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Development of data processing algorithm to calculate adherence for adults with cystic fibrosis using inhaled therapy – A multi-center observational study within the CFHealthHub Learning Health System

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1 **Development of data processing algorithm to calculate**

2 **adherence for adults with cystic fibrosis using inhaled therapy -**

3 **A multi-center observational study within the CFHealthHub**

4 **Learning Health System**

5 **1. Introduction**

6
7 Digital measures utilizing real-world patient data can be used in routine care or
8 as endpoints in clinical trials. Compared to traditional endpoints captured in
9 clinical settings, digital endpoints may offer greater insights into real-life patient
10 experiences that are not reliably captured in the clinical setting (1).

11
12 Adherence can be described as the extent to which a person follows healthcare
13 provider recommendations, such as taking medicine (2). Low adherence to
14 prescribed medicine in long-term conditions is a key contributor to suboptimal
15 clinical benefits and worse health outcomes (2, 3). Electronic adherence
16 monitoring devices enable adherence to function as a digital measure which offers
17 greater objectivity than alternatives, such as self-report (4-6).

18
19 Cystic fibrosis (CF) is an archetypal long-term condition where life expectancy is
20 approximately 50 years, driven by respiratory failure, resulting from chronic lung
21 inflammation and recurrent infection (7, 8). Most adults with CF are prescribed
22 medicine regimens including multiple daily doses of inhaled therapy, usually
23 delivered by an electronic nebulizer device. Higher adherence to inhaled therapy
24 is associated with better outcomes but real-world adherence is low at <40% (5, 9-
25 11).

26
27 CFHealthHub is a UK-based multi-center Learning Health System. A Learning
28 Health System is described as “a health system in which outcomes and experience
29 are continually improved by applying science, informatics, incentives and culture
30 to generate and use knowledge in the delivery of care”(12)

31

1
2
3 32 CFHealthHub centers have access to the cloud-based CFHealthHub digital
4
5 33 platform which continuously captures and displays adherence data from
6
7 34 nebulizer devices. This platform can be accessed by clinicians and adults with CF
8
9 35 at all times. Certain clinicians within each CFHealthHub center are also trained to
10
11 36 deliver a behavioural intervention which supports adults with CF to improve
12
13 37 adherence through habit formation (13, 14). CFHealthHub increased percent
14
15 38 adherence to inhaled therapy and reduced perceived treatment burden in a 607-
16
17 39 participant randomized controlled trial (RCT) (15). CFHealthHub is now active in
18
19 40 over 50% of adult CF centers in England, as an evidence-based digital platform
20
21 41 and behavioural intervention, which empowers adults with CF to self-manage
22
23 42 their condition. A recent report from The Health Foundation recognized
24
25 43 CFHealthHub as the only condition-based, full Learning Health System with
26
27 44 national reach in the UK, and is an exemplar for other long-term conditions (16).

26 45
27
28 46 The CFHealthHub digital platform requires the ability to accurately measure
29
30 47 objective adherence data from nebulizer devices with electronic data capture
31
32 48 (EDC) capability. The CFHealthHub digital platform is device agnostic, and
33
34 49 compatible with both of the EDC-capable nebulizer devices used in the UK, the I-
35
36 50 neb Adaptive Aerosol Delivery (AAD) System (Philips Respironics, Chichester, UK)
37
38 51 and eFlow Technology nebulizers with an eTrack data-logging Controller (PARI
39
40 52 Pharma GmbH, Starnberg, Germany), subsequently referred to as “eTrack
41
42 53 nebulizers”. AAD devices, such as the I-neb, can accurately determine whether a
43
44 54 dose is completely administered, as aerosolized medicine is only released on
45
46 55 breath activation of the user. Non-AAD devices, such as the eTrack nebulizer, do
47
48 56 not have this functionality and therefore require data processing algorithms to
49
50 57 determine completeness of the dose delivery with accuracy. Therefore, this work
51
52 58 focuses on data from eTrack nebulizers only. The component parts of the eTrack
53
54 59 nebulizer, referred to throughout this article, are shown in Figure 1.

52 60
53
54 61 To ensure accurate calculation of percent adherence, the nebulizer data must be
55
56 62 processed to count the number of doses of medicine which have been delivered
57
58 63 ‘completely’ each day. This figure, produced for each day, is referred to as the
59
60 64 “daily complete dose count”. Each time a dose of medicine is initiated via an

1
2
3 65 eTrack nebulizer, a log is created with the timestamp, duration of the dose, and a
4
5 66 numeric code (known as an interruption code) recording whether the dose was
6
7 67 considered 'complete' or not (Table 1). An interruption code of "4" denotes a
8
9 68 'complete' dose. Alternative interruption codes suggest the dose may have been
10
11 69 'incomplete'. For example, an interruption code of "1" suggests the dose was
12
13 70 interrupted due to loss of power supply to the eTrack nebulizer controller. Most
14
15 71 medicines delivered via an eTrack nebulizer are expected to take between 2-8
16
17 72 minutes to complete, therefore, all doses with a very short duration (<60s) are
18
19 73 likely 'incomplete' (Personal Communication, Dr C Fuchs, PARI GmbH, Email, Jan
20
21 74 2021).

22
23 76 The method of processing doses with varying duration and interruption codes can
24
25 77 result in different "daily complete dose counts". The example presented in
26
27 78 Appendix A demonstrates that the data processing algorithm must be carefully
28
29 79 considered, to accurately reflect the true "daily complete dose count". It is possible
30
31 80 for a singular dose to be misclassified, but the algorithm still yields an accurate
32
33 81 "daily complete dose count" as explained in Appendix 1. During the CFHealthHub
34
35 82 RCT, nebulizer data were processed using an algorithm based on expert advice
36
37 83 from PARI GmbH (15). This involved considering all doses with duration ≥ 60 s, and
38
39 84 an interruption code of 2 (indicating disconnection of the aerosol head from the
40
41 85 eTrack controller) or 4 (indicating that the dose completed as expected) as
42
43 86 'complete'. The algorithm excluded the following doses from the "complete daily
44
45 87 dose count":

- 46 88 • all duplicate doses, based on start time, duration, and interruption code,
- 47 89 • all doses of duration less than 60 seconds,
- 48 90 • all doses with interruption code 3 (suggesting there was no medicine in the
- 49 91 device at the initiation of the dose),
- 50 92 • all doses conducted in the *EasyCare* cleaning mode (identified by an
- 51 93 interruption code >100),
- 52 94 • all doses with a date of "01JAN2015" (suggesting device corruption).

53
54
55 95 After exclusions, the following doses are combined in calculating the "daily
56
57 96 complete dose count".

