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Corrigendum

Corrigendum to "Using a learning health system to understand the mismatch between medicines supply and actual medicines use among adults with cystic fibrosis" [J Cyst Fibros (2022), 21/2, 323-331]

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The authors regret an error has occurred in the description and calculation of dose-weighted composite MPR (dwcMPR) for participants on multiple medicines. We described dose-weighting according to the number of *dispensed* inhaled medications. In fact, the dose-weighting should be based on the number of *prescribed* inhaled medications to ensure there is no gap between the cMPR and electronic data capture (EDC) adherence if someone has indeed used all the medicines that were supplied. Therefore, the first step to calculate dwcMPR should have been: calculate the total prescribed doses of medicine by adding up of all individual values of daily prescribed dose × days.

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

	Results
Discrepancy between dwcMPR and EDC adherence	
Median (IQR)	9% (−2 to 21%)
Mean (95% CI)	10% (7 to 13%)
Discrepancy between dwcMPR and EDC adherence in different adherence levels	
EDC adherence <50%, Median (IQR)	15% (6 to 30%)
EDC adherence 50 to <80%, Median (IQR)	5% (−9 to 17%)
EDC adherence ≥80%, Median (IQR)	2% (−11 to 11%)
Discrepancy between dwcMPR with 20% contingency and EDC adherence	
Median (IQR)	−2% (−16 to 14%)
Mean (95% CI)	−1% (−4 to 3%)
Excess supply cost in £ for the overall cohort	
Median (IQR)	0 (0 to 760)
Mean (95% CI)	822 (587 to 1,057)
Excess supply cost in £ according to the source of recruitment, mean (95% CI)	
Learning health system	1,201 (590 to 1,812)
Usual care arm of the ACtiF trial	713 (446 to 979)
Intervention arm of the ACtiF trial	583 (313 to 853)
Excess supply cost in £ according to age categories, mean (95% CI)	
≤18 years	594 (96 to 1,091)
19 to 25 years	1,515 (977 to 2,055)
26 to 34 years	447 (236 to 658)
≥35 years	409 (0 to 831)
Excess supply cost in £ according to gender, mean (95% CI)	
Male	908 (522 to 1,293)
Female	731 (467 to 996)
Excess supply cost in £ according to *P. aeruginosa* status, mean (95% CI)	
Not chronic	732 (427 to 1,037)
Chronic infection	886 (545 to 1,227)
Excess supply cost in £ according to %FEV_1 categories, mean (95% CI)	
<40%	704 (219 to 1,188)
40 to 69.9%	917 (564 to 1,270)
≥70%	767 (351 to 1,183)
Excess supply cost in £ according to source of inhaled medicine supply, mean (95% CI)	
Hospital	1,020 (504 to 1,536)
Homecare only	1,086 (644 to 1,527)
≥2 supply sources	559 (230 to 887)
Excess supply cost in £ according to number of inhaled medicines, mean (95% CI)	
1 medicine only	595 (319 to 870)
≥2 different medicines	878 (593 to 1,163)
Excess supply cost in £ according to prescription of inhaled antibiotics, mean (95% CI)d	
Only on inhaled mucolytic	452 (246 to 658)
≥1 inhaled antibiotic	964 (649 to 1,278)
Excess supply cost in £ according to use of expensive antibiotics, mean (95% CI)	
Neither inhaled aztreonam nor levofloxacin	819 (564 to 1,074)
On inhaled aztreonam and/or levofloxacin	836 (215 to 1,457)
Excess supply cost in £ according to unadjusted EDC adherence, mean (95% CI)	
<50%	1,540 (1,078 to 2,001)
50 to <80%	422 (125 to 718)
≥80%	82 (15 to 148)

[†] **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 MPR data. Further explanation for the skewed MPR data is provided in Table S3.

We have now re-calculated the relevant values for the difference between dwcMPR and unadjusted EDC adherence, and the cost of excess supply using this method. We have also repeated the relevant analyses. A summary of the updated results are as follow:

1. Table 1 (demographics) – Median % dwcMPR 67 (IQR 39 to 91)
2. Figure 1 (Bland-Altman plot of dwcMPR versus EDC adherence) – Mean difference 10% (limits of agreement -38% to 59%). An updated Figure 1 is attached.
3. Table 2 (dwcMPR versus EDC adherence discrepancy and excess supply cost) – Discrepancy median 9% (IQR -2% to 21%). Mean excess supply cost for overall cohort £822 (95% CI £587 to £1057). The total excess supply cost was £226,104 among the 275 adults. An updated Table 2 is attached.
4. Table 3 (results from linear regression models) – With excess supply cost in £ as the outcome, the unadjusted regression coefficient for unadjusted EDC adherence was -739 (95% CI -986 to -491) and the adjusted regression coefficient was -660 (95% CI -908 to -410). Similar to the initial analyses, excess supply cost was higher among those with EDC adherence <50%, aged 19-25 years and on inhaled antibiotics rather than mucolytics only. An updated Table 3 is attached.

