
Article:
Bevan, A, Hoo, ZH orcid.org/0000-0002-7067-3783, Totton, N orcid.org/0000-0002-1900-2773 et al. (65 more authors) (2022) Using a learning health system to understand the mismatch between medicines supply and actual medicines use among adults with cystic fibrosis. Journal of Cystic Fibrosis, 21 (2). pp. 323-331. ISSN 1569-1993

https://doi.org/10.1016/j.jcf.2021.09.007

TITLE

Using a learning health system to understand the mismatch between medicines supply and actual medicines use among adults with cystic fibrosis

RUNNING TITLE

MPR vs actual medicine use in CF

AUTHORS' NAMES (surnames are underlined)

Amanda Bevan [1], Zhe Hui Hoo [2,3], Nikki Totton [2], Carla Girling [2], India R Davids [2], Pauline Whelan [4], Steven Antrobus [4], John Ainsworth [4], Iain Buchan [4], Alan Anderson [5], Stephen Bourke [5], Simon Doe [5], Carlos Echevarria [5], Jill Taylor [5], Nicholas J Bell [6], Kathryn Bateman [6], Carys Jones [6], Peter Moran [6], Giles Fitch [7], Michael Martin [7], Angela McGowan [7], Stephen Morrow [7], Heather Seabridge [7], Nicki Bush [8], Tracey Daniels [9], Katy Lee [9], Nicola Robson [9], Dejene Shiferaw [8], Dimah Sweis [9], Rebecca Thomas [9], Jayne Faulkner [10], William G Flight [10], Sarah Poole [10], Louise Warnock [10], Mark I Allenby [1], Mary Carroll [1,11], Thomas V Daniels [1,11], Helen Dunn [1], Julia A Nightingale [1], Elizabeth Shepherd [1], Chandra Ohri [12], Jessica Gadsby [12], Simon Range [12], Darren Tature [12], Helen L Barr [13], Sophie Dawson [13], Jane Dewar [13], Bryony Miller [13], Gauri Saini [13], Penny Galey [14], Jack Johnson [14], Mark C Pasteur [14], David Derry [15], Harriet Gledhill [15], Angharad Lawson [15], Michelle Thomas [15], David Waine [15], Josie Cunningham [16], Annant Damani [16], Alexandra Higton [16], Christopher Orchard [16], Charlotte Carolan [3], Misbah Tahir [3], Amanda Plummer[3], Marlene Hutchings[3], Frank P Edenborough [3], Rachael Curley [3], Martin J Wildman [3,2] *

AUTHORS' AFFILIATIONS

[1] Wessex Adult Cystic Fibrosis Service, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[2] School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

[3] Sheffield Adult Cystic Fibrosis Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[4] Centre for Health Informatics, University of Manchester, Manchester, UK

[5] Newcastle Adult Cystic Fibrosis Centre, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

[6] Bristol Adult Cystic Fibrosis Centre, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

[7] North West Midlands Cystic Fibrosis Centre, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

[8] York Hull Adult Cystic Fibrosis Centre, Hull University Teaching Hospitals NHS Trust, Hull, UK

[9] York Hull Adult Cystic Fibrosis Centre, York Teaching Hospital NHS Foundation Trust, York, UK

[10] Oxford Adult Cystic Fibrosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[11] Respiratory Biomedical Research Centre, University of Southampton, Southampton, UK

[12] Leicester Adult Cystic Fibrosis Centre, University Hospitals of Leicester NHS Trust, Leicester, UK

[13] Wolfson Adult Cystic Fibrosis Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK

[14] Adult Cystic Fibrosis Clinic, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK.

[15] Derriford Hospital Adult Cystic Fibrosis Centre, University Hospitals Plymouth NHS Trust, Plymouth, UK

[16] Cystic Fibrosis Unit, Frimley Health NHS Foundation Trust, Frimley, UK

* Corresponding author: martin.wildman3@nhs.net

Sheffield Adult Cystic Fibrosis Centre, Brearley Outpatient, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK.

HIGHLIGHTS

- Historic cohorts suggested that supply of inhaled medicines may exceed actual use
- This is the first study to directly compare medicine supply (MPR) against adherence
- Among 275 adults in 12 CF centres, MPR over-estimates adherence by a median of 14%
- Even with 20% contingency, mean annual cost of excess supply was £1,124/patient
- Excess supply cost was higher in those with adherence <50% (mean £2,017/patient)

ABSTRACT

Background

Studies in separate cohorts suggest possible discrepancies between inhaled medicines supplied (median 50-60%) and medicines used (median 30-40%). We performed the first study that directly compares CF medicine supply against use to identify the cost of excess medicines supply.

Methods

This cross-sectional study included participants from 12 UK adult centres with ≥1 year of continuous adherence data from data-logging nebulisers. Medicine supply was measured as medication possession ratio (MPR) for a 1-year period from the first suitable supply date. Medicine use was measured as electronic data capture (EDC) adherence over the same period. The cost of excess medicines was calculated as whole excess box(es) supplied after accounting for the discrepancy between EDC adherence and MPR with 20% contingency.

Results

Among 275 participants, 133 (48.4%) were females and mean age was 30 years (95% CI 29-31 years). Median EDC adherence was 57% (IQR 23-86%), median MPR was 74% (IQR 46-96%) and the discrepancy between measures was median 14% (IQR 2-29%). Even with 20% contingency, mean potential cost of excess medicines was £1,124 (95% CI £855-1,394), ranging from £183 (95% CI £29-338) for EDC adherence ≥80% to £2,017 (95% CI £1,507-2,526) for EDC adherence <50%.

Conclusions

This study provides a conservative estimate of excess inhaled medicines supply cost among adults with CF in the UK. The excess supply cost was highest among those with lowest EDC adherence, highlighting the importance of adherence support and supplying medicine according to actual use. MPR provides information about medicine supply but over-estimates actual medicine use.

1. INTRODUCTION

Inhaled medicines (antibiotics and mucolytics) reduce the risk of exacerbations and slow lung function decline in cystic fibrosis [1, 2]. However, real-world low adherence results in preventable morbidity and mortality [3-7].

Another consequence of low adherence is the accumulation of unused medicines, which potentially results in waste since medicines have limited shelf-lives. Among adults with CF, studies in separate cohorts (either measuring medication supply or actual use) suggest a substantial discrepancy between the amount of medicines supplied (median MPR 50-60% [6, 7]) and actually used (median adherence 30-40% [3-5]). Within the National Health Service (NHS) in the United Kingdom (UK), wasted medicines cost ~£300m/year, of which ~50% is preventable [8].

The Commissioning for Quality and Innovation (CQUIN) framework supports quality improvement to improve patient care and NHS efficiency. The CF Self-Care CQUIN [9] sought to embed electronic data capture (EDC) adherence within routine practice to support self-care and medicines optimisation. Currently, >50% of UK adult CF centres are part of the CFHealthHub Learning Health System (LHS; ISRCTN14464661) creating a community of practice that collaborates to optimise care. Real-time EDC data is automatically collected from data-logging nebulisers onto a cloud-based digital platform which displays adherence data, allowing benchmarking and collaborative improvement. Most of the LHS centres participated in ACtiF, a 19-centre 608-participant randomised controlled trial which demonstrated significantly higher adherence and reduced burden sustained to 80 weeks with the CFHealthHub-based intervention [10]. The CF Self-Care CQUIN had two over-arching aims. First, to use a digitally supported multi-faceted behaviour change intervention at scale to create habits of successful self-care that can reduce treatment burden [10]. Second, to support medicines optimisation by utilising EDC data to reduce excess medicine supply.

Managing medicine supply contributes to the burden of CF self-care [11, 12]. Thus using real-time data about actual medicine use via CFHealthHub to align medicine supply with medicine use may potentially reduce burden [13] and minimise excess medicine supply. Without real-time data regarding actual medicine use, the available medicine stock cannot be easily predicted by either clinicians or patients who struggle to accurately recall adherence [3].

No studies have directly compared real-world supply and EDC data for inhaled therapies. Quantifying the cost of excess medicines supply can inform whether it is economically viable to invest in a system that incorporates EDC data in the medicine supply chain. This study aims to compare medicines supplied against those used, and identify the cost of excess supply due to supply/use mismatch. A secondary aim is to explore the clinical characteristics and treatment factors which influence excess supply, since identifying the subset of people with particularly excessive supply is useful for targeting interventions.

2. METHODS

This cross-sectional study utilised data from 12 adult CF centres in England, UK (three first wave CFHealthHub LHS centres and nine ACtiF trial sites that are second wave centres). London-Brent Research Ethics Committee (17/LO/0032) provided regulatory approval. CFHealthHub LHS participants took ≥1 long-term inhaled therapy via a data-logging nebuliser, eTrack® (PARI Pharma GmbH) or I-neb® (Philips Healthcare). Screening in October 2019 identified 329 adults with CF recruited prior to October 2018 as potential participants. All included participants had ≥12 months of continuous EDC data collected between September 2017 and August 2020, since some participants only achieved 12 months of consecutive data-logging nebuliser use by August 2020. Participants were excluded if they had incomplete data capture over 12 months; for example if they had known periods of using nebulised therapy via devices without data-logging capability, stopped nebulised therapies or withdrew from CFHealthHub LHS.

Clinical data corresponding to the start of adherence data capture (age, gender, *Pseudomonas aeruginosa* status as defined by clinicians [14] and $\%FEV_1$ calculated using GLI equation) were extracted from clinical records by local investigators from each site. Prescription data were recorded in CFHealthHub. Records of medicines supply from primary care, hospital in- and out-patient pharmacies and home deliveries via homecare pharmacies were retrieved by a pharmacist at each centre. Included medicines are listed in Table S1.

Medicine supply was measured as medication possession ratio (MPR). MPR assesses whether medicines were available for use rather than whether medicines were taken appropriately. Proportion of days covered (PDC) is another refill record-based measure but PDC measures the proportion of days with supply instead of the actual amount of medicines supplied [15]. MPR was calculated by a central pharmacist and pharmacists at each centre as the percentage of the number of days of medicine supplied over a 1-year period since there were a variety of medicine supply sources with varying supply intervals. In keeping with convention, MPR calculation was started on the first supply date [16, 17] to reduce the impact of medicines supplies already in the home. Start dates corresponded to the availability of EDC data. Supply data were truncated if medicines provided during the data collection period exceeded 365 days. If medicines were prescribed for shorter time periods (e.g. month-on month-off prescriptions or medications started/stopped during the interval), the denominator was reduced to match the prescribed time course. Each box of antibiotic used in alternating regimens (e.g. tobramycin, aztreonam lysine and levofloxacin) has a supply for only 28 days, hence participants may be provided with >6 boxes even if they were meant to be using the antibiotic for six months in a year. Supplies of the same medicine from different sources were aggregated. CFHealthHub participants routinely continue to use their data-logging nebuliser during in-patient stays. Supplies provided and/or administered during an in-patient stay were taken into account according to individual centre policies, for example some centres routinely with-hold inhaled antibiotics during intravenous courses thereby reducing the number of days for the MPR calculation

which accounts for intentional supply gaps. Any discharge supplies from the hospital were also incorporated into the MPR calculations. MPR data may be skewed – analyses were repeated with skewed data in Appendix A.

Dose-weighted composite MPR (dwcMPR) was calculated for participants on multiple medicines with the following four steps: (1) Calculate total doses of medicine supplied by adding up of all individual values of MPR × days × daily dose (2) Calculate each medicine's weighting by calculating the proportion of the dose for each medicine out of sum of total doses (which will be obtained from 'Step 1') (3) Multiply each individual MPR by the relevant weight from 'Step 2' (4) Sum up all the values from 'Step 3' and multiple by 100% to obtain a percentage. All MPR calculations are labelled as "dwcMPR" moving forward.

Actual medicines use was measured using EDC as unadjusted adherence, which was calculated daily as the percentage of nebuliser dose taken against the prescribed dose agreed and discussed between adults with CF and clinicians during clinical encounters (reflecting concordance between clinicians and the adult), then averaged over the same 1-year period used for MPR calculation. CFHealthHub automatically captures EDC data and calculates unadjusted adherence, which was extracted by a pharmacist at each centre. Measures of medicines supply and use were not capped and may exceed 100% of prescription, for example if medicines were stopped but supplies continue.

Data were analysed using SPSS v25 (IBM Corp) and R v3.5.0 (www.r-project.org). Descriptive statistics were generated to summarise the clinical and adherence data. The difference between dwcMPR and unadjusted EDC adherence was described, and summarised using Bland-Altman plots. The cost of excess supply was determined by first calculating excess number of medicine boxes supplied based on the gap between dwcMPR with 20% contingency and EDC adherence, rounding down excess boxes to the nearest whole number, then multiplying with medicine prices according to the supply source (Table S1). Excess supply was counted as "0" if no excess medicine box was supplied or if EDC adherence exceeded MPR. A comparison of participants with and without excess supply cost is presented in Appendix B. Value added tax for hospital supplies and delivery charges for homecare were not included to ensure calculated excess supply cost was conservative and transferable across centres. A 20% contingency for dwcMPR was used since adults with CF may keep some buffer stock in case of delay in medicines delivery.

Excess supply cost was summarised according to clinical characteristics (source of recruitment, age, gender, *Pseudomonas aeruginosa* status, $\%FEV_1$) and treatment factors (EDC adherence, number of inhaled medicines, type of inhaled medicines, supply source). The age [6, 18], $\%FEV_1$ [19] and adherence categories [6, 18] were based on previous studies. Simple linear regressions were performed with excess supply cost as the dependent continuous variable, and clinical characteristics and treatment factors as covariates. A parsimonious multiple regression model was then built using covariates associated with excess supply cost in univariate analyses. Over-fitted model is a risk,

hence tree-based analysis [20] was performed to test if the covariates were true independent predictors of excess supply cost. P-values <0.05 were considered statistically significant.