1
2
3 97 • all doses which were interrupted due to power failure or pre-set timeout
4
5 98 (based on interruption codes 1,5,6,7,8) and duration ≥ 60 s would be
6
7 99 classified as partial dose, contributing 0.5 to the “daily complete dose
8
9 100 count”. If the subsequent dose is started within 1500s and had an
10
11 101 interruption code of 2 (cable disconnection) or 4 (dose complete as
12
13 102 expected), then these two doses would be combined to give 1 complete
14
15 103 dose.
16
17 104

17 105 There is ongoing, real-world learning in the CFHealthHub Learning Health System,
18
19 106 where many more adults are using eTrack nebulizers. Approximately 6% of all
20
21 107 doses recorded on the CFHealthHub digital platform had a duration of < 60 s and
22
23 108 24.5% were potentially ‘incomplete’, as per the interruption code, in the 12
24
25 109 months prior to this work. The most accurate method of processing data from
26
27 110 these doses is uncertain and requires stronger evidence than advice from the
28
29 111 manufacturer.
30
31 112

31 113 The objectives of this sub-analysis within CFHealthHub were: first, to understand
32
33 114 how doses could be identified as ‘complete’ based on their duration and
34
35 115 interruption code. Second, by triangulating eTrack nebulizer data with
36
37 116 participants’ records of taking each dose, to develop and validate a data processing
38
39 117 algorithm to optimize the accuracy of the “daily complete dose count” used in
40
41 118 percent adherence calculations. These objectives align with the key aim of
42
43 119 developing the CFHealthHub digital platform as one which maximizes the salience
44
45 120 of adherence data and may also serve as an exemplar for other platforms
46
47 121 capturing digital adherence data remotely.
48
49 122

50 123 2. Participants and Methods

51 124
52 125 In this sub-analysis, data collected from eTrack nebulizers were triangulated
53
54 126 against real-world records, created by adults with CF, of what happened during
55
56 127 each dose. Participants were all eTrack nebulizer users who had consented to the
57
58 128 CFHealthHub Learning Health System. Regulatory approval was provided by the
59
60 129 London-Brent Research Ethics Committee (Reference number: 17/LO/0032).

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3 130
4

5 131 This analysis included adults with CF who had ≥ 20 nebulizer doses that were
6
7 132 either < 60 s in duration or potentially 'incomplete', as per their interruption code.
8
9 133 There were no previous data to inform a target sample size. Since approximately
10
11 134 30% of doses were expected to be of short duration or potentially 'incomplete',
12
13 135 300 doses was chosen as a pragmatic target to provide 100 doses of interest,
14
15 136 which should encompass an adequate range of different interruption codes. Due
16
17 137 to constraints in clinical resources, the plan was to enrich the sample with the
18
19 138 doses of interest (short duration and/or potentially 'incomplete') so that an
20
21 139 adequate range of different interruption codes can be covered over a short time
22
23 140 duration. Therefore, purposive sampling was used to identify participants with a
24
25 141 particularly high number of doses of interest (≥ 20 doses of interest per week),
26
27 142 such that 10 participant-weeks of data each for derivation and validation datasets
28
29 143 was determined as sufficient.
30
31 144

32
33 145 Participants were included from three centers which are part of the CFHealthHub
34
35 146 Learning Health System. These centers were selected due to the relatively high
36
37 147 prevalence of eligible participants and the availability of clinicians to complete
38
39 148 this work. Approximately 8,000 doses from the CFHealthHub digital platform
40
41 149 were screened between 15th October 2021 and 31st October 2021 (two weeks
42
43 150 prior to the sub-analysis start date). Data collection was between 1st November
44
45 151 2021 and 15th December 2021.
46
47 152

48
49 153 Local clinicians approached eligible adults with CF from these three centers using
50
51 154 a standardized script to facilitate the initial discussion (Appendix B). In the first
52
53 155 telephone call, participants were informed about this work and invited to provide
54
55 156 verbal consent to participation. If they agreed, a longer call was arranged at a
56
57 157 future time to discuss their nebulizer data.
58
59 158

60

159 *2.1 Phase 1 (data calibration)*

160

161 Once relevant participants were identified for inclusion in this analysis local
162
163 clinicians were provided with a log of each participant's nebulizer data for the

1
2
3 163 preceding week, extracted from the CFHealthHub digital platform. These data
4
5 164 included the timestamp, duration, and interruption code for each recorded dose.
6
7 165 To mitigate recall bias, clinicians used these data to help prompt participant recall
8
9 166 of 1) the time the dose was started, 2) the medicine used for each dose, 3) if they
10
11 167 considered the dose 'complete' or not, and 4) if relevant, a reason why the dose
12
13 168 was considered '(in)complete'. Discussions around nebulizer usage are part of
14
15 169 routine clinical care in CF and the data used to inform these discussions is
16
17 170 available to all clinicians providing care to adults with CF enrolled in the
18
19 171 CFHealthHub Learning Health System on request.
20

21 172
22 173 The clinician and participant reached consensus as to whether each nebulizer
23
24 174 dose was likely to have been 'complete'. For example, the participant recognising
25
26 175 an appropriate residual volume of the medicine in the medication reservoir
27
28 176 suggests the dose was 'complete' even though the eTrack nebulizer had not
29
30 177 recognized the dose as complete. Clinicians then asked participants to keep a
31
32 178 record of their nebulizer usage for prospective data collection in Phase 2.
33
34 179 Participants were asked to record the name of the medicine being nebulized and
35
36 180 the date and time the dose was started. They were also asked to note anything
37
38 181 remarkable about that dose, for example if they experienced a power failure or
39
40 182 disruption, and if they considered the dose to be 'complete'. A follow-up call was
41
42 183 then arranged with each participant to review their prospective record.
43

44 184
45 185 The purpose of Phase 1 was to familiarize participants with the process of
46
47 186 discussing their nebulizer usage and to consider ways of determining whether a
48
49 187 dose was 'complete', in preparation for the prospective data collection. Data from
50
51 188 Phase 1 were not used in the analysis.
52

53 189 54 190 *Phase 2 (prospective data collection)*

55 191
56 192 Clinicians contacted participants at the agreed time to review 1-2 weeks of
57
58 193 nebulizer data, extracted from the CFHealthHub digital platform, as described in
59
60 194 Phase 1. These data were discussed with the participant and triangulated with
195
196 195 their record of the corresponding doses, which the clinicians then cross-checked

1
2
3 196 against the nebulizer data. Clinicians completed a data collection form using
4
5 197 Microsoft Excel (version 16.62). As in Phase 1, the clinician and participant
6
7 198 reached consensus as to whether each recorded dose was considered ‘complete’
8
9 199 or not, along with a brief description, e.g., “participant reported their device timed-
10
11 200 out after 20 minutes”. An example of a completed data collection form is shown in
12
13 201 Figure 2.

14 202

15 203 Following collection, the prospective data were divided into derivation and
16
17 204 validation sets, prior to any analysis being undertaken. Therefore, clinicians were
18
19 205 not aware of the resultant algorithm at the time of data collection. For participants
20
21 206 providing two separate weeks of data, one week of data was allocated to
22
23 207 derivation and the other week’s data to validation. This was done to ensure both
24
25 208 datasets contained an adequate range of interruption codes, given the small
26
27 209 number of participants (n=12) and doses (approximately 300 in each data set).

28 210

29 211 Researchers reviewed the derivation dataset, consisting of nebulizer data (date &
30
31 212 time, duration, and interruption code for each dose), and whether the dose was
32
33 213 considered ‘complete’ by the clinician-participant consensus, with associated free
34
35 214 text comments where available. First, all doses with duration of <60s were
36
37 215 reviewed. Next, all doses with duration ≥60s were stratified by the interruption
38
39 216 code listed in Table 1, and each resultant group was reviewed separately. With
40
41 217 this information, an algorithm to calculate a “daily complete dose count” from the
42
43 218 nebulizer data was developed, which used dose start time, duration, and
44
45 219 interruption code only, to determine if a dose was likely to be ‘complete’. Appendix
46
47 220 C contains a full description of the number of doses in each combination of
48
49 221 duration and interruption code, with a justification for how the algorithm would
50
51 222 process these combinations, based on the triangulated nebulizer data and
52
53 223 consensus “daily complete dose count”. If a dose was likely to be ‘complete’, then
54
55 224 it would be included and counted as a ‘complete’ dose, however if it was likely to
56
57 225 be ‘incomplete’, it would be excluded or combined with another dose to create a
58
59 226 single ‘complete’ dose.