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]	−739 (−986 to −491)	<0.001	−660 (−908 to −411)	<0.001
Age <19 years or >25 years [B] (reference)				
Age 19 to 25 years	1,072 (595 to 1,548)	<0.001	790 (324 to 1,256)	<0.001
Only on inhaled mucolytic [‡] (reference)				
≥1 inhaled antibiotic	476 (−38 to 990)	0.069	586 (111 to 1,062)	0.016
1 medicine only (reference)				
≥2 different medicines	283 (−309 to 876)	0.347		
Source of recruitment				
Learning health system (reference)				
Usual care arm of the ACtiF trial	−488 (−1,166 to 191)	0.158		
Intervention arm of the ACtiF trial	−618 (−1,251 to 16)	0.056		
Male (reference)				
Female	−177 (−648 to 295)	0.526		
Not chronic *P. aeruginosa* (reference)				
Chronic *P. aeruginosa* infection	154 (−324 to 632)	0.470		
$\%FEV_1$ <40% or ≥70% [C] (reference)				
$\%FEV_1$ 40 to 69.9%	157 (−325 to 638)	0.552		
≥2 medicine supply sources [D] (reference)				
Supply from hospital only or homecare only	504 (35 to 972)	0.035		
Neither aztreonam nor levofloxacin (reference)				
On inhaled aztreonam and/or levofloxacin	17 (−594 to 628)	0.956		

[†] Results exclude nine participants with skewed MPR data. Further explanation for the skewed MPR data is provided in Table S3.
[‡] Adjusted R^2 of the multiple regression model = 0.155. Unadjusted EDC adherence category and age category were included in the multiple regression analysis because both covariates reached statistical significance in the univariate analysis. Prescription of inhaled antibiotic were also included as a covariate because those prescribed inhaled antibiotics have substantially higher EDC adherence level compared to those who were not (median 61%, IQR 26–86% vs median 45%, IQR 13–83%, Mann-Whitney p-value 0.042). Therefore the lack of statistical significance in the univariate analysis of inhaled antibiotics prescription was simply due to confounding by adherence level rather than a genuine lack of association. This result is in keeping with the result for lowest excess supply cost in Appendix C Table 2.
[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 £739 (95% CI £491–986) in excess supply cost. For the multivariate analysis, an increase in one level of adherence category was associated with a decrease of £660 (95% CI £411–908) 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. In an exploratory multiple regression analysis accounting for EDC adherence level and age 19–25 years, source of inhaled medicine supply was not associated with excess supply cost in £ (adjusted regression coefficient of 432, 95% CI -6 to 869, p-value 0.053. The source of inhaled medicine supply reached statistical significance in the univariate analysis because those receiving supply from a single source have somewhat lower EDC adherence level compared to those receiving supply from ≥2 sources (median 48%, IQR 19–84% vs median 64%, IQR 28–87%, Mann-Whitney p-value 0.064).