A sensitivity analysis looking at best case (lowest cost) and worst case (highest cost) scenarios for the excess supply are presented in Appendix C. The sample size is pragmatic and all available clinical data were included. All analyses were on the basis of complete case since the only missing data was for %FEV_1 from a single participant who was unable to perform spirometry.

3. RESULTS

Among 328 adults screened as potentially eligible, 275 were included. Exclusion reasons included skewed dwcMPR data (*N*=9), EDC adherence data <1 year (*N*=19), withdrawn from CFHealthHub (*N*=16), death (*N*=2), medicine supply data from primary care unavailable (*N*=5) and siblings sharing medicine supplies (*N*=2). Among those excluded but adherence data were available in CFHealthHub albeit <1 year in duration (*N*=19), median EDC adherence was 30% (IQR 4-58%).

Among included participants, 133 (48.4%) were females, 161 (58.5%) had chronic *Pseudomonas aeruginosa* infection, mean age was 30 years (95% CI 29-31 years) and mean FEV_1 was 62% (95% CI 59-64%), a comparison with UK registry data is also provided in Table 1 [19, 21]. Most participants were prescribed ≥2 inhaled medicines (*N*=221, 80.4%) and inhaled antibiotic(s) (*N*=199, 72.4%). More detailed descriptions of the treatment regimens are in Table S2.

EDC adherence and dwcMPR were discrepant, with both limits of agreement exceeding 33% from zero (Figure 1). EDC adherence (median 57%, IQR 23-86%) was generally lower than dwcMPR (median 74%, IQR 46-96%), though EDC adherence exceeded dwcMPR among 53 (19.3%) participants. The discrepancies between both measures were median 14% (IQR 2-29%) and mean 17% (95% CI 14-20%). The magnitude of discrepancy was larger among those with lower EDC adherence, see Table 2.

A 20% contingency for dwcMPR reduced the discrepancy but there was still a substantial excess supply cost of £309,132 among the 275 adults, i.e. mean of £1,124 (95% CI £855-1,394). The sensitivity analysis in Appendix C found a minimum and maximum excess supply cost of £695 (95% CI £484-906) and £1,490 (95% CI £1,174-1,807) respectively. Univariate and multivariate analyses showed that excess supply cost was higher among those with EDC adherence <50%, aged 19-25 years and on inhaled antibiotics rather than mucolytics only (Table 3). These findings are confirmed by the tree-based analysis in Figure 2. EDC adherence was also a significant predictor when comparing those with vs without excess supply cost (Appendix B). Appendix A presents results including skewed dwcMPR data.

4. DISCUSSION

This is the first multi-centre study comparing supplied medicine (dwcMPR) against actual use (EDC adherence) in any respiratory condition. The median and mean differences between both measures were 14% and 17% respectively. MPR (measuring medicine supply) typically over-estimates EDC adherence (actual medicine use), indicating substantial amount of unused inhaled medicines among adults with CF. This over-estimation is most obvious among those with low EDC adherence. A conservative estimate of the cost of excess medicines supply among adults with CF was substantial at £1,124/person/year. This was highest among those with EDC adherence <50% at £2,017/person/year and lowest among those with EDC adherence ≥80% at £183/person/year. This cost is pertinent because healthcare systems have scarce resources and money spent on excess medicines supply may be better spent on other services.

Although the cost of excess medicines supply will depend on costs of medicines and types of pharmacy fill system which may vary from country to country (for example, refill in the US is instigated by patients instead of medicines supply being delivered automatically), it is possible that an excess medicines supply cost exists in other healthcare systems. Low adherence to CF inhaled therapies has been reported globally [22, 23] and MPR levels in other healthcare systems also tended to be higher than EDC adherence [24]. A study in the US estimated medicines waste based on self-report and found that 2/3 of dispensed medicines were unused with projected resultant waste of $2.4-5.4B [25]. However, self-report is unreliable [3, 26] and could under-estimate the extent of this problem. As such, our findings may have cost implications beyond the UK.

Potential waste from excess medicines supply can be reduced by improving adherence levels among adults with CF. In this study, adults with EDC adherence ≥80% have the lowest excess supply cost. Participants in the intervention arm of ACtiF trial achieved significantly increased EDC adherence (median 79% vs 47%) and also have lower excess supply cost (mean £789 vs £1,475) compared to those who were not part of the ACtiF trial. Accurate date- and time-stamped EDC data from CFHealthHub can support adherence by helping to identify potential cues or opportune moments for taking treatments [10]. When MPR is being collected in an attempt to support adherence, it is limited by an inability to capture the granularity of actual medicine use and also may not be able to identify those with the lowest EDC adherence levels. In terms of sustaining long-term adherence, there is evidence that habit is more strongly associated with adherence compared to reflective motivation [27] and habit-forming interventions are more effective at improving adherence compared to interventions without habit-formation.[28] Habit-formation to sustain adherence is an emerging topic in CF [29] and may be part of the solution to tackle excess medicines supply.

Stock of surplus medicines can also be reduced by aligning medicine supply with actual medicine use. For example, a person using 40% of once daily dornase alfa will only require a box to be delivered every other month instead of every month. However, adherence may be variable and

under-delivery of medicine supplies will cause inconvenience as well as impacting on adherence. Developing a just-in-time supply system, where medicines are delivered at variable intervals as guided by EDC data, has the potential to minimise excess medicines supply, reduce patient burden associated with ordering medicines and help avoid adherence being limited by inadequate medicine supplies. This works on the basis that medicines will be delivered only when existing supply is running low, i.e. medicines delivery is context-specific, targeted and personalised according to use. A just-in-time supply system would require accurate real-time measurement of the rate of actual medicine use with EDC data. Measuring MPR alone would be inadequate for a just-in-time supply system. Simply increasing medicines supply, for example with home delivery of medicines at fixed intervals [30] may increase stock of surplus medicines without increasing effective medicine use.

A limitation of this study is that excess medicines supply may be stored for future use instead of being wasted. However, excess supply is unlikely to occur only during the study – excess supply may well recur year-on-year and excess medicines past their expiry dates will be wasted. It is possible that some medicines may have been nebulised through an alternative device, though this is uncommon because most participants only have one nebuliser. Data-logging nebulisers are unable to determine which medicines were used among participants on ≥2 different medicines, hence excess supply cost was calculated from dwcMPR with the assumption that all medicine types were equally used. The lowest estimated excess supply cost, calculated by assuming supplies of more expensive medicines were used first, was ~£700/person/year (Appendix C). This conservative estimate (see next paragraph) still compares favourably with the system cost of ~£770/person/year in 150-patient centres (£1280/nebuliser which can last ~5 years, £140/nebuliser/year data transfer fees [9], £56,000/year interventionist cost) since such a system can potentially reduce burden of care and support self-care [10]. Among participants on single medicine regimens, whereby there is certainty regarding which medicine was being used, there was still mean excess supply cost of ~£600/person/year (Table 2).

Not many participants were on CFTR modulators and the intensity of nebuliser therapy may change as modulators become part of standard care. However, understanding how much of the agreed inhaled therapy is actually used will still remain helpful in optimising medicine supply. Another limitation is the generalisability of the study sample to the UK CF population. Since the excess supply cost was calculated across a 1-year period to ensure internally valid results, this sampling strategy of excluding adults with <1 year of continuous EDC data risks excluding the least engaged participants. Indeed, adults excluded due to shorter adherence data duration have lower EDC adherence (median 30%) compared to the study sample (median 57%). As a consequence, the study included a convenience sample with higher levels of adherence than would be expected across a total centre population and real-world studies suggested a median EDC adherence of only 30-40% [3-5]. In addition, the method of estimating excess supply cost in the study erred towards a

conservative estimate because it only included the cost of excess box(es) after taking into account 20% contingency.

5. CONCLUSIONS

This multi-centre observational study suggests that a conservative estimate of excess inhaled medicines supply cost among adults with CF in the UK is around £1,124/person/year. Excess supply cost can vary substantially from person to person and differed according to EDC adherence. The estimates are conservative and sensitivity analyses suggest they are robust. In addition, the study highlights the inaccuracy of inferring actual medicine use from MPR and the potential for cost-savings by using EDC data to match medicine supply according to medicine use. This further emphasises the importance of routinely available real-time EDC data in the management of people with CF. It will be important to evaluate if implementing a just-in-time medicine delivery system can reduce the identified excess supply cost.

COMPETING INTERESTS

The University of Manchester software team (P Whelan, S Antrobus, J Ainsworth, I Buchan) received funding from PARI Pharma GmbH to create a medication reporting component within the CFHealthHub software. This has not had any direct influence on the findings reported here. P Whelan also reports consultancy fees from Affigo CIC (a digital mental health company) in which she is a director and other fees from Prism Life Ltd (a small research and consultancy company) in which she is the sole owner-director. There is no other competing interests to disclose.

FUNDING

This report presents independent research funded by the NHS England Commissioning for Quality and Innovation. The funder has no role in study design, analysis, interpretation or decision to publish.

CONTRIBUTORS

AB: methodology, investigation, project administration, data curation, formal analysis, original draft. ZHH: methodology, formal analysis, validation, review & editing. NT: formal analysis. CG & IRD: project administration. PW, SA, JA, IB: resources. AA, SB, SD, CE, JT, NJB, KB, CJ, PM, GF, MM, AM, SM, HS, NB, TD, KL, NR, DS, DS, RT, JF, WGF SP, LW, MIA, MC, TVD, HD, JAN, ES, OC, JG, SR, DT, HLB, SD, JD, BM, GS, PG, JJ, MCP, DD, HG, AL, MT, DW, JC, AD, AH, CO, CC, MT, AP, FPE & RC: investigation. MJW: funding acquisition, conceptualisation, methodology, resources, review & editing. All authors contributed to and approved of the final submitted manuscript.

REGULATORY APPROVAL

Regulatory approval for this study was obtained from London-Brent NHS Research Ethics Committee (reference number: 17/LO/0032).

ACKNOWLEDGEMENT

We are grateful to David Crowther for developing the framework for this programme.

REFERENCES

1. Smith S, Rowbotham NJ, Regan KH. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. Cochrane Database Syst Rev 2018;3:CD001021.

2. Yang C, Montgomery M. Dornase alfa for cystic fibrosis. Cochrane Database Syst Rev 2018;9:CD001127.

3. Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. Chest 2011;140:425–32.

4. Hoo ZH, Totton N, Waterhouse S, et al. Real-world adherence among adults with cystic fibrosis is low – a retrospective analysis of the CFHealthHub digital learning health system. Chest Published Online First: 26 June 2021. doi: 10.1016/j.chest.2021.06.039.

5. Hoo ZH, Curley R, Walters SJ, Campbell MJ, Wildman MJ. 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. J Cyst Fibros 2020;19:162–7.

6. Quittner AL, Zhang J, Marynchenko M, et al. Pulmonary medication adherence and health-care use in cystic fibrosis. Chest 2014;146:142–51.

7. White H, Shaw N, Denman S, Pollard K, Wynne S, Peckham DG. Variation in lung function as a marker of adherence to oral and inhaled medication in cystic fibrosis. *Eur Respir J* 2017; 49: 1600987.

8. Trueman P, Lowson K, Blighe A, et al. Evaluation of the scale, causes and costs of waste medicines. Published November 2010. https://discovery.ucl.ac.uk/id/eprint/1350234/1/Evaluation_of_NHS_Medicines_Waste__web_publication_version.pdf. Date last accessed: December 18 2020.

9. NHS England. PSS3 cystic fibrosis supporting self-care PSS CQUIN indicator. Published March 2019. https://www.england.nhs.uk/publication/pss3-cystic-fibrosis-self-care-pss-cquin-indicator/. Date last accessed: December 18 2020.

10. Wildman MJ, O'Cathain A, Maguire C, et al. Self-management intervention to reduce pulmonary exacerbations by supporting treatment adherence in adults with cystic fibrosis: a randomised controlled trial. Thorax Accepted: 20 August 2021. doi: 10.1136/thoraxjnl-2021-217594.

11. Hollin IL, Donaldson SH, Roman C, et al. Beyond the expected: Identifying broad research priorities of researchers and the cystic fibrosis community. J Cyst Fibros 2019;18:375–7.

12. Rowbotham NJ, Smith S, Leighton PA, et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. Thorax 2018;73:388–90.

13. Davies G, Rowbotham NJ, Smith S, et al. Characterising burden of treatment in cystic fibrosis to identify priority areas for clinical trials. J Cyst Fibros 2020;19:499–502.

14. Hoo ZH, Edenborough FP, Curley R, et al. Understanding Pseudomonas status among adults with cystic fibrosis: a real-world comparison of the Leeds criteria against clinicians' decision. Eur J Clin Microbiol Infect Dis 2018;37:735–43.

15. Zhu VJ, Tu W, Rosenman MB, Overhage JM. A comparison of data driven-based measures of adherence to oral hypoglycemic agents in Medicaid patients. AMIA Annu Symp Proc 2014;2014:1294–301.

16. Kozma CM, Dickson M, Phillips AL, Meletiche DM. Medication possession ratio: implications of using fixed and variable observation periods in assessing adherence with disease-modifying drugs in patients with multiple sclerosis. Patient Prefer Adherence 2013;7:509–16.

17. Sperber CM, Samarasinghe SR, Lomax GP. An upper and lower bound of the medication possession ratio. Patient Prefer Adherence 2017,11:1469–78.

18. Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA. Longitudinal association between medication adherence and lung health in people with cystic fibrosis. J Cyst Fibros 2011;10: 258–64.