60 227

1
2
3 228 The agreement between algorithm-derived “daily complete dose count” and
4
5 229 consensus-derived “daily complete dose count” in the derivation dataset were
6
7 230 determined using both percent accuracy and kappa values. In view of the clustered
8
9 231 nature of the dataset, bootstrapping was used to calculate kappa and agreement
10
11 232 values (17). This involved bootstrapping of 1000 samples from the original
12
13 233 dataset, calculation of kappa and agreement values for each sample (i.e. 1000
14
15 234 values were calculated for each participant) and then ascending re-order of those
16
17 235 values to provide a median, 2.5th and 97.5th centile as measures of central
18
19 236 tendency and dispersion. In addition, the extent to which the algorithm under- or
20
21 237 over-estimated the consensus-derived “daily complete dose counts” were
22
23 238 quantified with absolute differences in both “daily complete dose counts” and
24
25 239 percent adherence between the two measures.

240

26 241 An a-priori target was to proceed to validation if the algorithm-derived “daily
27
28 242 complete dose count” was $\geq 80\%$ accurate in comparison to the consensus-derived
29
30 243 “daily complete dose count”, which was considered as the ‘reference standard’. If
31
32 244 the accuracy was $< 80\%$, then the derivation dataset would be re-reviewed to
33
34 245 refine the algorithm.

246

247 3. Results

248

249 Twenty-two adults with CF receiving care in Center 1 (n=8), Center 2 (n=8) and
250
251 Center 3 (n=6) were identified as potentially eligible for inclusion.

251

252 Eight of these 22 adults were excluded after approach, and two excluded after
253
254 review of their nebulisation data prior to Phase 2. Twelve participants were
255
256 included in the analysis. Their baseline characteristics are shown in Table 2. The
257
258 flow of recruitment, reasons for exclusion and allocation are shown in Figure 3.

256

257 One week of data from 10 participants comprised the derivation dataset, with one
258
259 week of data from 10 participants comprising the validation dataset. Eight of the
260
261 12 participants contributed data to both derivation and validation sets, as they

1
2
3 260 each provided two weeks of data, compared to the four other participants,
4
5 261 contributing one week of data each who were assigned to either the derivation or
6
7 262 validation datasets in a 1:1 ratio. A total of 74 patient days (with 295 doses) from
8
9 263 10 patients were used in the derivation dataset and 69 patient days (with 309
10
11 264 doses) from 10 patients in the validation dataset. Dose durations and interruption
12
13 265 codes for the derivation dataset were reviewed and results are reported in Table
14
15 266 3.

16 267

17 268 *3.1 Proposed screening algorithm*

18
19 269 We proposed the following process for identifying ‘complete’ doses from the
20
21 270 nebulizer data.

22
23 271

24 272 1) Initially screen out:

- 25
26 273 • All doses with duration <60s.
- 27
28 274 • All doses that had a timeout during pause mode (interruption code = 8).
- 29
30 275 • All doses in cleaning mode (interruption code = 101-108).

31
32 276

33 277 2) Combine

- 34
35 278 • Any 2 or more doses starting within 120s of each other.

36
37 279

38
39 280 3) Finally screen out:

- 40
41 281 • Doses with duration <480s due to loss of supply voltage or battery power
42
43 282 to the eTrack nebulizer (interruption code = 1 or 6).

44
45 283

46
47 284

48 285 *3.2 Accuracy of the proposed screening algorithm*

49 286 In the derivation dataset, there was a high level of agreement between the
50
51 287 algorithm-derived “daily complete dose count” and the consensus-derived “daily
52
53 288 complete dose count”. The kappa co-efficient was 0.85 with 95% confidence
54
55 289 interval of 0.71-0.91 and accuracy was 87.5% (77.0-95.7). Similar agreement and
56
57 290 accuracy were seen in the validation dataset (kappa co-efficient 0.86 [0.77-0.94],
58
59 291 accuracy 89.9% [84.3-95.5]). These results along with the total numbers of doses
60
292 considered ‘complete’ by both the algorithm and consensus are reported in Table

1
2
3 293 4. The absolute differences in “daily complete dose count” between these two
4
5 294 measures were 10 (out of 266 ‘complete’ doses by consensus) in the derivation
6
7 295 dataset and 7 (out of 267 ‘complete’ doses by consensus) in the validation dataset.
8
9 296 The absolute differences in mean percent adherence calculated using the “daily
10
11 297 complete dose count” from these two measures were 3.2% and 2.8% respectively,
12
13 298 as reported in Table 5.
14
15 299

16 17 300 4. Discussion

18 301
19 302 Through examination of nebulizer data and triangulation of these data with
20
21 303 participant records, we have developed an algorithm to generate a “daily complete
22
23 304 dose count”. This algorithm involved excluding all doses of <60s, combining doses
24
25 305 which start within 120s of each other and then using a combination of the
26
27 306 interruption code and dose duration to determine which other doses are likely to
28
29 307 be ‘complete’. The resultant “daily complete dose count” was 87.5% accurate in
30
31 308 the derivation dataset and 89.9% accurate in an internal validation dataset.
32

33 309
34 310 By outlining the process for designing and validating a data processing algorithm
35
36 311 in collaboration with adults with CF, we aim to inspire trust in adherence data
37
38 312 from the CFHealthHub digital platform as a digital measure. At a patient-level,
39
40 313 adherence data from the CFHealthHub digital platform is central to the
41
42 314 development of personalized care plans, an essential part of caring for people with
43
44 315 long term conditions (18). A tangible benefit of the greater objectivity is that
45
46 316 actual pattern of nebulizer use can be understood by clinicians, who can then
47
48 317 provide personalized advice on how to fit nebulizer use within the other routines
49
50 318 of the person with CF.
51

52 319
53 320 An erroneously high “daily complete dose count” risks overestimating adherence,
54
55 321 which risks then falsely reassuring both adults with CF and clinicians that
56
57 322 adherence is higher than it is. The consequence of this is that some people may be
58
59 323 under-served by the health care system by not being offered adherence support
60
324 when they could benefit from it. Furthermore, overestimating adherence may
325 result in unnecessary treatment escalation in the event of clinical deterioration.