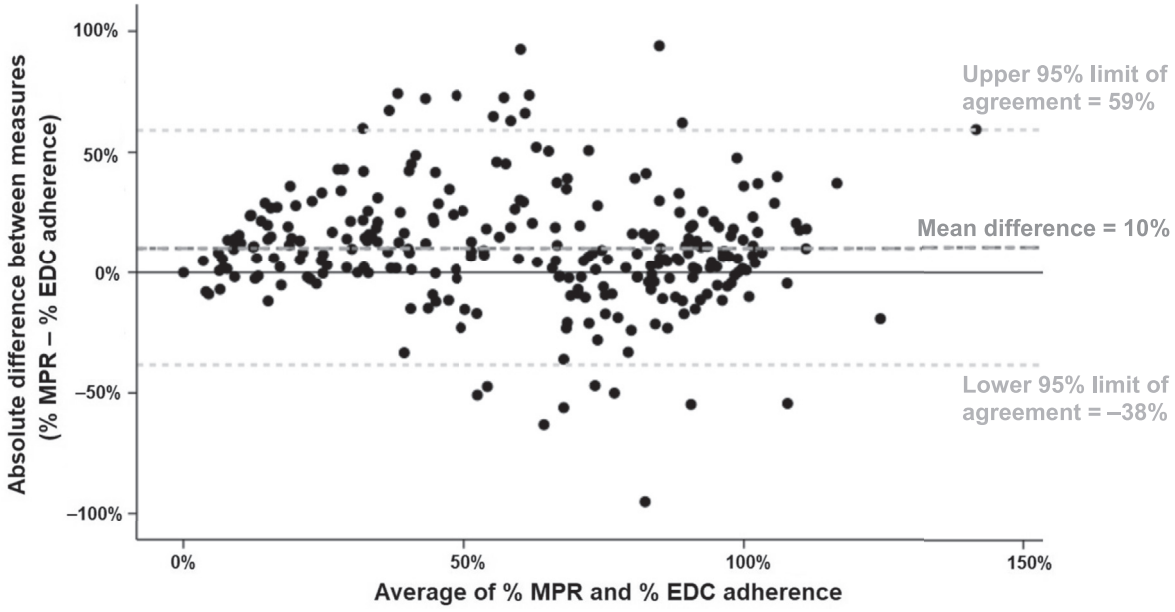

Figure 1. Bland-Altman plot for dwcMPR versus unadjusted EDC adherence, excluding skewed MPR data (N = 275) †.
[†] Nine participants with skewed MPR data (three with excessive supply of bronchodilator, three with excessive supply of hypertonic saline, two with excessive supply of antibiotic and one with inadequate antibiotic supply) were excluded from this plot. Further explanation for the skewed MPR data is provided in Table S3.

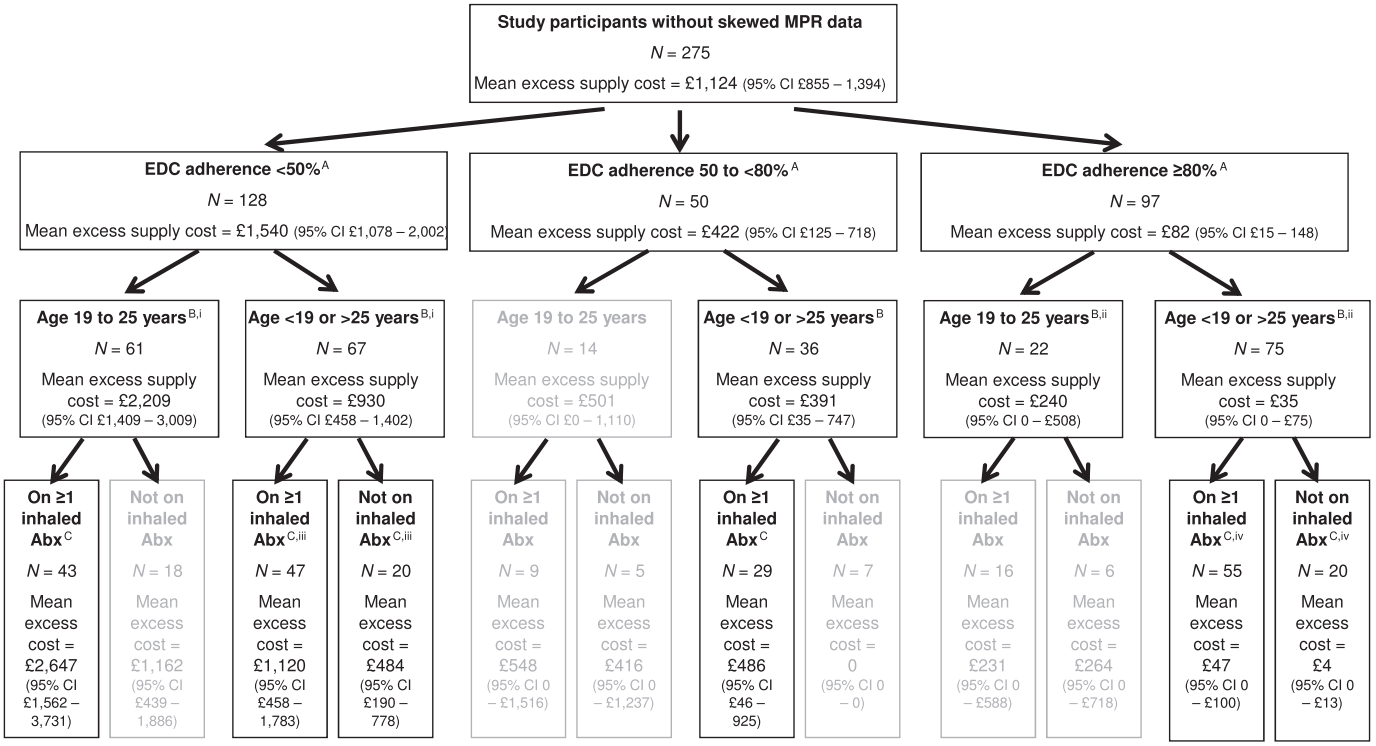

Figure 2. Tree-based diagram † summarising excess supply cost ‡ according to different subgroups Ω.