19. Hoo ZH, Wildman MJ, Curley R, Walters SJ, Campbell MJ. Rescue therapy within the UK cystic fibrosis registry: an exploration of predictors of intravenous antibiotic use amongst adults with CF. Respirology 2018;23:190–7.

20. Zhang H, Bracken MB. Tree-based, two-stage risk factor analysis for spontaneous abortion. Am J Epidemiol 1996;144:989–96.

21. UK Cystic Fibrosis Registry. Annual data report 2019. Published August 2020. https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources. Date last accessed: December 18 2020.

22. Burrows JA, Bunting JP, Masel PJ, Bell SC. Nebulised dornase alpha: adherence in adults with cystic fibrosis. J Cyst Fibros 2002;1:255–9.

23. Solé A, Gartner S, Alvarez A, et al. Adherence to the inhaled antibiotic treatment in patients with cystic fibrosis. Am J Respir Crit Care Med 2013;187(C49):A4358.

24. Siracusa CM, Ryan J, Burns L, et al. Electronic monitoring reveals highly variable adherence patterns in patients prescribed ivacaftor. J Cyst Fibros 2015;14: 621–6.

25. Law AV, Sakharkar P, Zargarzadeh A, et al. Taking stock of medication wastage: unused medications in US households. Res Social Adm Pharm 2015;11:571–8.

26. Quittner AL, Modi AC, Lemanek KL, Ievers-Landis CE, Rapoff MA. Evidence-based assessment of adherence to medical treatments in pediatric psychology. J Pediatr Psychol 2008;33:916–36.

27. Durand H, Hayes P, Harhen B, et al. Medication adherence for resistant hypertension: Assessing theoretical predictors of adherence using direct and indirect adherence measures. Br J Health Psychol 2018;23:949–66.

28. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. Prev Med 2017;99:269–76.

29. Hoo ZH, Gardner B, Arden MA, et al. Role of habit in treatment adherence among adults with cystic fibrosis. Thorax 2019;74:197–9.

30. Dooney MK, Martin KJ, Iqbal N, Jones AM, Barry PJ. Home delivery influences medicines possession ratio in adult cystic fibrosis. Thorax 2018;73(Suppl 4):A162–3.

Table 1: Baseline characteristics of the participants

Characteristics	Study participants (*N*=275)	UK CF registry data for adults[F] (*N*=6104)
Source of recruitment		
Learning health system, *N* (%)	89 (32.4)	
Usual care arm of the ACtiF trial[A], *N* (%)	83 (30.2)	
Intervention arm of the ACtiF trial[A], *N* (%)	103 (37.5)	
Age in years[B], mean (95% CI)	30 (29 to 31)	32
≤18 years, *N* (%)	14 (5.1)	
19 to 25 years, *N* (%)	97 (35.3)	
26 to 34 years, *N* (%)	96 (34.9)	
≥35 years, *N* (%)	68 (24.7)	
Gender		
Male, *N* (%)	142 (51.6)	3,294 (54.0)
Female, *N* (%)	133 (48.4)	2,810 (46.0)
Pseudomonas aeruginosa status		
Not chronic, *N* (%)	114 (41.5)	3,478 (59.6)
Chronic infection, *N* (%)	161 (58.5)	2,358 (40.4)
%FEV_1[C], mean (95% CI)	62 (59 to 64)	69
<40%, *N* (%)	57 (20.8)	
40 to 69.9%, *N*(%)	109 (39.8)	
≥70%, *N* (%)	108 (39.4)	
Source of inhaled medicine supply		
Hospital, *N* (%)	52 (18.9)	
Homecare only, *N* (%)	92 (33.5)	
≥2 supply sources, *N* (%)	131 (47.6)	
Number of inhaled medicines[D]		
1 medicine only, *N* (%)	54 (19.6)	
2 different medicines, *N* (%)	101 (36.7)	
3 different medicines, *N* (%)	80 (29.1)	
4 different medicines, *N* (%)	28 (10.2)	
5 different medicines, *N* (%)	12 (4.4)	
6 different medicines, *N* (%)	0	
Prescription of inhaled antibiotics[D]		
Only on mucolytic, *N* (%)	76 (27.6)	
1 inhaled antibiotic, *N* (%)	123 (44.7)	
2 inhaled antibiotics, *N* (%)	68 (24.7)	
3 inhaled antibiotics, *N* (%)	7 (2.5)	
4 inhaled antibiotics, *N* (%)	1 (0.4)	
Prescribed inhaled aztreonam and/or levofloxacin, *N* (%)	50 (18.2)	
Unadjusted % EDC adherence[E], median (IQR)	57 (23 to 86)	
<50%, *N* (%)	128 (46.5)	
50 to <80%, *N*(%)	50 (18.2)	
≥80%, *N* (%)	97 (35.3)	
% MPR, median (IQR)	74 (46 to 96)	

[A] ACtiF trial is a two-arm, open-label, parallel-group usual care-controlled randomised trial at 19 UK CF centres (ISRCTN55504164) which evaluated a CFHealthHub-based adherence intervention among 608 adults with CF [10].

[B] The age categories were based on previous CF studies which demonstrated the strong association between age and adherence [6, 18].

[C] One participant was unable to perform spirometry, hence the missing FEV_1 data. The %FEV_1 categories were used internationally and have been shown to be applicable to other UK datasets [19]. Other than FEV_1, there is no other missing data.

[D] Not all the different medicines were used concurrently. Some participants were on alternating antibiotics regimen.

[E] The adherence categories were based on previous CF studies [6, 18].

[F] These results are summarised from Section 1.2 and Appendix B of the UK CF registry annual data report 2019 [21]. "Chronic *Pseudomonas aeruginosa*" is defined in the UK CF registry as ≥3 positive samples in the previous year, Data for gender were available from 6,104 adults but only 5,836 adults had annual review at adult centres (thus providing data for age & Pseudomonas status) and 5,463 adults provided data for best FEV_1. That means 268 (4%) of the adults had annual review at paediatric centres prior to transition and their data were not possible to identify from the summary statistics in the UK CF registry annual data report.

Table 2: dwcMPR versus EDC adherence discrepancy; and excess supply cost[†,‡]

	Results
Discrepancy between dwcMPR and EDC adherence	
Median (IQR)	14% (2 to 29%)
Mean (95% CI)	17% (14 to 20%)
Discrepancy between dwcMPR and EDC adherence in different adherence levels	
EDC adherence <50%, Median (IQR)	22% (12 to 39%)
EDC adherence 50 to <80%, Median (IQR)	12% (1 to 28%)
EDC adherence ≥80%, Median (IQR)	4% (–7 to 17%)
Discrepancy between dwcMPR with 20% contingency and EDC adherence	
Median (IQR)	3% (–11 to 21%)
Mean (95% CI)	6% (2 to 9%)
Excess supply cost in £ for the overall cohort	
Median (IQR)	0 (0 to 1,414)
Mean (95% CI)	1,124 (855 to 1,394)
Excess supply cost in £ according to the source of recruitment, mean (95% CI)	
Learning health system	1,475 (801 to 2,148)
Usual care arm of the ACtiF trial	1,164 (796 to 1,532)
Intervention arm of the ACtiF trial	789 (479 to 1,099)
Excess supply cost in £ according to age categories, mean (95% CI)	
≤18 years	1,026 (234 to 1,817)
19 to 25 years	1,907 (1,328 to 2,486)
26 to 34 years	673 (408 to 939)
≥35 years	664 (120 to 1,207)
Excess supply cost in £ according to gender, mean (95% CI)	
Male	1,149 (713 to 1,584)
Female	1,098 (785 to 1,411)
Excess supply cost in £ according to *P. aeruginosa* status, mean (95% CI)	
Not chronic	1,006 (652 to 1,361)
Chronic infection	1,208 (819 to 1,596)
Excess supply cost in £ according to %FEV_1 categories, mean (95% CI)	
<40%	1,063 (457 to 1,669)
40 to 69.9%	1,394 (954 to 1,834)
≥70%	864 (443 to 1,284)
Excess supply cost in £ according to source of inhaled medicine supply, mean (95% CI	
Hospital	1,301 (716 to 1,887)
Homecare only	1,344 (805 to 1,884)
≥2 supply sources	899 (541 to 1,257)
Excess supply cost in £ according to number of inhaled medicines, mean (95% CI)	
1 medicine only	595 (319 to 870)
≥2 different medicines	1,254 (926 to 1,581)
Excess supply cost in £ according to prescription of inhaled antibiotics, mean (95% CI)	
Only on inhaled mucolytic	553 (329 to 776)
≥1 inhaled antibiotic	1,342 (983 to 1,701)
Excess supply cost in £ according to use of expensive antibiotics, mean (95% CI)	
Neither inhaled aztreonam nor levofloxacin	1,041 (768 to 1,314)
On inhaled aztreonam and/or levofloxacin	1,499 (651 to 2,347)
Excess supply cost in £ according to unadjusted EDC adherence, mean (95% CI)	
<50%	2,017 (1,507 to 2,526)
50 to <80%	665 (304 to 1,205)
≥80%	183 (29 to 338)

[†] **Estimates of excess supply cost are highly conservative because of contingency**, see 'Discussion' paragraph 6. Excess supply cost was calculated as the cost of excess medicine box(es) delivered or collected after accounting for the discrepancy between EDC adherence and dwcMPR with 20% contingency. For example, if a person has an excess supply of 83 aztreonam nebules, the excess supply cost was calculated as "0" because each box of aztreonam has 84 nebules.

[‡] Results exclude nine participants with skewed dwcMPR data. Results for all participants with ≥1 year of EDC data are available in Appendix A.

Table 3: Summary of the excess supply cost results from linear regression models[†]

Variable	Excess supply cost in £			
	Unadjusted regression coefficient (95% CI)	P-value	Adjusted regression coefficient[‡] (95% CI)	P-value
Unadjusted EDC adherence[A]	–928 (–1,208 to –648)	<0.001	–831 (–1,110 to –552)	<0.001
Age <19 years or >25 years[B] (reference)				
Age 19 to 25 years	1,210 (663 to 1,756)	<0.001	869 (345 to 1,393)	0.001
Only on inhaled mucolytic (reference)				
≥1 inhaled antibiotic	789 (193 to 1,386)	0.010	876 (332 to 1,420)	0.002
1 medicine only (reference)				
≥2 different medicines	659 (–16 to 1,334)	0.056		
Source of recruitment				
Learning health system (reference)				
Usual care arm of the ACtiF trial	–310 (–1,088 to 467)	0.432		
Intervention arm of the ACtiF trial	–686 (–1,390 to 18)	0.056		
Male (reference)				
Female	–50 (–591 to 490)	0.854		
Not chronic *P. aeruginosa* (reference)				
Chronic *P. aeruginosa* infection	201 (–346 to 749)	0.470		
$\%FEV_1$ <40% or ≥70%[C] (reference)				
$\%FEV_1$ 40 to 69.9%	447 (–102 to 997)	0.110		
≥2 medicine supply sources[D] (reference)				
Supply from hospital only or homecare only	430 (–108 to 968)	0.117		
Neither aztreonam nor levofloxacin (reference)				
On inhaled aztreonam and/or levofloxacin[E]	458 (–239 to 1,156)	0.197		

[†] Results exclude nine participants with skewed dwcMPR data. Results for all participants with ≥1 year of EDC data are available in Appendix A.

[‡] Adjusted R^2 of the multiple regression model = 0.186. The three covariates included in the multiple regression analysis were unadjusted EDC adherence category, age category and prescription of inhaled antibiotic because these covariates reached statistical significance in the univariate analysis.

[A] EDC adherence category was analysed as an ordinal variable because Table 2 showed a step-wise reduction in excess supply cost with increasing level of adherence category. For the univariate analysis, an increase in one level of adherence category (e.g. from <50% to 50–79%) was associated with a decrease of £937 (95% CI £662–1,211) in excess supply cost. For the multivariate analysis, an increase in one level of adherence category was associated with a decrease of £836 (95% CI £561–1,110) in excess supply cost, all else being equal.