1
2
3 326 Conversely, underestimating adherence could create conflict between adults with
4 327 CF and their clinicians and lead to both parties losing faith in the adherence data
5 328 available on the CFHealthHub digital platform.
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9 329

10 330 We recognize that the algorithm produced a marginally higher “daily complete
11 331 dose count” than the participant-clinician consensus, which was considered the
12 332 ‘reference standard’ in this project. However, the difference in percent adherence
13 333 derived from the “daily complete dose count” (around 3% against an average
14 334 adherence exceeding 90%) was clinically negligible. It is worth noting that a
15 335 participant-clinician consensus for whether each dose of treatment is ‘complete’
16 336 is not feasible outside of a dedicated research project. It would be unreasonably
17 337 burdensome for all participants on CFHealthHub to keep a detailed daily diary of
18 338 all their nebulizer doses. Therefore, we are reassured by the small differences
19 339 noted in this study.
20
21
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28 340

29 341 Within a Learning Health System where data used to generate knowledge which
30 342 drives and measures improvement work, optimising data quality is critical (12).
31 343 Previous quality improvement work, underpinned by large datasets, has focussed
32 344 on measures of completeness, conformance and plausibility, through the
33 345 production of automated functions with statistical software (19). In this work, we
34 346 have developed an algorithm to improve calculation of “daily complete dose
35 347 counts”. This was strengthened by working alongside adults with CF to gain a
36 348 qualitative understanding of circumstances of doses, from which quantitative data
37 349 were produced.
38
39
40
41
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45 350

46 351 A key strength is that this is the first report triangulating nebulizer data with the
47 352 real-world experiences of adults with CF using eTrack nebulizers within the
48 353 CFHealthHub Learning Health System, using a parsimonious study design to
49 354 minimize the burden of adults with CF. Putting people at the center of research
50 355 into their condition is a key priority for improving care in long-term conditions
51 356 (18). Continuous patient engagement is recommended during the evaluation
52 357 phase of digital measures such as this (20, 21).
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60 358

1
2
3 359 There are however some limitations. To minimize the burden of adults with CF,
4 360 there is a need to use a parsimonious study design enriching the cohort with
5 361 participants with relatively high numbers of short or “potentially incomplete”
6 362 nebulizer doses. By applying a purposive sampling strategy within three of the 15
7 363 CFHealthHub centers, the sample of participants could be criticized as being less
8 364 generalizable. For example, the mean adherence of the sample exceeded 90%
9 365 when real-world median adherence is only around 30% (9). However, this study
10 366 design allowed us to capture an adequate range of short and/or ‘potentially
11 367 incomplete’ doses to enhance the applicability of the resultant algorithm in a
12 368 larger population.
13 369

14 370 Due to the limited number of participants imposed by scarce resources, data from
15 371 different weeks by the same participant were included in both the derivation and
16 372 validation datasets. This ensured an adequate range of interruption codes in both
17 373 datasets. Whilst no individual dose appeared in both datasets, the inclusion of the
18 374 same participant in both datasets meant that the validation dataset is not external
19 375 to the derivation dataset. Further validation of this algorithm in other
20 376 CFHealthHub centers would be useful. The fact that CF is a rare disease, with
21 377 approximately 7,000 adults with CF in the UK and the relative infrequency of
22 378 potentially incomplete doses (<25% of all doses on the CFHealthHub digital
23 379 platform) contributed to the small sample size of 12 participants and 604 doses
24 380 (22).
25 381

26 382 Another limitation was reliance on patient self-report as to which medicine was
27 383 being administered for each dose, and circumstances around doses which were
28 384 considered potentially ‘incomplete’. Currently, eTrack nebulizers lack the
29 385 technology to identify the specific medicine being administered. We also cannot
30 386 identify, from data alone, whether prolonged nebulisation duration is due to
31 387 equipment malfunction or patient factors. We mitigated potential recall bias by
32 388 prospectively asking participants to keep contemporaneous records for data
33 389 collection during the study period, rather than relying on retrospective recall. We
34 390 also cross-referenced their records against the nebulizer data. An alternate
35 391 approach of direct observation of nebulizer usage in a controlled environment

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2
3 392 would have allowed the gold standard data collection around whether a dose was
4
5 393 'complete' or not. This was considered unfeasible given the time and resource
6
7 394 burden for clinicians and participants, which is a known barrier to participation
8
9 395 in research within CF (23). Our chosen methods were parsimonious and better
10
11 396 captured the real-world experience of adults with CF using eTrack nebulizers
12
13 397 where factors such as consumable wear and dose interruptions come into play.

14 398

15 399 Finally, this study was limited to adults with CF who were using eTrack nebulizer
16
17 400 devices, which represents 88% of the approximately 1400 adults with CF who are
18
19 401 enrolled in CFHealthHub. At the time of this study, only two data-logging nebulizer
20
21 402 devices are used in the UK: eTrack nebulizer and the I-neb. As an adaptive aerosol
22
23 403 delivery device, the I-neb already provides dose completeness information in the
24
25 404 following scale: "Full"; ">12.5%; <100%"; "<12.5%" and "none". Therefore, such
26
27 405 an algorithm is not required for I-neb users.

28 406

29 407 This data processing algorithm will now be embedded within the CFHealthHub
30
31 408 digital platform, where further validation in larger and more diverse cohort is
32
33 409 recommended. These data are used to support adherence in the real-world setting
34
35 410 (24). CFHealthHub also has a research arm, currently undertaking a large
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37 411 observational study, exploring the role of co-adherence to inhaled therapy for
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39 412 adults with CF who are taking novel oral treatments (25). Digital endpoints may
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41 413 present unique challenges in the value assessment of pharmaceuticals or cost
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43 414 evaluation of consumed medications. Recognising this, CFHealthHub adherence
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45 415 data are also used to optimize medicines supply by aligning supply with actual
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47 416 usage, with the potential to realize significant cost savings (26, 27). For both of
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49 417 these workstreams to be effective, data accuracy, which is strengthened by this
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51 418 work, is critical.

52 419

53 420 Inspired by information uncovered during this work, we have since completed a
54
55 421 formal study of how these data can identify adults with CF who are having
56
57 422 frequently prolonged nebulizer durations. Troubleshooting and replacement of
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59 423 consumable parts led to mean 37% reduction in the time adults with CF spent on
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424 nebulizer treatment each day (28). This is a further demonstration of how paying

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3 425 attention to data from digital measures can have real-world benefits for people
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5 426 with long-term conditions.
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10 428 5. Conclusion

11 429
12 430 We have developed a data processing algorithm by triangulating nebulizer usage
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14 431 data with participants' real-world records, which was then tested in a multi-center
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16 432 dataset. The algorithm has high levels of accuracy. Co-designing and validating
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18 433 this algorithm helps optimize the accuracy of, and trust in, adherence data from
19
20 434 the CFHealthHub digital platform. These data can be used to optimize clinical
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22 435 interactions at a patient-level, underpin quality improvement work at an
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24 436 organisation-level and facilitate national benchmarking at a system-level. The
25
26 437 methods we use could also be applied by other platforms capturing digital
27
28 438 adherence data remotely. Publication of data processing algorithms encourages
29
30 439 confidence in Learning Health Systems embedded within routine clinical care.
31

32 441 **Declaration of Interest**

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34
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36
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38
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40
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42
43 447 entity with a financial interest in or financial conflict with the subject matter or
44
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50
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52
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54

55 454 56 455 **Article Highlights**

- 57
58 456 • Supporting adherence to medicine regimens in long-term conditions requires
59
60 457 accurate measurement of adherence.

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2
3 458 • The CFHealthHub Learning Health System offers a digital platform which can
4
5 459 collect inhaled medicine usage data from nebuliser devices capable of
6
7 460 electronic data capture.
8
9 461 • Clinicians and people with cystic fibrosis collaborated to develop a data
10
11 462 processing algorithm for these usage data to calculate the number of complete
12
13 463 doses taken each day (“daily complete dose count”).
14
15 464 • The resultant data processing algorithm was considered highly accurate for
16
17 465 calculating the “daily complete dose count”.
18
19 466 • Accurate nebuliser usage data processing allows for calculation of accurate
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21 467 adherence measurement, which can be used as both a digital study endpoint
22
23 468 in but also as part of optimising routine care.
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Appendix A

An example of how different data processing methods can yield different “daily complete dose counts”.

