid the most attention to the adherence of adults with objective data.

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Appendix B: A summary of the methods to calculate normative adherence

The full details of the adjustments required to calculate normative adherence and the rationale for those adjustments are outlined in our previous paper [1]. To calculate normative adherence, the numerator was initially adjusted for the following:

1. accounting for incomplete doses – a "full" dose was counted as "1 dose", "12.5%–100%" was counted as "½ dose" while "<12.5%" and "none" doses were counted as 0
2. capping maximum daily dose at 100% according to prescribed doses – nebuliser use in excess of the agreed dose was not counted
3. accounting for doses taken after midnight – counting a day as starting at 5am and ending at 4.59am
4. accounting for device dose delivery characteristics – each complete nebulisation of tobramycin solution via the I-neb® was counted as "½ dose", so that the complete dose (two complete nebulisations) would count as "1 dose"
5. minimum dose spacing for inhaled antibiotics – inhaled antibiotic doses that were used <6 hours after an initial dose were not counted

The denominator was then adjusted according to the following rules:

1. For every study subject, their *Pseudomonas aeruginosa* status was determined using the Leeds criteria [2].
2. For every study subject identified as not having chronic *P. aeruginosa* infection, no denominator adjustment was carried out.
3. For every study subject identified as having chronic *P. aeruginosa* infection, the minimum denominator was set at once daily mucolytic and twice daily antibiotics (taking into account on/off long-term antibiotic regimens). For example, in a study subject with chronic *P. aeruginosa* infection but only prescribed mucolytic, two extra nebuliser doses per day will be added to the denominator. For someone with chronic *P. aeruginosa* infection but only prescribed twice daily antibiotic without any mucolytic, one extra nebuliser dose per day will be added to the denominator.

Of note, denominator adjustments were only carried out among adults with chronic *P. aeruginosa* infection if they were not already on at least one daily dose of mucolytic and at least two daily doses of antibiotics (taking in account on/off long-term antibiotic regimens). There would be no denominator adjustment if the minimum required doses were already fulfilled, for example in someone who was already on twice daily hypertonic saline and thrice daily Aztreonam. As such, whilst there may be some variation in the calculated normative adherence according to differences in prescribing practices, this variation is unlikely to be significant. For example, someone with chronic *P. aeruginosa* infection but using their prescribed once daily dornase alfa with 100% unadjusted adherence would have normative adherence of 33%, whereas someone with chronic *P. aeruginosa* infection only on hypertonic saline twice daily with 100% unadjusted adherence would have

normative adherence of 50%. The median unadjusted adherence of only ~50% among the study subjects would reduce the absolute difference in normative adherence. The two people in the example above would have normative adherence of 17% and 25% respectively if their unadjusted adherence was 50%, or normative adherence of 8% and 13% respectively if their unadjusted adherence was 25%. The full details for the denominator adjustments of the cohort are detailed in Table 1B.

Table 1B: Full details of the denominator adjustments from 2013 to 2016

The actual prescription †	**The denominator adjustment that was carried out**	**Number of adults using I-neb® with this denominator adjustment for each year, n (%)**			
		2013 *(n = 89)*	**2014** *(n = 97)*	**2015** *(n = 104)*	**2016** *(n = 102)*
(Not chronic *Pseudomonas aeruginosa* infection)	No denominator adjustment	42 (47.2)	45 (46.4)	53 (51.0)	53 (52.0)
(Chronic *Pseudomonas aeruginosa* infection, already on at least once daily dose of mucolytic and twice daily doses of inhaled antibiotic, taking into account on/off long-term antibiotic regimens)	No denominator adjustment	35 (39.3)	40 (41.2)	35 (33.7)	33 (32.4)
<u>Chronic *Pseudomonas aeruginosa* infection, on inadequate prescription</u>					
Once daily dornase alfa	Daily normative denominator of "3" (instead of "1")	4 (4.5)	3 (3.1)	3 (2.9)	7 (6.9)
Once daily dornase alfa (was on month-on / month-off tobramycin which was stopped between May and July 2013)	Daily normative denominator of "3"‡ (instead of "1") for the month of June 2013, otherwise no denominator adjustment	1 (1.1)	0	0	0
Once daily colistin (Promixin®)	Daily normative denominator of "3" (instead of "1")	0	0	1 (1.0)	0
Twice daily colistin (Promixin®)	Daily normative denominator of "3" (instead of "2")	7 (7.9)	9 (9.3)	12 (11.5)	9 (8.8)

† Aztreonam was not nebulised through an I-neb®, hence no adjustments for people on Aztreonam was required. However, the same principle applies for calculating normative adherence with other devices (e.g. an eTrack®). For example, if someone with chronic *Pseudomonas aeruginosa* infection was only on thrice daily Aztreonam nebuliser, then the normative adherence convention would be to add an extra dose to the normative denominator to account for the missing mucolytic (i.e. daily normative denominator of "4" instead of "3"). In addition, very few of the cohort were on on-off inhaled antibiotics regimen since it is not the centre practise to recommend this and few of the cohort were on nebulised hypertonic saline since dornase alfa is the first choice mucolytic for the centre. Of note, there was no much denominator adjustments in our centre because we have an agreed strategy of using normative regimens universally where possible. In centres where therapeutic inertia is more common, there would be a larger proportion of people with CF requiring denominator adjustments.

‡ Tobramycin requires double-loading via an I-neb® for adequate dosing but numerator adjustment accounting for device dose delivery characteristics converts a complete Tobramycin dose (i.e. two complete nebulisations) into "1 dose", hence the normative denominator stays at "3" instead of "5" for someone using twice daily tobramycin and once daily dornase alfa via an I-neb®.

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