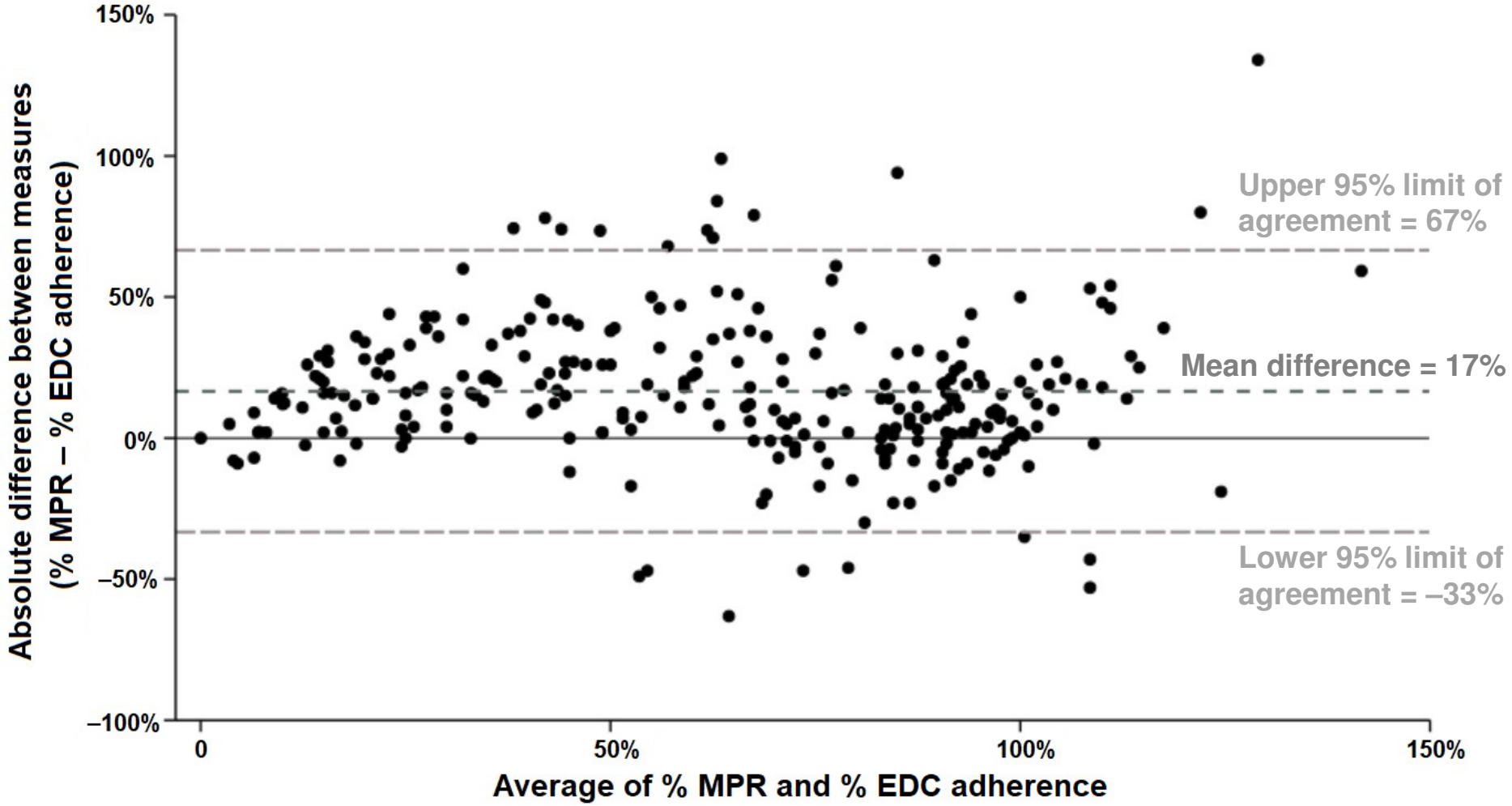
[B] Age was dichotomised because Table 2 showed similar amount of excess supply cost for the following categories: ≤18 years, 26–34 years and ≥35 years.

[C] $\%FEV_1$ was dichotomised because Table 2 showed similar amount of excess supply cost for the following categories: <40% and ≥70%.

[D] The source of inhaled medicine supply was dichotomised because Table 2 showed similar amount of excess supply cost for those who received all supply from hospital only and all supply via homecare only.

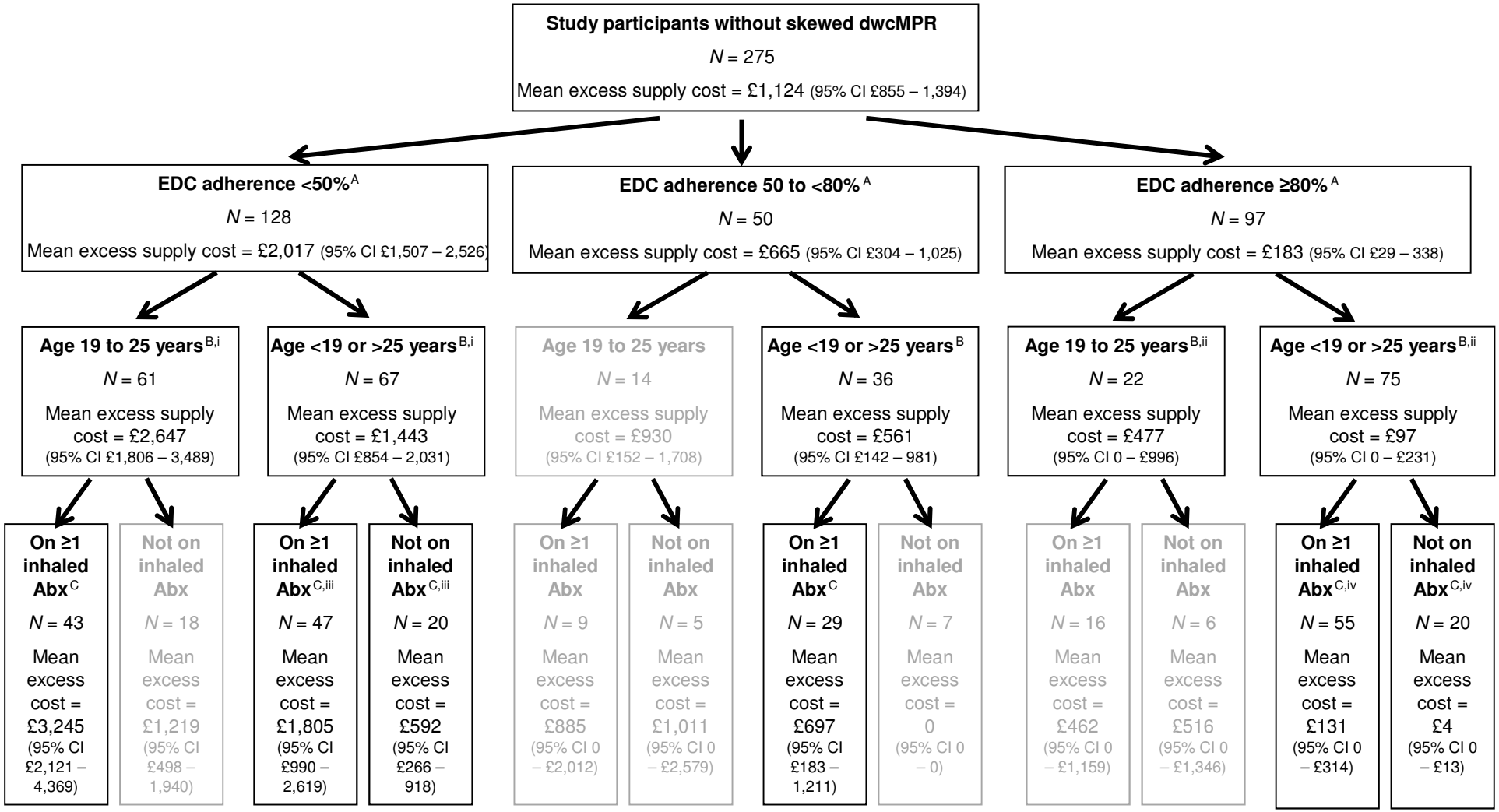
[E] In an exploratory multiple regression analysis accounting for EDC adherence level and age 19–25 years, prescription of expensive inhaled antibiotic was associated with an increase in excess supply cost of £896 (95% CI £253–1,539), p-value 0.006. Prescription of expensive inhaled antibiotic did not reach statistical significance in the univariate analysis because those prescribed expensive antibiotics have much higher EDC adherence level compared to those who were not (median 77%, IQR 48–93% vs median 50%, IQR 19–84%, Mann-Whitney p-value 0.001).

Figure 1: Bland-Altman plot for dwcMPR versus EDC adherence, excluding excessively skewed dwcMPR data ($N = 275$)[†]



[†]Nine participants with skewed dwcMPR data (three with excessive supply of bronchodilator, three with excessive supply of hypertonic saline, two with excessive supply of antibiotic and one with inadequate antibiotic supply) were excluded from this plot. The Bland-Altman plot including all participants is displayed in Appendix A. Further explanation for the excessively skewed dwcMPR data is also provided in Appendix A.

FIGURE 2: Tree-based diagram† summarising excess supply cost‡ according to different subgroups Ω



† The tree-based method is an efficient approach to look inside the "black box" of regression analysis and allows the comparison of excess supply cost between clinically meaningful subgroups. EDC adherence level (the covariate most strongly associated with excess supply cost) was used for the first 'layer' division of the study sample, age (the next strongest associated covariate) was used for the second 'layer' and prescription of inhaled antibiotic (the other associated covariate) was used for the third 'layer'. For all divisions, similar categories used in the multiple regression analysis were applied, i.e. <50% versus 50 to <80% versus ≥80% for EDC adherence level; 19 to 25 years versus <19 years or >25 years for age; and prescribed ≥1 inhaled antibiotic versus on mucolytic only for the prescription of inhaled medicines.

‡ Results exclude nine participants with skewed dwcMPR data. Results for all participants are available in Appendix A. The minimum value for excess supply cost was "0", as stated in the 'Methods'. Therefore, if the confidence interval returned a negative value due to imprecise estimate from small sample sizes, the lower limit of the confidence interval was summarised as "0".

Ω Statistical tests were not performed for subgroups with sample size <20 due to imprecise estimate from the small sample size. These subgroups are marked in grey.

A For the comparison of excess supply cost between three subgroups in this 'layer', ANOVA p-value was <0.001

B For the comparison of excess supply cost between five subgroups with sample size ≥20 in this 'layer', ANOVA p-value was <0.001

C For the comparison of excess supply cost between six subgroups with sample size ≥20 in this 'layer', ANOVA p-value was <0.001

i T-test p-value = 0.021

ii T-test p-value = 0.155

iii T-test p-value = 0.007

iv T-test p-value = 0.411

SUPPLEMENTARY MATERIAL

Using a learning health system to understand the mismatch between medicines supply and actual medicines use among adults with cystic fibrosis

Amanda Bevan, Zhe Hui Hoo, Nikki Totton, Carla Girling, India R Davids, Pauline Whelan, Steven Antrobus, John Ainsworth, Iain Buchan, Alan Anderson, Stephen Bourke, Simon Doe, Carlos Echevarria, Jill Taylor, Nicholas J Bell, Kathryn Bateman, Carys Jones, Peter Moran, Giles Fitch, Michael Martin, Angela McGowan, Stephen Morrow, Heather Seabridge, Nicki Bush, Tracey Daniel, Katy Lee, Nicola Robson, Dejene Shiferaw, Dimah Sweis, Rebecca Thomas, Jayne Faulkner, William G Flight, Sarah Poole, Louise Warnock, Mark I Allenby, Mary Carroll, Thomas V Daniels, Helen Dunn, Julia A Nightingale, Elizabeth Shepherd, Chandra Ohri, Jessica Gadsby, Simon Range, Darren Tature, Helen L Barr, Sophie Dawson, Jane Dewar, Bryony Miller, Gauri Saini, Penny Galey, Jack Johnson, Mark C Pasteur, David Derry, Harriet Gledhill, Angharad Lawson, Michelle Thomas, David Waine, Josie Cunningham, Annant Damani, Alexandra Higton, Christopher Orchard, Charlotte Carolan, Misbah Tahir, Amanda Plummer, Frank P Edenborough, Rachael Curley, Martin J Wildman

Contents:

TABLE S1 Types of medicines and prices of medicine boxes according to supply source[†]

Medicine	Brand name	Number of nebules in each box	Price per box in £[‡]	
			Hospital prices (List price)	Supply via primary care (BNF – 79)
Amikacin (500mg/2ml)	N/A	5	60.00	N/A
Aztreonam 75mg	Cayston	84	2181.53	N/A
Colistimethate 2mu	Colomycin	10	32.40	32.40
Colistimethate 1mu	Promixin	30	204.00	204.00
Colistimethate 2mu	ColoFin	56	261.72	N/A
Dornase alfa (2.5mg/2.5ml)	Pulmozyme	30	496.43	496.43
Levofloxacin 240mg/2.4ml	Quinsair	56	2181.53	N/A
Meropenem 500mg	Meronem	10	103.14	N/A
Salbutamol 2.5mg	N/A	20	Brand specific	2.48
Salbutamol 5mg	N/A	20	Brand specific	3.90
Sodium chloride 7%	Nebusal	60	27.00	27.00
Sodium chloride 7%	Pulmoclear	60	18.94	18.94
Sodium chloride 7%	Respi-clear	60	16.97	16.97
Sodium chloride 7%	Resp Ease	60	21.60	21.60
Sodium chloride 7%	Salineb	60	20.60	20.60
Sodium chloride 6%	Mucoclear	60	27.00	27.00
Sodium chloride 6%	Pulmoclear	60	18.94	18.94
Sodium chloride 6%	Resp Ease	60	21.60	21.60
Tobramycin 300mg/5ml	Tobi	56	1305.92	780.00
Tobramycin 300mg/5ml	(Sun Pharma)	56	1187.00	780.00
Tobramycin 300mg/5ml	Tymbrineb	56	780.00	780.00
Tobramycin 300mg/4ml	Bramitob	56	1187.00	1187.00
Tobramycin 170mg/1.7ml	Vantobra	56	1305.00	N/A
Vancomycin 500mg	Vancocin	1	8.50	N/A

[†]Medicine prices were obtained from British National Formulary (BNF) 79 March 2020 and a regional homecare contract (S Gilbert 2020, personal communication, 16 March).

[‡]The following medicine brands are available via Homecare: Cayston, Colomycin, Promixin, Pulmozyme, Quinsair, Nebusal, Pulmoclear, Respi-clear, Resp Ease, Salineb, Mucoclear, Pulmoclear, Resp Ease, Tobi, Tymbrineb, Bramitob and Vantobra. However, Homecare prices are confidential and cannot be displayed in this table.