Date	Start Time	Duration (seconds)	Interruption Code
26/05/2021	10:44:15	366	2
26/05/2021	11:00:13	69	4
26/05/2021	11:24:45	49	4
26/05/2021	19:27:14	13	3
26/05/2021	19:28:04	102	2
26/05/2021	20:24:26	250	2
26/05/2021	21:02:04	61	2
26/05/2021	21:32:01	46	2

These are data from one CFHealthHub participant (not involved in this sub-analysis). To create a “daily complete dose count”, there needs to be a data processing algorithm. If every recorded dose were considered complete, the “daily complete dose count” would be eight. By combining the 19:27:14 and 19:28:04 doses (on the assumption that two doses starting in such quick succession were likely to be two attempts to administer the same dose of nebulized medicine), the “daily complete dose count” would be seven. Excluding the three doses with duration <60s (too short to be a ‘complete’ dose) would give a “daily complete dose count” of five. Including only those marked with an interruption code of 4 (indicating a dose was completed as expected) and excluding doses with duration <60s would give a “daily complete dose counts” of one. This example demonstrates that the data processing algorithm must be carefully considered to accurately reflect the true “daily complete dose count”.

It must be emphasized that the ‘outcome’ of interest is the number of nebulizer doses taken each day, i.e. the “daily complete dose count”. It may be possible that certain complete doses are inaccurately identified but the “daily complete dose count” remains correct. For example, take someone with two recorded doses

1
2
3 (dose A and dose B) on a single day. If the reality was that dose A was complete
4 and dose B was incomplete, but the algorithm determined dose A was incomplete,
5 but dose B was complete, the “daily complete dose count” would still, correctly, be
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Appendix B

A script to guide the initial approach of eligible people with CF to participate in the sub-analysis.

At the start of the call

"I am ringing to see if now might be a convenient time to have a quick chat? I wondered if you may be happy to help us with a small project, we are conducting to improve the quality of the data on CFHealthHub.

[If yes, continue. If no, see if you can arrange to speak with participant at a more convenient time.]

As part of a bigger piece of work, CFHealthHub aims to improve the medicines supply process, by ensuring that people with CF get the right amount of their nebulizer treatments when they need them. It's therefore really important that the data on CFHealthHub is as accurate as possible.

As you (may) know, CFHealthHub displays the days and the times that treatments are taken but it doesn't show which treatment has been taken at a given time. To ensure the data is as accurate as possible on CFHealthHub and provides a true reflection of the treatments taken at a given time, some things are screened out and don't appear on CFHealthHub. E.g., if you ever use "easycare" mode on your eTrack to clean your mesh (or aerosol head), this doesn't show on CFHealthHub as a treatment (it is screened out because it's not a treatment).

Sometimes people experience technical issues with their devices (e.g. cable issues, batteries lose power), which means they experience interruptions mid-treatment. This can sometimes show as two treatments on CFHealthHub (e.g., if you've had to turn your eTrack on again to deliver the remainder of the treatment), even though it is actually just a split dose. We are carrying out a small project to see if we can understand more about where treatments have been taken and where some have been screened out, along with the reasons for these.

I am ringing to see if we could have a look at your nebulizer data for the past week. It might take around 10 minutes in total – is now a good time to do that?

[If yes, continue. If no, see if you can arrange to speak with participant at a more convenient time.]

I've got a list of the times and days in front of me here. It would be great if we could have a look at the doses recorded on a given day and if you could say which treatments you think were taken on that day (some of these might have been screened out and so don't appear on CFHealthHub). Does that make sense? Have you any questions?"

[Go through times and dates provided by LL with the participant and ask the participant to recall what they think happened at each time point e.g. did they take a treatment, and if so, which treatment? Ask participant to try to recall anything out of the ordinary too, to identify any split doses, and reasons for these etc.]

At the end of the call

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2
3 “Thank you very much for your time today. Please can I give you a ring in another week
4 to do the same thing again? It would be great if we could do this for another week to help
5 us see if we can understand these in more detail. Would that be ok?”
6

7 *[If yes, arrange time to call again in a week. Ask participant if they might be happy to keep*
8 *a log of the times and days they do a treatment for the next week (e.g. on their phone, or a*
9 *piece of paper). Ask them to note the: 1) date; 2) time; 3) name of treatment; 4) and anything*
10 *to note with each treatment or the eTrack in general e.g. Did they see two ticks – one when*
11 *the treatment had finished and one when the data had transferred? Did the device lose*
12 *power? Did they do an “easycare” clean? Did the grey cable disconnect? Did they pause their*
13 *treatment? Did they turn the device off or did it turn off itself? etc.]*
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Appendix C

Detailed explanation of how doses with different combinations of durations and interruption codes were triangulated with experiences of participants taking these doses and the participant-clinician consensus decision on completeness. This also describes how decisions were reached on which doses to screen out from the calculator of the “daily complete dose count” in the algorithm.

Doses with duration <60s (not likely to be ‘complete’, as per the manufacturer’s recommendation)

Dose <60s and interruption code = 4

Two individual doses from two participants were identified. Of these, one (50%) was considered ‘complete’ by the clinician-participant consensus.

- 1) One dose was considered ‘incomplete’ and was immediately followed by a dose of the same medicine lasting >60s with interruption code 4, indicating a ‘complete’ dose.
- 2) One dose was considered ‘complete’ and had interruption code 4, despite being <60s duration.

Dose <60s and interruption code ≠ 4

Twenty-five individual doses from eight participants were identified. Of these, 23 (92%) were considered ‘incomplete doses’. Of the two doses considered as ‘complete’:

- 1) One dose was felt to be ‘complete’ by the participant.
- 2) One dose reflected an ‘incomplete’ dose followed by a ‘complete’ dose within one minute.

Given the low likelihood of doses <60s being genuinely ‘complete’, and the manufacturer’s recommendation that no nebulized medicine dose should be delivered in <60s, we proposed screening out all doses that were <60s duration, irrespective of interruption code.

Doses with duration ≥60s and interruption code 4 but considered incomplete.

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2
3 Three individual doses from two participants were identified.
4

- 5 1) One dose was complicated by technical issues with the power cable
6 (despite the interruption code not recognising this), and this was followed
7 by a second attempt by the patient to administer the medicine.
8
9 2) One was the second attempt of the aforementioned dose.
10
11 3) One dose was interrupted, as the eTrack Controller seemed to lose power,
12 though this was not reflected in the interruption code. It was followed by
13 another dose of duration >60s and interruption code 4 which resulted in
14 'complete' delivery of the same medicine as this dose.
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21 We propose considering doses of duration ≥ 60 s and an interruption code of 4 as
22 'complete'.
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26 Doses with duration ≥ 60 s and interruption code 1 (mains supply power failure)
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28 One dose was identified. The dose was considered complete as the participant
29 manually disconnected the main power supply as the dose had already taken 590
30 seconds and they could see that the appropriate volume of liquid medicine has
31 been administered.
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36 We propose screening including doses which have an interruption code 1 and
37 above a duration threshold which is likely to represent a 'complete' dose. This
38 duration threshold will be discussed in section xxx. We recognize that this may
39 inaccurately increase the "daily complete dose count" in certain circumstances.
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45 Doses with duration ≥ 60 s and interruption code 2 (disconnection of handset from
46 eTrack Controller)
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48 Seventy-nine doses from six participants were identified. Three were considered
49 'incomplete', and seventy-six were considered 'complete'. Two of the incomplete
50 doses were from one participant. On one occasion, this participant felt the dose
51 was taking too long and terminated it manually, recognising that the residual
52 volume of non-aerosolized medicine left in the medication reservoir was greater
53 than usual. On the second occasion, the dose was manually terminated again as
54 the participant felt the medicine was not aerosolizing. For the third dose in this
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3 category, the participant also terminated the dose early as they felt it was not
4 aerosolising correctly.
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8 In view of this, we do not propose screening out doses which have an interruption
9 code of 2 and duration $\geq 60s$.
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14 *Doses with interruption code 3 (dose started without medicine in reservoir)*