† 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 MPR data. Further explanation for the skewed MPR data is provided in Table S3. 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 i T-test p-value = 0.007 ii T-test p-value = 0.130.

C For the comparison of excess supply cost between six subgroups with sample size ≥20 in this 'layer', ANOVA p-value was <0.001 iii T-test p-value = 0.081 iv T-test p-value = 0.346.

5. Figure 2 (tree-based analysis) – Similar to the initial analyses, excess supply cost was higher among those with EDC adherence <50%, aged 19-25 years and on inhaled antibiotics rather than mucolytics only. An updated Figure 2 is attached.
6. Appendix A (participants with skewed MPR data) – the details for skewed MPR data and the values of dwcMPR, 'standard' composite MPR (i.e. a mean of all individual MPR) and unadjusted EDC adherence are now tabulated in Table S3 (attached). Where MPR data were skewed, EDC adherence is more similar to dwcMPR compared to 'standard' cMPR.

In Appendix C, we calculated the minimum excess supply cost based on the assumption that more expensive medications were used first and maximum excess supply cost based on the assumption that cheaper medications were used first. The minimum and maximum excess supply costs were calculated directly from the total doses of supplied medications without the need to calculate a composite MPR. Therefore, the results in Appendix C are unaffected.

Overall, the reduction in excess supply cost (mean £822, 95% CI £587-1057 with the revised method vs mean £1124, 95% CI £855-1394 with the method as originally described) does not alter the conclusions of the paper. MPR provides information about medicine supply but over-estimates actual medicine use. The excess supply cost was highest among those with lowest EDC adherence. Our study provides a conservative estimate of excess inhaled medicines supply cost among adults with CF in the UK. Importantly, the lowest excess supply cost of £1,325/patient/year among those with EDC adherence <50%, suggests there are potential annual savings of around £2.5 million.

The authors would like to apologise for any inconvenience caused.

Table S3
Details of participants with skewed MPR data; and a comparison between unadjusted EDC adherence, dwcMPR and 'standard' cMPR.

Details of skewed MPR data †	Unadjusted EDC adherence	dwcMPR	'Standard' cMPR
Person #1 – 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%.	90%	115%	142%
Person #2– salbutamol prescription was for only 20 days but 12 months of supplies (48 boxes) were delivered, hence MPR for salbutamol was >2000%.	78%	90%	445%
Person #3 – salbutamol prescription was for only 30 days but 6 months of supplies (27 boxes) were delivered, hence MPR for salbutamol was 900%.	73%	119%	278%
Person #4 – MPR for hypertonic saline was 190%.	2%	139%	139%
Person #5 – MPR for salbutamol was 99% compared to MPR for hypertonic saline of 5%.	33%	30%	52%
Person #6 – MPR for dornase alfa was 36% compared to MPR for colistimethate of 6%.	5%	18%	21%
Person #7– unable to find evidence for the supply of piperacillin-tazobactam post hospital admission although the prescription was continued, hence MPR for piperacillin-tazobactam was only 5%.	19%	56%	55%
Person #8 – tobramycin prescription was stopped after 2 days but one box was supplied, hence MPR for tobramycin was 1400%.	24%	76%	297%
Person #9 – this person was only prescribed colistin for 18 days but on-going supply resulted in an MPR of 570% for colistin.	39%	57%	203%

† The skewed (i.e. excessively high or excessively low) MPR reflect the fact that on occasion, lack of system optimisation in medicine management can create quite marked over-supply. Most of the excessively skewed MPR occurred in short-term prescriptions, for example a salbutamol prescription for only 20 days in Person #2. In the extant CF literature, composite MPR (cMPR) is calculated simply as a mean of all individual MPR [1,2]. That means the skewed individual MPR data can have a disproportionate impact on the cMPR. For example, salbutamol MPR of >2000% for Person #2 resulted in 'standard' cMPR of 445%. With dose-weighting, short-term prescriptions by the virtue of fewer prescribed doses are given a lower weight compared to longer-term prescriptions. For example, the salbutamol for Person #2 was only given a weight of 0.021 (out of 1.000) because five other medications were prescribed for longer durations (dornase alfa for 365 days, colistimethate for 162 days, hypertonic saline for 365 days, tobramycin for 141 days and aztreonam lysine for 40 days). As a result, dwcMPR is more resistant to skewed MPR data and more accurately reflect the overall amount of supplied medications.

References

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