TABLE S2 Common treatment regimens among participants

Description of treatment regimen	Study participants (*N*=275), *N* (%)
x1 mucolytic	48 (17.5)
x2 mucolytics	23 (8.4)
x1 bronchodilator	1 (0.4)
x1 mucolytic + bronchodilator	2 (0.7)
x2 mucolytics + bronchodilator	2 (0.7)
x1 standard antibiotic[A]	5 (1.8)
x1 standard antibiotic[A] + x1 mucolytic	72 (26.2)
x1 standard antibiotic[A] + x2 mucolytics	22 (8.0)
x1 standard antibiotic[A] + x1 mucolytic + bronchodilator	8 (2.9)
x1 standard antibiotic[A] + x2 mucolytics + bronchodilator	3 (1.1)
Alternating standard antibiotics[A] + x1 mucolytic	24 (8.7)
Alternating standard antibiotics[A] + x2 mucolytics	13 (4.7)
Alternating standard antibiotics[A] + x2 mucolytics + bronchodilator	2 (0.7)
x1 expensive antibiotic[B] + x1 mucolytic	5 (1.8)
x1 expensive antibiotic[B] + x2 mucolytics	4 (1.5)
x1 expensive antibiotic[B] + x1 mucolytic + bronchodilator	4 (1.5)
x1 expensive antibiotic[B] + x2 mucolytics + bronchodilator	1 (0.4)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	21 (7.6)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics	5 (1.8)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic + bronchodilator	5 (1.8)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics + bronchodilator	5 (1.8)
<u>Centre 1[C] (*N* = 7)</u>	
x1 mucolytic	1 (14.3)
x1 standard antibiotic[A] + x1 mucolytic	1 (14.3)
x1 standard antibiotic[A] + x2 mucolytics	1 (14.3)
x1 expensive antibiotic[B] + x1 mucolytic	1 (14.3)
x1 expensive antibiotic[B] + x2 mucolytics + bronchodilator	1 (14.3)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	1 (14.3)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics + bronchodilator	1 (14.3)
<u>Centre 2[C] (*N* = 20)</u>	
x1 mucolytic	3 (15.0)
x2 mucolytics	2 (10.0)
x1 mucolytic + bronchodilator	1 (5.0)
x2 mucolytics + bronchodilator	1 (5.0)
x1 standard antibiotic[A]	1 (5.0)
x1 standard antibiotic[A] + x1 mucolytic	3 (15.0)
x1 standard antibiotic[A] + x2 mucolytics	2 (10.0)
x1 standard antibiotic[A] + x1 mucolytic + bronchodilator	1 (5.0)
Alternating standard antibiotics[A] + x1 mucolytic	3 (15.0)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	2 (10.0)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic + bronchodilator	1 (5.0)

Centre 3[D] (*N* = 11)	
x1 mucolytic	4 (36.4)
x2 mucolytics	1 (9.1)
x1 standard antibiotic[A]	1 (9.1)
x1 standard antibiotic[A] + x2 mucolytics	2 (18.2)
Alternating standard antibiotics[A] + x1 mucolytic	1 (9.1)
Alternating standard antibiotics[A] + x2 mucolytics	2 (18.2)
Centre 4[C] (*N* = 21)	
x1 mucolytic	5 (23.8)
x2 mucolytics	3 (14.3)
x1 mucolytic + bronchodilator	1 (4.8)
x1 standard antibiotic[A] + x1 mucolytic	3 (14.3)
x1 standard antibiotic[A] + x1 mucolytic + bronchodilator	1 (4.8)
Alternating standard antibiotics[A] + x1 mucolytic	1 (4.8)
x1 expensive antibiotic[B] + x1 mucolytic	1 (4.8)
x1 expensive antibiotic[B] + x2 mucolytics	1 (4.8)
x1 expensive antibiotic[B] + x1 mucolytic + bronchodilator	1 (4.8)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	1 (4.8)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics	1 (4.8)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic + bronchodilator	2 (9.5)
Centre 5[C] (*N* = 26)	
x1 mucolytic	6 (23.1)
x2 mucolytics	3 (11.5)
x1 standard antibiotic[A] + x1 mucolytic	9 (34.6)
x1 standard antibiotic[A] + x2 mucolytics	2 (7.7)
Alternating standard antibiotics[A] + x1 mucolytic	2 (7.7)
Alternating standard antibiotics[A] + x2 mucolytics	2 (7.7)
Alternating standard antibiotics[A] + x2 mucolytics + bronchodilator	1 (3.8)
x1 expensive antibiotic[B] + x1 mucolytic	1 (3.8)
Centre 6[C] (*N* = 8)	
x1 bronchodilator	1 (12.5)
x1 standard antibiotic[A] + x1 mucolytic	2 (25.0)
x1 standard antibiotic[A] + x2 mucolytics	2 (25.0)
x1 standard antibiotic[A] + x2 mucolytics + bronchodilator	1 (12.5)
Alternating standard antibiotics[A] + x1 mucolytic	1 (12.5)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics + bronchodilator	1 (12.5)
Centre 7[C] (*N* = 28)	
x1 mucolytic	5 (17.9)
x2 mucolytics	1 (3.6)
x1 standard antibiotic[A] + x1 mucolytic	4 (14.3)
x1 standard antibiotic[A] + x2 mucolytics	3 (10.7)
x1 standard antibiotic[A] + x1 mucolytic + bronchodilator	3 (10.7)
Alternating standard antibiotics[A] + x1 mucolytic	5 (17.9)
Alternating standard antibiotics[A] + x2 mucolytics	4 (14.3)
x1 expensive antibiotic[B] + x2 mucolytics	1 (3.6)
x1 expensive antibiotic[B] + x1 mucolytic + bronchodilator	1 (3.6)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	1 (3.6)
Centre 8[C] (*N* = 31)	
x1 mucolytic	3 (9.7)
x1 standard antibiotic[A]	1 (3.2)
x1 standard antibiotic[A] + x1 mucolytic	17 (54.8)
x1 standard antibiotic[A] + x2 mucolytics	3 (9.7)
Alternating standard antibiotics[A] + x1 mucolytic	2 (6.5)
Alternating standard antibiotics[A] + x2 mucolytics	1 (3.2)

x1 expensive antibiotic[B] + x1 mucolytic	1 (3.2)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	2 (6.5)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics + bronchodilator	1 (3.2)
Centre 9[C] (*N* = 43)	
x1 mucolytic	5 (11.6)
x1 standard antibiotic[A] + x1 mucolytic	19 (44.2)
x1 standard antibiotic[A] + x2 mucolytics	1 (2.3)
x1 standard antibiotic[A] + x1 mucolytic + bronchodilator	1 (2.3)
Alternating standard antibiotics[A] + x1 mucolytic	6 (14.0)
Alternating standard antibiotics[A] + x2 mucolytics	2 (4.7)
x1 expensive antibiotic[B] + x1 mucolytic + bronchodilator	1 (2.3)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	7 (16.3)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic + bronchodilator	1 (2.3)
Centre 10[C] (*N* = 28)	
x1 mucolytic	2 (7.1)
x2 mucolytics	7 (25.0)
x2 mucolytics + bronchodilator	1 (3.6)
x1 standard antibiotic[A] + x1 mucolytic	2 (7.1)
x1 standard antibiotic[A] + x2 mucolytics	3 (10.7)
x1 standard antibiotic[A] + x1 mucolytic + bronchodilator	2 (7.1)
x1 standard antibiotic[A] + x2 mucolytics + bronchodilator	1 (3.6)
Alternating standard antibiotics[A] + x2 mucolytics	2 (7.1)
Alternating standard antibiotics[A] + x1 mucolytic + bronchodilator	1 (3.6)
x1 expensive antibiotic[B] + x1 mucolytic + bronchodilator	1 (3.6)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	1 (3.6)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics	3 (10.7)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics + bronchodilator	2 (7.1)
Centre 11[C] (*N* = 25)	
x1 mucolytic	8 (32.0)
x2 mucolytics	5 (20.0)
x1 standard antibiotic[A]	1 (4.0)
x1 standard antibiotic[A] + x1 mucolytic	6 (24.0)
x1 standard antibiotic[A] + x2 mucolytics	2 (8.0)
Alternating standard antibiotics[A] + x1 mucolytic	2 (8.0)
x1 expensive antibiotic[B] + x2 mucolytics	1 (4.0)
Centre 12[C] (*N* = 27)	
x1 mucolytic	6 (22.2)
x2 mucolytics	1 (3.7)
x1 standard antibiotic[A]	1 (3.7)
x1 standard antibiotic[A] + x1 mucolytic	6 (22.2)
x1 standard antibiotic[A] + x2 mucolytics	1 (3.7)
x1 standard antibiotic[A] + x2 mucolytics + bronchodilator	1 (3.7)
Alternating standard antibiotics[A] + x1 mucolytic	1 (3.7)
x1 expensive antibiotic[B] + x1 mucolytic	1 (3.7)
x1 expensive antibiotic[B] + x2 mucolytics	1 (3.7)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic	6 (22.2)
Expensive antibiotic[B] alternating with another antibiotic + x2 mucolytics	1 (3.7)
Expensive antibiotic[B] alternating with another antibiotic + x1 mucolytic + bronchodilator	1 (3.7)

[A] 'Standard' antibiotic include nebulised amikacin, vancomycin, meropenem, colistimethate sodium and tobramycin.

[B] Expensive antibiotic include nebulised aztreonam lysine and levofloxacin.

[C] There was substantial intra-centre variation in prescription regimens, with 11/12 (92%) of the centres have participants on bronchodilator and/or expensive antibiotic as part of their regimen.

[D] Centre 3 was the only centre without anyone on bronchodilator or expensive antibiotic (though only 11 participants were included). Centre 3 was also the only centre without anyone on x1 standard antibiotic + x1 mucolytic, which is the common prescription regimen.

APPENDIX A Sensitivity analyses including participants with skewed dwcMPR data

There were nine adults with CF, ≥1 year of EDC adherence data and on ≥2 different medicines that had excessively skewed dwcMPR data for the following reasons:

- Person #1 (dwcMPR = 128%) – this person was only prescribed salbutamol for 5 days but one box (10 days' worth of supply) was supplied, hence MPR for salbutamol was 200%. The salbutamol MPR skewed the excess box calculations for other medicines.
- Person #2 (dwcMPR = 1407%) – salbutamol prescription was for only 20 days but 12 months of supplies (48 boxes) were delivered, hence MPR for salbutamol was >2000%. The salbutamol MPR skewed the excess box calculations for other medicines.
- Person #3 (dwcMPR = 416%) – salbutamol prescription was for only 30 days but 6 months of supplies (27 boxes) were delivered, hence MPR for salbutamol was 900%. The salbutamol MPR skewed the excess box calculations for other medicines.
- Person #4 (dwcMPR = 160%) – MPR for hypertonic saline was 190%, resulting in a dwcMPR which indicated 19 boxes of dornase alfa being supplied.
- Person #5 (dwcMPR = 89%) – dwcMPR indicated 11 boxes of hypertonic saline being supplied but participant only received 1 box.
- Person #6 (dwcMPR = 30%) – dwcMPR indicated 12 boxes of colistin being supplied but participant only received 3 boxes.
- Person #7 (dwcMPR = 73%) – unable to find evidence for the supply of piperacillin-tazobactam post hospital admission although prescription was continued, hence MPR for piperacillin-tazobactam was only 5%. This resulted in lower-than-expected dwcMPR.
- Person #8 (dwcMPR = 114%) – tobramycin prescription was stopped after 2 days but one box was supplied, hence MPR for tobramycin was 1400%. The tobramycin MPR skewed the excess box calculations for other medicines.
- Person #9 (dwcMPR = 196%) – this person was only prescribed colistin for 18 days but on-going supply resulted in an MPR of 570% for colistin. The colistin MPR skewed the excess box calculations for other medicines.

These skewed dwcMPR data reflect the fact that on occasion, lack of system optimisation in medicine management can create quite marked over-supply. Busy clinical teams are often unable to pay sufficient attention to unexpected variation in the system. Thus, the skewed data are not errors in calculating dwcMPR but are simply infrequent features of a complex system.

Compared to participants with non-skewed dwcMPR data, those with skewed data have much higher MPR (median 128%, IQR 81–306% vs median 74%, IQR 46–96%; Mann-Whitney p-value 0.003) yet their electronic data capture (EDC) adherence was slightly lower (median 33%, IQR 12–76% vs median 57%, IQR 23–86%; Mann-Whitney p-value 0.196). The baseline characteristics of all 284 participants with ≥1 year of EDC adherence data are provided in Appendix A Table 1.