15 No doses with interruption code 3 were identified. By definition, all doses with
16 interruption code 3 would be $< 60s$ duration and would be screened out by the
17 proposed algorithm.
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23 *Doses with interruption code 5 (manual shutdown of eTrack Controller)*

24 Two doses from one participant were identified. Of these:

- 25
26 1) One dose was considered complete, with a duration of 1079s.
27
28 2) One dose followed a preceding dose which had been considered
29 incomplete, in an attempt by the participant to deliver one 'complete dose'.
30
31 The combination of these two doses made for one 'complete' dose.
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35 We do not propose screening out doses with interruption code 5. However, we
36 recognize that, in situations such as number two described above there is a risk of
37 an additional 'complete' dose being counted using this algorithm.
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42 *Doses with interruption code 6 (battery empty)*

43 Eighteen doses from six participants were identified. Of these, five were
44 considered 'complete' and 13 'incomplete'. As an interruption code 6 denotes a
45 non-user-initiated early interruption, we can be confident, but not certain that it
46 is unlikely that a 'complete' dose has been delivered, as seen in 13/18 (72%) of
47 examples.
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54 *Doses with non-user-initiated early termination (interruption code 1 and*
55 *interruption code 6) and duration $> 60s$*

56 When analysing all doses with interruption code 1 or 6 ($n=21$), six (28%) were
57 considered 'complete' and 15 (71%) 'incomplete'. Applying a duration threshold
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3 of <480s (eight minutes) for exclusion left three remaining doses, all of which
4 were considered complete and had durations of 590s, 606s and 707s respectively.
5 Applying lower duration thresholds captured a combination of doses which were
6 considered 'complete' and 'incomplete', hence the decision to apply the duration
7 threshold of 480s.
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13 We therefore propose screening out doses with interruption code 1 and
14 interruption code 6 and duration <480s.
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19 *Doses with interruption code 7 (timeout during inhalation mode)*
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21 Three doses from one participant was identified. All three doses were considered
22 'complete'. The duration of a dose with interruption code 7 will always be 1201s,
23 as the eTrack Controller times out at this time during inhalation mode. Prolonged
24 dose durations may suggest the handset, through which the liquid medicine is
25 aerosolized, is worn, or clogged.
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31 We do not propose screening out doses with interruption code 7, as after 20
32 minutes of nebulisation, we would expect a 'complete' dose to have been
33 administered, though this is not a certainty and is a recognized limitation of this
34 algorithm.
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40 *Doses with interruption code 8 (timeout during pause mode)*
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42 No doses were identified. As interruption code 8 denotes a dose which has timed
43 out during pause mode, we would expect that, by virtue of the dose being paused
44 (rather than terminated) by the patient, then the dose would not be considered
45 'complete'. The eTrack nebulizer will generate an interruption code of 8 if the
46 device is paused for >600s without being un-paused.
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52 We propose screening out doses with interruption code 8.
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56 *Doses with interruption code 101-108*
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3 One dose was identified. As these doses refer to the “*easycare*” cleaning mode, we
4 do not expect any therapeutic doses to be administered with this interruption
5 code. We propose screening out all doses with interruption code 101-108.
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10 **Multiple doses starting within 120s.**

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14 Forty-three doses were identified across all participants. In most cases, they
15 resulted from multiple attempts (recorded as individual doses) to deliver one
16 ‘complete’ dose. We propose that all doses starting within 120s of the preceding
17 dose start time should be combined with the preceding dose into a single dose and
18 then processed as per the algorithm with respect to duration and interruption
19 code.
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1 Development of data processing algorithm to calculate 2 adherence for ~~people~~ adults with cystic fibrosis using inhaled 3 therapy – A multi-center observational study within the 4 CFHealthHub ~~Learning Health System~~ Learning Health System

6 1. Introduction

8 Digital measures utilizing real-world patient data can be used in routine care or
9 as endpoints in clinical trials. Compared to traditional endpoints captured in
10 clinical settings, digital endpoints may offer greater insights into real-life patient
11 experiences that are not reliably captured in the clinical setting (1).

13 Adherence can be described as the extent to which a person follows healthcare
14 provider recommendations, such as taking medicine. (2). Low adherence to
15 prescribed medicine in long-term conditions is a key contributor to suboptimal
16 clinical benefits and worse health outcomes (2, 3). Electronic adherence
17 monitoring devices enable adherence to function as a digital measure which offers
18 greater objectivity than alternatives, such as self-report (4-6).

20 Cystic fibrosis (CF) is an archetypal long-term condition where life expectancy is
21 approximately 50 years, driven by respiratory failure, resulting from chronic lung
22 inflammation and recurrent infection (7, 8). Most ~~people~~ adults with CF (~~PwCF~~)
23 are prescribed medicine regimens including multiple daily doses of inhaled
24 therapy, usually delivered by an electronic ~~nebuliser~~ nebulizer device. Higher
25 adherence to inhaled therapy is associated with better outcomes but real-world
26 adherence is low at <40% (5, 9-11).

28 CFHealthHub is a UK-based multi-~~center~~ center ~~L~~ learning ~~H~~ health ~~S~~ system. A
29 Learning Health System is described as “a health system in which outcomes and
30 experience are continually improved by applying science, informatics, incentives
31 and culture to generate and use knowledge in the delivery of care”(12) , which

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describes a group of organisations that use routinely collected data to deliver continuous improvement (12).

CFHealthHub ~~centers have access to~~ combines a the -cloud-based CFHealthHub digital platform which continuously captures and displays adherence data from ~~nebuliser~~nebulizer devices. This platform can be accessed by clinicians and adults with CF at all times. Certain clinicians within each CFHealthHub center are also trained to ~~, with a~~ deliver a multi-component behavioural intervention which supports adults with CF to improve adherence through habit formation (13, 14). CFHealthHub increased percent adherence to inhaled therapy and reduced perceived treatment burden in a recent 607-participant randomized controlled trial (RCT) (15). CFHealthHub is now available-active in over 50% of adult CF centers in England, as an evidence-based ~~platform~~-digital platform and behavioural intervention, which empowers people-adults with CF to self-manage their condition. A recent report from The Health Foundation recognized CFHealthHub as the only condition-based, full learning-health-system Learning Health System with national reach in the UK, and is an exemplar for other long-term conditions (16).

The CFHealthHub digital platform requires the ability to accurately measure objective adherence data from ~~nebuliser~~nebulizer devices with electronic data capture (EDC) ~~capability~~-capability. The CFHealthHub digital platform is device agnostic, and compatible with both of the EDC-capable nebulizer devices used in the UK~~available~~-devices, the I-neb Adaptive Aerosol Delivery (AAD) System (Philips Respironics, Chichester, UK) and eFlow[®] Technology ~~nebuliser~~nebulizers with an eTrack[®] data-logging Controller (PARI Pharma GmbH, Starnberg, Germany), subsequently referred to as “eTrack ~~nebuliser~~nebulizers”. AAD devices, such as the I-neb, can accurately determine whether a dose is completely administered, as aerosolized medicine is only released on breath activation of the user. Non-AAD devices, such as the eTrack ~~nebuliser~~nebulizer, do not have this functionality and therefore require data processing algorithms to most accurately determine completeness of the dose deliverydetermine completeness of the dose delivery with accuracy.