APPENDIX A TABLE 1: Baseline characteristics of the participants

Characteristics	Results excluding skewed dwcMPR† (*N* = 275)	Results for all with ≥1 year EDC data‡ (*N* = 284)
Source of recruitment		
Learning health system, *N* (%)	89 (32.4)	92 (32.4)
Usual care arm of the ACtiF trial[A], *N* (%)	83 (30.2)	86 (30.3)
Intervention arm of the ACtiF trial[A], *N* (%)	103 (37.5)	106 (37.3)
Age in years[B], mean (95% CI)	30 (29 to 31)	30 (29 to 31)
≤18 years, *N* (%)	14 (5.1)	14 (4.9)
19 to 25 years, *N* (%)	97 (35.3)	101 (35.6)
26 to 34 years, *N* (%)	96 (34.9)	97 (34.2)
≥35 years, *N* (%)	68 (24.7)	72 (25.4)
Gender		
Male, *N* (%)	142 (51.6)	146 (51.4)
Female, *N* (%)	133 (48.4)	138 (48.6)
Pseudomonas aeruginosa status		
Not chronic, *N* (%)	114 (41.5)	117 (41.2)
Chronic infection, *N* (%)	161 (58.5)	167 (58.8)
%FEV_1[C], mean (95% CI)	62 (59 to 64)	61 (59 to 64)
<40%, *N* (%)	57 (20.8)	60 (21.2)
40 to 69.9%, *N*(%)	109 (39.8)	112 (39.6)
≥70%, *N* (%)	108 (39.4)	111 (39.2)
Source of inhaled medicine supply		
Hospital, *N* (%)	52 (18.9)	57 (20.1)
Homecare only, *N* (%)	92 (33.5)	92 (32.4)
≥2 supply sources, *N* (%)	131 (47.6)	135 (47.5)
Number of inhaled medicines[D]		
1 medicine only, *N* (%)	54 (19.6)	54 (19.0)
2 different medicines, *N* (%)	101 (36.7)	103 (36.3)
3 different medicines, *N* (%)	80 (29.1)	81 (28.5)
4 different medicines, *N* (%)	28 (10.2)	32 (11.3)
5 different medicines, *N* (%)	12 (4.4)	12 (4.2)
6 different medicines, *N* (%)	0	2 (0.7)
Prescription of inhaled antibiotics[D]		
Only on mucolytic, *N* (%)	76 (27.6)	77 (27.1)
1 inhaled antibiotic, *N* (%)	123 (44.7)	125 (44.0)
2 inhaled antibiotics, *N* (%)	68 (24.7)	73 (25.7)
3 inhaled antibiotics, *N* (%)	7 (2.5)	8 (2.8)
4 inhaled antibiotics, *N* (%)	1 (0.4)	1 (0.4)
Prescribed inhaled aztreonam and/or levofloxacin, *N* (%)	50 (18.2)	53 (18.7)
Unadjusted % EDC adherence[E], median (IQR)	57 (23 to 86)	57 (22 to 86)
<50%, *N* (%)	128 (46.5)	134 (47.2)
50 to <80%, *N*(%)	50 (18.2)	52 (18.3)
≥80%, *N* (%)	97 (35.3)	98 (34.5)
% MPR, median (IQR)	74 (46 to 96)	75 (46 to 98)

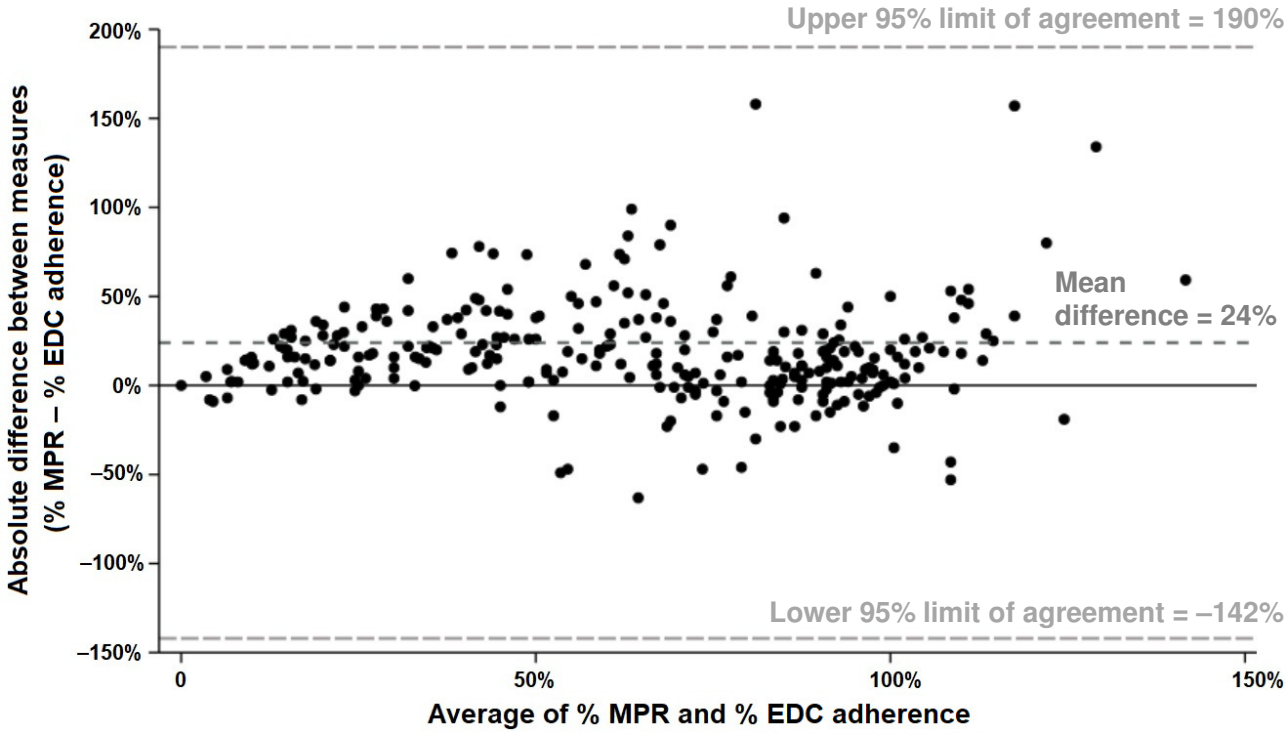
†These are the results as displayed in Table 1 of the main manuscript. The results are included here for comparison with the analysis of all 284 participants with ≥1 year of EDC adherence data (including nine participants with skewed dwcMPR data).

‡One of participants without excessively skewed dwcMPR data was unable to perform spirometry, hence the missing FEV_1 data. There is no missing data for all nine participants with skewed dwcMPR data.

The Bland-Altman plot comparing dwcMPR versus EDC adherence have larger limits of agreement with the inclusion of skewed dwcMPR data – the limits of agreement exceeded 100% from zero with

the skewed dwcMPR data (Appendix A Figure 1) and exceeded 33% from zero without the skewed dwcMPR data (Figure 1 in the main manuscript).

APPENDIX A FIGURE 1: Bland-Altman plot for dwcMPR versus EDC adherence, including all adults with ≥1 year of EDC adherence data ($N = 284$) †



† Two outlying points (due to MPR values of 416% and 1407%) were outside the range of this plot.

To investigate the potential for skewed dwcMPR data to bias the results on potential excess supply cost, two sensitivity analyses were carried out.

First, descriptive analyses in the main manuscript were repeated by including nine participants with skewed dwcMPR data. Results from analyses including all 284 participants in Appendix A Table 2 were similar in direction and within the ranges observed in comparison to the results from analyses excluding skewed dwcMPR data in Table 2 of the main manuscript. For example, those prescribed expensive antibiotic (aztreonam and/or levofloxacin) still have higher excess supply cost. The inclusion of skewed dwcMPR data had minimal impact on the overall excess supply cost (mean £1,145, 95% CI £881–1,409 vs mean £1,124, 95% CI £855–1,394).

Second, regression analyses in the main manuscript were also repeated by including nine participants with skewed dwcMPR data. The same covariates (EDC adherence level, age 19–25 years, and prescription of inhaled antibiotic) were still independently associated with excess supply cost by including all 284 participants (Appendix A Table 3).

Therefore, it is unlikely for the results of this study to be biased by skewed dwcMPR data.

APPENDIX A TABLE 2: dwcMPR vs EDC adherence discrepancy; and excess supply cost[†]

	Results excluding skewed dwcMPR[‡] (*N* = 275)	Results for all participants (*N* = 284)
Discrepancy between dwcMPR and EDC adherence		
Median (IQR)	14% (2 to 29%)	15% (2 to 30%)
Mean (95% CI)	17% (14 to 20%)	24% (14 to 34%)
Discrepancy between dwcMPR and EDC adherence for different adherence levels, median (IQR)		
EDC adherence <50%	22% (12 to 39%)	23% (12 to 42%)
EDC adherence 50% to <80%	12% (1 to 28%)	12% (1 to 30%)
EDC adherence ≥80%	4% (–7 to 17%)	5% (–6 to 18%)
Discrepancy between dwcMPR with 20% contingency and EDC adherence		
Median (IQR)	3% (–11 to 21%)	5% (–10 to 24%)
Mean (95% CI)	6% (2 to 9%)	13% (3 to 23%)
Excess supply cost in £ for the overall cohort		
Median (IQR)	0 (0 to 1,414)	0 (0 to 1,473)
Mean (95% CI)	1,124 (855 to 1,394)	1,145 (881 to 1,409)
Excess supply cost in £ according to the source of recruitment		
Learning health system, mean (95% CI)	1,475 (801 to 2,148)	1,500 (841 to 2,158)
Usual care arm of the ACtiF trial, mean (95% CI)	1,164 (796 to 1,532)	1,188 (827 to 1,549)
Intervention arm of the ACtiF trial, mean (95% CI)	789 (479 to 1,099)	801 (499 to 1,105)
Excess supply cost in £ according to age categories		
≤18 years, mean (95% CI)	1,026 (234 to 1,817)	1,026 (234 to 1,817)
19 to 25 years, mean (95% CI)	1,907 (1,328 to 2,486)	1,932 (1,369 to 2,495)
26 to 34 years, mean (95% CI)	673 (408 to 939)	666 (403 to 930)
≥35 years, mean (95% CI)	664 (120 to 1,207)	709 (191 to 1,227)
Excess supply cost in £ according to gender		
Male, mean (95% CI)	1,149 (713 to 1,584)	1,189 (760 to 1,619)
Female, mean (95% CI)	1,098 (785 to 1,411)	1,098 (794 to 1,402)
Excess supply cost in £ according to *Pseudomonas aeruginosa* status		
Not chronic, mean (95% CI)	1,006 (652 to 1,361)	1,036 (688 to 1,384)
Chronic infection, mean (95% CI)	1,208 (819 to 1,596)	1,221 (841 to 1,600)
Excess supply cost in £ according to %FEV_1 categories		
<40%, mean (95% CI)	1,063 (457 to 1,669)	1,027 (450 to 1,604)
40 to 69.9%, mean (95% CI)	1,394 (954 to 1,834)	1,462 (1,026 to 1,900)
≥70%, mean (95% CI)	864 (443 to 1,284)	869 (459 to 1,278)
Excess supply cost in £ according to source of inhaled medicine supply		
Hospital, mean (95% CI)	1,301 (716 to 1,887)	1,368 (827 to 1,908)
Homecare only, mean (95% CI)	1,344 (805 to 1,884)	1,344 (805 to 1,884)
≥2 supply sources, mean (95% CI)	899 (541 to 1,257)	915 (560 to 1,270)
Excess supply cost in £ according to number of inhaled medicines		
1 medicine only, mean (95% CI)	595 (319 to 870)	595 (319 to 870)
≥2 different medicines, mean (95% CI)	1,254 (926 to 1,581)	1,274 (956 to 1,592)
Excess supply cost in £ according to prescription of inhaled antibiotics		
Only on inhaled mucolytic, mean (95% CI)	553 (329 to 776)	620 (362 to 877)
≥1 inhaled antibiotic, mean (95% CI)	1,342 (983 to 1,701)	1,340 (994 to 1,687)
Excess supply cost in £ according to prescription of expensive antibiotics		
Neither inhaled aztreonam nor levofloxacin, mean (95% CI)	1,041 (768 to 1,314)	1,083 (813 to 1,353)
On inhaled aztreonam and/or levofloxacin, mean (95% CI)	1,499 (651 to 2,347)	1,415 (610 to 2,219)
Excess supply cost in £ according to unadjusted EDC adherence		
<50%, mean (95% CI)	2,017 (1,507 to 2,526)	2,038 (1,547 to 2,529)
50 to <80%, mean (95% CI)	665 (304 to 1,025)	639 (291 to 987)
≥80%, mean (95% CI)	183 (29 to 338)	192 (38 to 346)

[†] **Estimates of excess supply cost are highly conservative because of contingency**, see 'Discussion' paragraph 6. Excess supply cost was calculated as the cost of excess medicine box(es) delivered or collected after accounting for the discrepancy between EDC adherence and dwcMPR with 20% contingency. For example, if a person has an excess supply of 83 aztreonam nebules, the excess supply cost was calculated as "0" because each box of aztreonam has 84 nebules.

[‡] These are the results as displayed in Table 2 of the main manuscript. The results are included here for comparison with the analysis of all 284 participants with ≥1 year of EDC adherence data (including nine participants with skewed dwcMPR data).

APPENDIX A TABLE 3: Summary of the excess supply cost results from linear regression models

Variable	Excess supply cost in £			
	Results excluding skewed dwcMPR data[Ω] (*N* = 275)		Results for all participants (*N* = 284)	
	Regression coefficient (95% CI)	P-value	Regression coefficient (95% CI)	P-value
Univariate analysis[†]				
Unadjusted EDC adherence[A]	–928 (–1,208 to –648)	<0.001	–937 (–1,211 to –662)	<0.001
Age <19 years or >25 years (reference)				
Age 19 to 25 years	1,210 (663 to 1,756)	<0.001	1,221 (688 to 1,309)	<0.001
Only on inhaled mucolytic (reference)				
≥1 inhaled antibiotic	789 (193 to 1,386)	0.010	721 (132 to 1,309)	0.017
1 medicine only (reference)				
≥2 different medicines	659 (–16 to 1,334)	0.056	680 (10 to 1,348)	0.047
Source of recruitment				
Learning health system (reference)				
Usual care arm of the ACtiF trial	–310 (–1,088 to 467)	0.432	–311 (–1,072 to 448)	0.419
Intervention arm of the ACtiF trial	–686 (–1,390 to 18)	0.056	–698 (–1,388 to –8)	0.047
Male (reference)				
Female	–50 (–591 to 490)	0.854	–92 (–621 to 437)	0.733
Not chronic *P. aeruginosa* (reference)				
Chronic *P. aeruginosa* infection	201 (–346 to 749)	0.470	184 (–353 to 721)	0.499
$\%FEV_1$ <40% or ≥70% (reference)				
$\%FEV_1$ 40 to 69.9%	447 (–102 to 997)	0.110	525 (–13 to 1,062)	0.056
≥2 medicine supply sources (reference)				
Supply from hospital only or homecare only	430 (–108 to 968)	0.117	439 (–88 to 966)	0.103
Neither aztreonam nor levofloxacin (reference)				
On inhaled aztreonam and/or levofloxacin[B]	458 (–239 to 1,156)	0.197	332 (–346 to 1,009)	0.336
Multivariate analysis[‡]				
Unadjusted EDC adherence[A]	–831 (–1,110 to –552)	<0.001	–836 (–1,110 to –561)	<0.001
Age <19 years or >25 years (reference)				
Age 19 to 25 years	869 (345 to 1,393)	0.001	879 (366 to 1,392)	0.001
Only on inhaled mucolytic (reference)				
≥1 inhaled antibiotic	876 (332 to 1,420)	0.002	810 (273 to 1,346)	0.003

[Ω] These are the results as displayed in Table 3 of the main manuscript. The results are included here for comparison with the analysis of all 284 participants with ≥1 year of EDC adherence data (including nine participants with skewed dwcMPR data).

[†] The regression coefficients from univariate analyses are unadjusted coefficients.

[‡] The regression coefficients from multivariate analyses are adjusted coefficients.
Adjusted R^2 of the multiple regression model which excluded all nine participants with skewed dwcMPR data = 0.186.
Adjusted R^2 of the multiple regression model which included all 284 participants = 0.186.

[A] As explained in the footnote of main manuscript Table 3, EDC adherence category was analysed as an ordinal variable because there was a step-wise reduction in excess supply cost with increasing level of adherence category.

[B] An exploratory multiple regression analysis of all 284 participants accounting for EDC adherence level and age 19–25 years found that the prescription of expensive inhaled antibiotic was associated with an increase in excess supply cost of £752 (95% CI £128–1,376), p-value 0.018. This finding is similar to the exploratory multiple regression analysis after excluding all nine participants with skewed dwcMPR data, which showed an increase in excess supply cost of £896 (95% CI £253–1,539), p-value 0.006.

APPENDIX B Sensitivity analyses comparing participants with and without excess supply cost

Appendix A highlighted the fact that some of the dwcMPR data were skewed and explored the impact of the skewed dwcMPR data on excess supply cost. Appendix B further explored the impact of data distribution for excess supply cost. In the manuscript and appendices, we have used the term "excess supply cost" to refer to a composite of excess medicine doses and the financial impact of those excess supplies, which will also depend on the cost of medicines. In Appendix B, we explore how the odds of having excess supply relates to the excess supply cost. The sensitivity analyses in this appendix also identifies the baseline characteristics of those with excess supply cost.

In this study, a high threshold was set before excess supply can be accrued in order to obtain a conservative estimate and to avoid over-estimating excess supply cost. As a consequence of the high threshold, most of the participants without skewed dwcMPR data (*N*=149, 54.2%) were deemed to have no excess supply. Therefore, the distribution of excess supply cost was somewhat positively skewed with a cluster of participants without any excess supply cost. To explore the impact of data distribution on the results for excess supply cost, analyses in the main manuscript were repeated by dichotomising participants into those with excess supply cost (excess supply cost ≥£1) and those without excess supply cost (zero excess supply cost). The percentage of participants with excess supply cost was described according to clinical characteristics and treatment factors as per the main manuscript. Then logistic regression was performed using participants with excess supply cost versus without excess supply cost as the dependent binary variable; and clinical characteristics and treatment factors as the covariates.

Results from analyses which dichotomise participants were displayed in Appendix B Tables 1 & 2. Some of the results from analyses which dichotomise participants were in different direction to the results from analyses which use excess supply cost in £ as a continuous variable. For example, those prescribed expensive antibiotics (aztreonam and/or levofloxacin) have somewhat higher excess supply cost (unadjusted regression coefficient of £458, 95% CI –£239 to £1,156) but have somewhat lower odds of having excess supply (unadjusted odds ratio of 0.68, 95% CI 0.36 to 1.27). This was because where there was excess supply cost, substantially greater amount of excess supply cost occurred in those prescribed expensive antibiotics. Only 19/50 (38.0%) of those prescribed expensive antibiotic accrued any excess supply cost compared to 107/225 (47.6%) of those not prescribed expensive antibiotics. However, the mean excess supply cost among the 19 participants prescribed expensive antibiotic of £3,945 (95% CI £2,137 to £5,753) was much higher compared to the mean excess supply cost of £2,189 (95% CI £1,697 to £2,680) among the 107 participants not prescribed expensive antibiotic, T-test p-value 0.012.

Those prescribed expensive antibiotics have lower odds of having excess supply because of higher EDC adherence levels (median 77%, IQR 48–93% vs median 50%, IQR 19–84%, Mann-Whitney p-

value 0.001). This may in part relate to the availability of CFHealthHub data allowing centres to only escalate to aztreonam lysine or levofloxacin if participants had demonstrated treatment failure despite adequate adherence to first line inhaled antibiotics, which is the approach advocated by NHS guidelines. Such an approach is only possible with routinely available EDC adherence data.

APPENDIX B TABLE 1: Results for excess supply cost among 275 study participants without skewed dwcMPR data†

Characteristics	Excess supply cost in £, Mean (95% CI)‡	Number of adults with excess supply cost, *N* (%)
Overall cohort	1,124 (855 to 1,394)	126 (45.8)
Source of recruitment		
Learning health system	1,475 (801 to 2,148)	41 (46.1)
Usual care arm of the ACtiF trial	1,164 (796 to 1,532)	43 (51.8)
Intervention arm of the ACtiF trial	789 (479 to 1,099)	42 (40.8)
Age categories		
≤18 years	1,026 (234 to 1,817)	9 (64.3)
19 to 25 years	1,907 (1,328 to 2,486)	63 (64.9)
26 to 34 years	673 (408 to 939)	34 (35.4)
≥35 years	664 (120 to 1,207)	20 (29.4)
Gender		
Male	1,149 (713 to 1,584)	56 (39.4)
Female	1,098 (785 to 1,411)	70 (52.6)
Pseudomonas aeruginosa status		
Not chronic	1,006 (652 to 1,361)	50 (43.9)
Chronic infection	1,208 (819 to 1,596)	76 (47.2)
%FEV_1 categories		
<40%	1,063 (457 to 1,669)	19 (33.3)
40 to 69.9%	1,394 (954 to 1,834)	62 (56.9)
≥70%	864 (443 to 1,284)	44 (40.7)
Source of inhaled medicine supply		
Hospital	1,301 (716 to 1,887)	29 (55.8)
Homecare only	1,344 (805 to 1,884)	41 (44.6)
≥2 supply sources	899 (541 to 1,257)	56 (42.7)
Number of inhaled medicines		
1 medicine only	595 (319 to 870)	25 (46.3)
≥2 different medicines	1,254 (926 to 1,581)	101 (45.7)
Prescription of inhaled antibiotics		
Only on inhaled mucolytic	553 (329 to 776)	31 (40.8)
≥1 inhaled antibiotic	1,342 (983 to 1,701)	95 (47.7)
Prescription of expensive antibiotics		
Neither inhaled aztreonam nor levofloxacin	1,041 (768 to 1,314)	107 (47.6)
On inhaled aztreonam and/or levofloxacin	1,499 (651 to 2,347)	19 (38.0)
Unadjusted EDC adherence		
<50%	2,017 (1,507 to 2,526)	97 (75.8)
50 to <80%	665 (304 to 1,025)	15 (30.0)
≥80%	183 (29 to 338)	14 (14.4)

† **Estimates of excess supply cost are highly conservative because of contingency**, see 'Discussion' paragraph 6. Excess supply cost was calculated as the cost of excess medicine box(es) delivered or collected after accounting for the discrepancy between EDC adherence and dwcMPR with 20% contingency. For example, if a person has an excess supply of 83 aztreonam nebules, the excess supply cost was calculated as "0" because each box of aztreonam has 84 nebules.

‡ These are the results as displayed in Table 2 of the main manuscript. The results are included here for comparison with the analysis dichotomising participants into those with excess supply cost and without excess supply cost.

APPENDIX B TABLE 2: Summary of linear and logistic regression models for excess supply cost

Variable	Linear regression models for excess supply cost in £[Ω]		Logistic regression models for zero excess supply cost vs excess supply cost ≥£1	
	Regression coefficient (95% CI)	P-value	Odds ratio (95% CI)	P-value
Univariate analysis[†]				
Unadjusted EDC adherence[A]	–928 (–1,208 to –648)	<0.001	0.22 (0.16 to 0.31)	<0.001
Age <19 years or >25 years (reference)				
Age 19 to 25 years	1,210 (663 to 1,756)	<0.001	3.38 (2.02 to 5.68)	<0.001
Only on inhaled mucolytic (reference)				
≥1 inhaled antibiotic	789 (193 to 1,386)	0.010	1.33 (0.78 to 2.27)	0.302
1 medicine only (reference)				
≥2 different medicines	659 (–16 to 1,334)	0.056	0.98 (0.54 to 1.77)	0.937
Source of recruitment				
Learning health system (reference)				0.432
Usual care arm of the ACtiF trial	–310 (–1,088 to 467)	0.432	1.26 (0.69 to 2.29)	0.452
Intervention arm of the ACtiF trial	–686 (–1,390 to 18)	0.056	0.81 (0.46 to 1.43)	0.461
Male (reference)				
Female	–50 (–591 to 490)	0.854	1.71 (1.06 to 2.75)	0.029
Not chronic *P. aeruginosa* (reference)				
Chronic *P. aeruginosa* infection	201 (–346 to 749)	0.470	1.14 (0.71 to 1.85)	0.583
$\%FEV_1$ <40% or ≥70% (reference)				
$\%FEV_1$ 40 to 69.9%	447 (–102 to 997)	0.110	2.10 (1.29 to 3.44)	0.003
≥2 medicine supply sources (reference)				
Supply from hospital only or homecare only	430 (–108 to 968)	0.117	1.27 (0.79 to 2.04)	0.330
Neither aztreonam nor levofloxacin (reference)				
On inhaled aztreonam and/or levofloxacin	458 (–239 to 1,156)	0.197	0.68 (0.36 to 1.27)	0.222
Multivariate analysis model 1[‡]				
Unadjusted EDC adherence[A]	–831 (–1,110 to –552)	<0.001	0.23 (0.16 to 0.33)	<0.001
Age <19 years or >25 years (reference)				
Age 19 to 25 years	869 (345 to 1,393)	0.001	2.62 (1.41 to 4.87)	0.002
Only on inhaled mucolytic (reference)				
≥1 inhaled antibiotic	876 (332 to 1,420)	0.002	1.82 (0.94 to 3.54)	0.077
Multivariate analysis model 2[‡]				
Unadjusted EDC adherence[A]			0.23 (0.16 to 0.33)	<0.001
Age <19 years or >25 years (reference)				
Age 19 to 25 years			2.83 (1.51 to 5.32)	0.001
$\%FEV_1$ <40% or ≥70% (reference)				
$\%FEV_1$ 40 to 69.9%			2.74 (1.47 to 5.11)	0.002
Male (reference)				
Female			1.38 (0.76 to 2.51)	0.290

[Ω] These are the results as displayed in Table 3 of the main manuscript. The results are included here for comparison with the analysis dichotomising participants into those with excess supply cost and without excess supply cost.

[†] The regression coefficients and odds ratios from univariate analyses are unadjusted coefficients and unadjusted odds ratios.

[‡] The regression coefficients and odds ratios from multivariate analyses are adjusted coefficients and adjusted odds ratios.
For the multiple linear regression model: Adjusted $R^2 = 0.186$.
For multiple logistic regression model 1: pseudo-$R^2 = 0.429$ (Nagelkerke); model $\chi^2(3) = 106.3$, $p < 0.001$
For multiple logistic regression model 2: pseudo-$R^2 = 0.457$ (Nagelkerke); model $\chi^2(4) = 115.0$, $p < 0.001$

[A] As explained in the footnote of main manuscript Table 3, EDC adherence category was analysed as an ordinal variable because there was a step-wise reduction in excess supply cost with increasing level of adherence category.

Nonetheless, there were broad similarities in the direction and magnitude of results from the analyses which dichotomise participants in comparison to results from the analyses using excess supply cost in £ as a continuous variable. In the univariate logistic regression model, an increase in one level of adherence category (e.g. from <50% to 50–79%) was associated with a drop of 78% in the odds of having excess supply cost (95% CI 69% to 84%). In contrast, those aged 19–25 years have an increase of 238% in the odds of having excess supply cost (95% CI 102% to 468%). EDC adherence and age 19-25 years were independent predictors for the odds of having excess supply cost in multivariate logistic regression (including a second logistic regression model using EDC adherence, age 19–25 years, FEV_1 40–69.9% and gender as covariates).

The analyses in the main manuscript used excess supply cost in £ as a continuous variable because the main aim of the study is to quantify the amount of potential financial cost since this allows us to explore the potential savings that might result from using CFHealthHub to support medicines optimisation, which in turn has the potential to unlock NHS funding to incorporate a system that provides EDC data on actual medicine use data into the medicines supply chain. There are currently around 6,500 adults with CF in the UK with ≥70% of them on inhaled therapy [1]. The mean excess supply cost in this study sample was £1,124/patient/year and the cost of incorporating a comprehensive EDC system in medicine supply chain is around £770/patient/year ('Discussion' paragraph 5). Extrapolating from the mean excess supply cost observed in this study sample gives a potential annual savings of around £1.6 million. However, if we consider that the overall real-world adherence level to be closer to 30-40% [2] where excess supply cost was £2,017/patient/year, then the potential annual savings may exceed £5.7 million.

The odds or probability of having excess supply will influence the amount of excess supply cost. However, as shown in the example of expensive antibiotic prescription, the actual amount of excess supply cost will also depend on other factors such as the cost of supplied medicines. Where there is excess supply, the actual of amount of excess supply cost can vary substantially from one participant to another. Hence simply calculating the odds or probability of having excess supply is inadequate to quantify the amount of excess supply cost. Nonetheless, the logistic regression analyses in this appendix provide reassurance that the findings of the study are robust and are not biased by the data distribution of excess supply cost.