65 ~~This~~ Therefore, this work focuses on data from eTrack ~~nebuliser~~nebulizers only.
66 The component parts of the eTrack ~~nebuliser~~nebulizer, referred to throughout
67 this article, are shown in Figure 1.

68
69 To ensure accurate calculation of percent adherence ~~measurement~~, the ~~raw~~
70 ~~inhalation data~~ nebulizer data must be processed to count the number of doses of
71 ~~nebulised~~ medicine which have been delivered 'completely' each day. This figure,
72 produced for each day, is referred to as the "daily complete dose count". Each time
73 a dose of medicine is initiated via an eTrack ~~nebuliser~~nebulizer, a log is created
74 with the timestamp, duration of the dose, and a numeric code (known as an
75 interruption code) recording whether the dose was considered 'complete' or not
76 (Table 1). An interruption code of "4" denotes a 'complete' dose. Alternative
77 interruption codes suggest the dose may have been 'incomplete'. For example, an
78 interruption code of "1" suggests the dose was interrupted due to loss of power
79 supply to the eTrack ~~nebulizer~~ controller. Most medicines delivered via an
80 eTrack ~~nebuliser~~nebulizer are expected to take between 2-8 minutes to complete.
81 ~~t~~Therefore, all doses with a very short duration (<60s) are likely 'incomplete'
82 (Personal Communication, Dr C Fuchs, PARI GmbH, Email, Jan 2021).

83
84 The method of processing doses with varying duration and interruption codes can
85 result in different ~~counts of 'complete' daily doses~~ "daily complete dose counts".
86 The example presented in Appendix A demonstrates that the data processing
87 algorithm must be carefully considered, to accurately reflect the true "daily
88 complete dose count" ~~daily dose count~~. It is possible for a singular dose to be
89 misclassified, but the algorithm still yields an accurate "daily complete dose
90 count" ~~as explained in Appendix 1~~. During the CFHealthHub RCT,
91 ~~nebuliser~~nebulizer usage data were processed using an algorithm based on expert
92 advice from PARI GmbH (15). This involved considering all doses with duration
93 ≥60s, and an interruption code of 2 (indicating disconnection of the aerosol head
94 from the eTrack controller) or 4 (indicating that the dose completed as expected)
95 as 'complete'. The algorithm excluded the following doses from the "complete
96 daily dose count":

- 97 • all duplicate doses, based on start time, duration and interruption code

- 98 • all doses of duration less than 60 seconds,
- 99 • all doses with interruption code 3 (suggesting there was no medicine in the
- 100 device at the initiation of the dose),
- 101 • all doses conducted in the *EasyCare* cleaning mode (identified by an
- 102 interruption code >100)
- 103 • all doses with a date of “01JAN2015’ (suggesting device corruption),

104 After exclusions, the following doses are combined in calculating the “daily

105 complete dose count”.

- 106 • all doses which were interrupted due to power failure or pre-set timeout
- 107 (based on interruption codes 1,5,6,7,8) and duration ≥60s would be
- 108 classified as partial dose, contributing 0.5 to the “daily complete dose
- 109 count”. If the subsequent dose is started within 1500s and had an
- 110 interruption code of 2 (cable disconnection) or 4 (dose complete as
- 111 expected), then these two doses would be combined to give 1 complete
- 112 dose.

113

114 There is ongoing, real-world learning in the CFHealthHub ~~learning health~~

115 ~~system~~Learning Health System, where many more adults are using ~~the~~ eTrack

116 ~~nebuliser~~nebulizers. Approximately 6% of all doses recorded on ~~the~~ CFHealthHub

117 digital platform had a duration of <60s and 24.5% were potentially ‘incomplete’,

118 ~~(as per the interruption code,)~~ over-in the 12 months prior to this work. The most

119 accurate method of processing data from these doses is uncertain and requires

120 stronger evidence than ~~just expert~~ advice from the manufacturer.

121

122 The objectives of this sub-analysis within CFHealthHub were: first, to understand

123 how doses could be identified as ‘complete’ based on their duration and

124 interruption code. Second, by triangulating eTrack ~~nebuliser~~nebulizer usage data

125 with participants’ ~~experiences~~records of taking each dose, to develop and validate

126 a data processing algorithm to ~~optimiz~~se the accuracy of the ~~“complete~~ daily

127 complete dose count”: used in percent adherence calculations. ~~It is possible for a~~

128 ~~singular dose to be misclassified, but the algorithm still yield an accurate ‘daily~~

129 ~~complete dose count’ as explained in Appendix 1.~~ These objectives align with the

130 key aim of developing ~~the~~ CFHealthHub digital platform as a platform as one which

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2
3 131 maximise the salience of adherence data and may also serve as an exemplar
4
5 132 for other platforms capturing digital adherence data remotely.
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8 9 10 134 2. Participants and Methods

11 135
12 136 In this sub-analysis, data collected from eTrack ~~nebuliser~~nebulizers were
13
14 137 triangulated against ~~the~~real-world ~~experiences-records, created by adults with~~
15
16 138 ~~CF, of what happened during each dose~~of adults with CF. Participants were all
17
18 139 eTrack ~~nebuliser~~nebulizer users who had consented to the CFHealthHub ~~learning~~
19
20 140 ~~health-system~~Learning Health System. Regulatory approval was provided by the
21
22 141 London-Brent Research Ethics Committee (Reference number: 17/LO/0032).
23
24 142

25 143 This analysis included ~~people~~adults with CF who had ≥ 20 ~~nebuliser~~nebulizer d
26
27 144 ~~medication-doses~~doses that were either < 60 s in duration or potentially
28
29 145 'incomplete', ~~(as per their interruption code)~~. There were no previous data to
30
31 146 inform a target sample size. Since approximately 30% of doses were expected to
32
33 147 be of short duration or potentially 'incomplete', 300 doses was chosen as a
34
35 148 pragmatic target to provide 100 doses of interest, which should encompass an
36
37 149 adequate range of different interruption codes. ~~Due to constraints in clinical~~
38
39 150 ~~resources, the plan was to enrich the sample with the doses of interest (short~~
40
41 151 ~~duration and/or potentially 'incomplete')~~ so that an adequate range of different
42
43 152 ~~interruption codes can be covered over a short time duration. Therefore,~~
44
45 153 ~~p~~Purposive sampling was used to identify participants with a particularly high
46
47 154 number ~~of doses of interests of relevant (short duration or potentially~~
48
49 155 ~~'incomplete' doses~~ (≥ 20 doses of interest per week), ~~hence-such that 10~~
50
51 156 participant-weeks' of data ~~each~~ for ~~each-derivation and validation~~ datasets ~~-~~was
52
53 157 determined as sufficient.
54
55 158

56
57 159 Participants were included from three centers which are part of the CFHealthHub
58
59 160 ~~learning health-system~~Learning Health System. These centers were selected due
60
161 to the relatively high prevalence of eligible participants and the availability of
162 clinicians to complete this work. Approximately 8,000 doses ~~within-from the~~
163 CFHealthHub digital platform were screened between 15th October 2021 and 31st

1
2
3 164 October 2021 (two weeks prior to the sub-analysis start date). Data collection was
4
5 165 between 1st November 2021 and 15th December 2021.
6
7 166

8 167 Local clinicians approached eligible ~~people~~ adults with CF from these three
9
10 168 centers using a standard iseized script to facilitate the initial discussion (Appendix
11
12 169 B). In the first telephone call, participants were informed about this work and
13
14 170 invited to provide verbal consent to participation. If they agreed, a longer call was
15
16 171 arranged at a future time to discuss their ~~nebuliser~~ nebulizer usage data.
17
18 172

19 173 2.1

20 174 *Phase 1 (data calibration)*

21 175 1.