References

1. UK Cystic Fibrosis Registry. Annual data report 2019. Published August 2020. https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources. Date last accessed: December 18 2020.
2. Hoo ZH, Totton N, Waterhouse S, et al. Real-world adherence among adults with cystic fibrosis is low – a retrospective analysis of the CFHealthHub digital learning health system. Chest Published Online First: 26 June 2021. doi: 10.1016/j.chest.2021.06.039.

APPENDIX C Sensitivity analyses of best case (lowest cost) and worst case (highest cost) scenarios in terms the excess supply cost

A limitation of this study is the inability of data-logging nebulisers to determine which collected medicines were used in a regimen with ≥2 different medicines (though when interventionists work closely with participants, working out which treatment is which can be straightforward). Therefore, excess supply cost was calculated from dwcMPR with the assumption that all medicine types were equally used. Previous studies have suggested broadly similar medication possession ratio (MPR) for nebulised mucolytics (median MPR ~55%) and nebulised antibiotics (median MPR ~60%) [1]. Nonetheless, this may not be an universal finding hence Appendix C explored the lowest and highest excess supply cost by making assumptions regarding potential differential use of medicines.

The excess supply cost will be lowest if all the most expensive medication were used first, followed by the second most expensive medication, followed by the third most expensive medication, and so on. In other words, all excess supply will be the cheapest medication, followed by the second cheapest medication, and so on. The excess supply cost will be highest if all the cheapest medication were used first, followed by the second cheapest medication, followed by the third cheapest medication, and so on. In other words, all excess supply will be the most expensive medication, followed by the second most expensive medication, and so on.

We provide the following example to illustrate the method of calculating the lowest and highest excess supply cost: a participant has used a total of 526 doses of nebulised medicine over a 1-year period but was supplied with 11 boxes of dornase alfa (330 doses, £17 per dose) and 20 boxes of promixin i.e. colistin (600 doses, £7 per dose). First, a 20% contingency was included, i.e. 526 doses multiplied by 1.2 = 631 doses. Excess doses were calculated by subtracting 631 doses from the total supplied (330 + 600 = 930 doses), i.e. there were 299 excess doses. To calculate the highest excess supply cost, it is assumed that all promixin doses (each promixin dose is cheaper than each dornase alfa dose) have been used i.e. all 299 excess doses were dornase alfa. This gave 9 excess boxes of dornase alfa (rounded down from 9.97 boxes) and an excess supply cost of 9 × £496.43 = £4,468. To calculate the lowest excess supply cost, it is assumed that all dornase alfa doses (each dornase alfa dose is more expensive than each promixin dose) have been used i.e. all 299 excess doses were promixin. This gave 9 excess boxes of promixin (rounded down from 9.97 boxes) and an excess supply cost of 9 × £204.00 = £1,836. This method of calculating the lowest excess supply cost gives an unrealistically low estimate because it is unlikely for a participant to use medicines sequentially according to cost, especially when medicines delivery is staggered throughout the 1-year period instead of all medicines being supplied up front at the start of the 1-year period. It should also be noted that aztreonam lysine is a thrice daily medicine which can make 100% adherence challenging. Nonetheless, it is still useful to obtain a lowest possible excess supply cost since the direction of bias would then be known. After calculating the lowest and highest excess supply cost for the participants, two sensitivity analyses were carried out.

First, descriptive analyses in the main manuscript were repeated using the lowest and highest excess supply cost. Results for lowest and highest excess supply cost in Appendix C Tables 1 were broadly similar in direction to the results based on the assumption that all medicine types were equally used in Table 2 of the main manuscript. For example, those with EDC adherence <50% have higher excess supply cost with lowest and highest excess supply cost of £1,325 (95% CI £909 to £1,741) and £2,468 (95% CI £1,912 to £3,025) respectively. The exception was those prescribed expensive antibiotics have lowest excess supply cost that was lower than those not on expensive antibiotics, since the method of calculating lowest excess supply cost assumes that expensive antibiotics were preferentially used.

APPENDIX C TABLE 1: Lowest and highest excess supply cost among 275 study participants without skewed dwcMPR data[†]

Characteristics	Lowest excess supply cost in £, Mean (95% CI)	'Average' excess supply cost in £, Mean (95% CI)[‡]	Highest excess supply cost in £, Mean (95% CI)
Overall cohort	695 (484 to 906)	1,124 (855 to 1,394)	1,490 (1,174 to 1,807)
Source of recruitment			
Learning health system	1,001 (449 to 1,553)	1,475 (801 to 2,148)	1,718 (1,019 to 2,416)
Usual care arm of the ACtiF trial	665 (399 to 930)	1,164 (796 to 1,532)	1,603 (1,121 to 2,085)
Intervention arm of the ACtiF trial	455 (239 to 671)	789 (479 to 1,099)	1,203 (741 to 1,665)
Age categories			
≤18 years	549 (54 to 1,045)	1,026 (234 to 1,817)	1,400 (336 to 2,463)
19 to 25 years	1,359 (862 to 1,856)	1,907 (1,328 to 2,486)	2,562 (1,903 to 3,220)
26 to 34 years	346 (161 to 531)	673 (408 to 939)	949 (563 to 1,336)
≥35 years	271 (0 to 601)	664 (120 to 1,207)	745 (184 to 1,305)
Gender			
Male	766 (424 to 1,107)	1,149 (713 to 1,584)	1,472 (990 to 1,955)
Female	620 (376 to 863)	1,098 (785 to 1,411)	1,510 (1,099 to 1,921)
Pseudomonas aeruginosa status			
Not chronic	685 (386 to 983)	1,006 (652 to 1,361)	1,334 (905 to 1,763)
Chronic infection	702 (408 to 997)	1,208 (819 to 1,596)	1,601 (1,150 to 2,052)
%FEV_1 categories			
<40%	649 (151 to 1,147)	1,063 (457 to 1,669)	1,478 (696 to 2,260)
40 to 69.9%	753 (462 to 1,043)	1,394 (954 to 1,834)	1,683 (1,207 to 2,159)
≥70%	663 (288 to 1,038)	864 (443 to 1,284)	1,216 (733 to 1,699)
Source of inhaled medicine supply			
Hospital	989 (434 to 1,544)	1,301 (716 to 1,887)	1,568 (924 to 2,211)
Homecare only	888 (511 to 1,264)	1,344 (805 to 1,884)	1,669 (1,059 to 2,279)
≥2 supply sources	443 (162 to 724)	899 (541 to 1,257)	1,334 (884 to 1,784)
Number of inhaled medicines			
1 medicine only	595 (319 to 870)	595 (319 to 870)	595 (319 to 870)
≥2 different medicines	720 (465 to 974)	1,254 (926 to 1,581)	1,709 (1,325 to 2,093)
Prescription of inhaled antibiotics			
Only on inhaled mucolytic	420 (216 to 624)	553 (329 to 776)	684 (410 to 959)
≥1 inhaled antibiotic	800 (520 to 1,080)	1,342 (983 to 1,701)	1,798 (1,380 to 2,217)
Prescription of expensive antibiotics			
Neither inhaled aztreonam nor levofloxacin	716 (484 to 949)	1,041 (768 to 1,314)	1,414 (1,085 to 1,744)
On inhaled aztreonam and/or levofloxacin	599 (86 to 1,112)	1,499 (651 to 2,347)	1,833 (895 to 2,771)
Unadjusted EDC adherence			
<50%	1,325 (909 to 1,741)	2,017 (1,507 to 2,526)	2,468 (1,912 to 3,025)
50 to <80%	278 (48 to 507)	665 (304 to 1,025)	1,142 (476 to 1,808)
≥80%	79 (0 to 165)	183 (29 to 338)	379 (129 to 630)

[†] **Estimates of excess supply cost are highly conservative because of contingency**, see 'Discussion' paragraph 6. Excess supply cost was calculated as the cost of excess medicine box(es) delivered or collected after accounting for the discrepancy between EDC adherence and dwcMPR with 20% contingency. For example, if a person has an excess supply of 83 aztreonam nebules, the excess supply cost was calculated as "0" because each box of aztreonam has 84 nebules.

[‡] These are the results as displayed in Table 2 of the main manuscript. The results for excess supply cost based on the assumption that all medicine types were equally used are included here for comparison with lowest and highest excess supply cost.

APPENDIX C TABLE 2: Summary of lowest and highest excess supply cost results from linear regression models

Variable	Linear regression models for lowest excess supply cost in £		Linear regression models for 'average' excess supply cost in £[Ω]		Linear regression models for highest excess supply cost in £	
	Regression coefficient (95% CI)	P-value	Regression coefficient (95% CI)	P-value	Regression coefficient (95% CI)	P-value
Univariate analysis[†]						
Unadjusted EDC adherence[A]	–633 (–856 to –410)	<0.001	–928 (–1,208 to –648)	<0.001	–1,052 (–1,382 to –721)	<0.001
Age <19 years or >25 years (reference)						
Age 19 to 25 years	1,026 (601 to 1,451)	<0.001	1,210 (663 to 1,756)	<0.001	1,655 (1,021 to 2,289)	<0.001
Only on inhaled mucolytic (reference)						
≥1 inhaled antibiotic	380 (–90 to 850)	0.113	789 (193 to 1,386)	0.010	1,114 (417 to 1,811)	0.002
1 medicine only (reference)						
≥2 different medicines	125 (–406 to 657)	0.644	659 (–16 to 1,334)	0.056	1,115 (327 to 1,902)	0.006
Source of recruitment						
Learning health system (reference)						
Usual care arm of the ACtiF trial	–336 (–959 to 286)	0.287	–310 (–1,088 to 467)	0.432	–115 (–967 to 740)	0.792
Intervention arm of the ACtiF trial	–546 (–1,105 to 13)	0.055	–686 (–1,390 to 18)	0.056	–515 (–1,327 to 297)	0.213
Male (reference)						
Female	–146 (–568 to 277)	0.497	–50 (–591 to 490)	0.854	37 (–598 to 673)	0.908
Not chronic *P. aeruginosa* (reference)						
Chronic *P. aeruginosa* infection	18 (–411 to 446)	0.935	201 (–346 to 749)	0.470	267 (–377 to 910)	0.415
$\%FEV_1$ <40% or ≥70% (reference)						
$\%FEV_1$ 40 to 69.9%	95 (–336 to 527)	0.664	447 (–102 to 997)	0.110	320 (–328 to 967)	0.332
≥2 medicine supply sources (reference)						
Supply from hospital only or homecare only	481 (62 to 900)	0.025	430 (–108 to 968)	0.117	299 (–336 to 933)	0.355
Neither aztreonam nor levofloxacin (reference)						
On inhaled aztreonam and/or levofloxacin	–117 (–665 to 430)	0.673	458 (–239 to 1,156)	0.197	419 (–402 to 1,241)	0.316
Multivariate analysis[‡]						
Unadjusted EDC adherence[A]	–539 (–762 to –316)	<0.001	–831 (–1,110 to –552)	<0.001	–907 (–1,231 to –583)	<0.001
Age <19 years or >25 years (reference)						
Age 19 to 25 years	801 (381 to 1,220)	<0.001	869 (345 to 1,393)	0.001	1,292 (684 to 1,901)	<0.001
Only on inhaled mucolytic (reference)						
≥1 inhaled antibiotic	445 (10 to 881)	0.045	876 (332 to 1,420)	0.002	1,222 (591 to 1,854)	<0.001

[Ω] These are the results as displayed in Table 3 of the main manuscript. The results for excess supply cost based on the assumption that all medicine types were equally used are included here for comparison with lowest and highest excess supply cost.

[†] The regression coefficients from univariate analyses are unadjusted coefficients.

[‡] The regression coefficients from multivariate analyses are adjusted coefficients. Adjusted R^2 of the multiple regression models: 0.149 for lowest excess supply cost; 0.186 for excess supply cost based on the assumption that all medicine types were equally used; 0.207 for highest excess supply cost.

[A] As explained in the footnote of main manuscript Table 3, EDC adherence category was analysed as an ordinal variable because there was a step-wise reduction in excess supply cost with increasing level of adherence category.

Second, regression analyses in the main manuscript were repeated using the lowest and highest excess supply cost separately as the dependent continuous variables. EDC adherence level and age 19–25 years were also independently associated with lowest and highest excess supply cost (Appendix C Tables 2). All else being equal, an increase in one level of adherence category (e.g. from <50% to 50–79%) was associated with a decrease of £539 (95% CI £316–762) in the lowest excess supply cost.

These sensitivity analyses highlights the fact that even in the best case scenario with an unrealistically low estimate of excess supply cost, incorporating a comprehensive EDC system in medicine supply chain is still likely to generate savings. In Appendix B, we estimated that potential annual savings among adults with CF in the UK exceeded £5.7 million based on an excess supply cost of £2,017/patient/year. That excess supply cost was based on the assumption that all medicine types were equally used. If we use the lowest excess supply cost of £1,325/patient/year among those with EDC adherence <50% and the other parameters used in Appendix B (6,500 adults with CF in the UK with ≥70% of them on inhaled therapy [2] and a cost of around £770/patient/year), there is still potential annual savings of around £2.5 million.

References

1. White H, Shaw N, Denman S, Pollard K, Wynne S, Peckham DG. Variation in lung function as a marker of adherence to oral and inhaled medication in cystic fibrosis. Eur Respir J 2017;49:1600987.
2. UK Cystic Fibrosis Registry. Annual data report 2019. Published August 2020. https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources. Date last accessed: December 18 2020.