22
23 176 Once relevant participants were identified for inclusion in this analysis local
24
25 177 clinicians were provided with a log of each participant's ~~nebuliser~~ nebulizer usage
26
27 178 data for the preceding week, extracted from the CFHealthHub digital platform.
28
29 179 These data included the timestamp, duration, and interruption code for each
30
31 180 recorded dose. To mitigate recall bias, clinicians used these data to help prompt
32
33 181 participant recall of 1) the time the dose was started, 2) the ~~medication~~ medicine
34
35 182 used for each dose, 3) if they considered the dose 'complete' or not, and 4) if
36
37 183 relevant, a reason why the dose was considered '(in)complete'. Discussions
38
39 184 around ~~nebuliser~~ nebulizer usage are part of routine clinical care in CF and the
40
41 185 data used to inform these discussions is available to all clinicians providing care
42
43 186 to ~~people~~ adults with CF enrolled in the CFHealthHub ~~learning~~ health
44
45 187 system Learning Health System on request.
46
47 188

48 189 The ~~participant and clinicians~~ clinician and participant reached consensus as to
49
50 190 whether each ~~logged~~ nebulizer dose was likely to have been 'complete'. For
51
52 191 example, the participant recognising ~~that~~ an appropriate residual volume of the
53
54 192 medicine in the medication reservoir suggests the dose was 'complete' even
55
56 193 though the eTrack ~~nebulizer~~ Controller had not ~~recognise~~ iseized the dose as
57
58 194 complete. Clinicians then asked participants to keep a ~~log~~ record of their
59
60 195 ~~nebuliser~~ nebulizer usage for prospective data collection in Phase 2. Participants
196 were asked to record the name of the medicine being ~~nebulise~~ ized and the date

1
2
3 197 and time the dose was started. They were also asked to note anything remarkable
4
5 198 about that dose, for example if they experienced a power failure or disruption, and
6
7 199 if they considered the dose to be 'complete'. A follow-up call was then arranged
8
9 200 with each participant to review their prospective logrecord.

10 201

11
12 202 The purpose of Phase 1 was to familiarise participants with the process of
13
14 203 discussing their nebulisation experiences nebulizer usage and to consider ways of
15
16 204 determining whether a dose of nebulised medicine was 'complete', in preparation
17
18 205 for the prospective data collection. ~~The~~ data from Phase 1 was/were not used in
19
20 206 the analysis.

21 207

22 208 2.2 Phase 2 (prospective data collection)

23 209

24
25 210 Clinicians contacted participants at the agreed time to review 1-2 weeks of
26
27 211 objective nebulisation nebulizer data, extracted from the CFHealthHub digital
28
29 212 platform, (as described in Phase 1). These data were discussed with the
30
31 213 participant and triangulated with using their contemporaneous record records of
32
33 214 the corresponding nebulisations doses, which the clinicians then cross-checked
34
35 215 against the nebulizer CFHealthHub data. Clinicians completed a data collection
36
37 216 form using Microsoft Excel (version 16.62). As in Phase 1, the participant and
38
39 217 clinician reached clinician and participant reached consensus as to whether each
40
41 218 recorded dose was considered 'complete' or not, along with a brief description,
42
43 219 e.g., "participant reported their device timed-out after 20 minutes". An example of
44
45 220 a completed data collection form is shown in Figure 2.

46 221

47
48 222 Following collection, the The prospective data were divided into derivation and
49
50 223 validation sets, prior to any analysis being undertaken. Therefore, clinicians were
51
52 224 not aware of the resultant algorithm at the time of data collection. To ensure both
53
54 225 datasets comprised an adequate range of interruption codes and considering the
55
56 226 small number of participants, f for participants providing two separate weeks of
57
58 227 data, one week of data was allocated to derivation and the other week's-weeks'
59
60 228 data to validation. This was done to ensure both datasets contained an adequate

229 range of interruption codes, given the small number of participants (n=12) and
230 doses (approximately 300 in each data set).

231

232 Researchers reviewed the derivation dataset, consisting of ~~CFHealthHub~~
233 ~~nebulisation-nebulizer~~ data (date & time, duration, and interruption code for each
234 dose), and whether the dose was considered 'complete' by the clinician-
235 participant by the participant and clinician-consensus-~~discussion~~, with associated
236 free text comments where available. First, all doses with duration of <-60s were
237 reviewed. Next, all doses with duration ≥-60s were stratified by the interruption
238 code listed in Table 1, and each resultant group was reviewed separately. With
239 this information, an algorithm to calculate a "daily complete dose count" ~~complete~~
240 ~~daily dose count~~' from the ~~CFHealthHub-datanebulizer data~~ was developed, which
241 ~~based on dose used~~ dose start time, duration and interruption code only, to
242 determine if a dose was likely to be 'complete'. Appendix C contains a full
243 description of the number of doses in each combination of duration and
244 interruption code, with a justification for how the algorithm would process these
245 combinations, based on the triangulated ~~CFHealthHub-datanebulizer data~~ and
246 consensus "daily complete dose count" ~~'complete-daily dose count'~~.

247

248 If a dose was likely to be 'complete', then it would be included and counted as a
249 'complete' dose, however if it was likely to be 'incomplete', it would be excluded
250 or combined with another dose to create a single 'complete' dose.

251

252 The agreement between algorithm-derived "daily complete dose count" and
253 consensus-derived "daily complete dose count" in the derivation dataset were
254 determined using both percent accuracy and kappa values. In view of the clustered
255 nature of the dataset, bootstrapping was used to calculate kappa and agreement
256 values (17). This involved bootstrapping of 1000 samples from the original
257 dataset, calculation of kappa and agreement values for each sample (i.e. 1000
258 values were calculated for each participant) and then ascending re-order of those
259 values to provide a median, 2.5th and 97.5th centile as measures of central
260 tendency and dispersion. In addition, the extent to which the algorithm under- or
261 over-estimated the consensus-derived "daily complete dose counts" were

262 quantified with absolute differences in both “daily complete dose counts” and
263 percent adherence between the two measures.

264

265 ~~The ability of this algorithm to calculate ‘complete’ daily doses was then tested~~
266 ~~against the consensus ‘complete daily dose count’ in the derivation dataset. Both~~
267 ~~percent accuracy and kappa values were calculated.~~

268 An a-priori target was to proceed to validation if the algorithm-derived “daily
269 complete dose count” was ≥80% accurate in comparison to the ~~joint clinician-~~
270 ~~participant consensus-derived “daily complete dose count”, which was considered~~
271 ~~as the ‘reference standard’ on ‘complete daily dose count’ (considered as the~~
272 ~~reference). If the accuracy was <80%, then the derivation dataset would be re-~~
273 reviewed to refine the algorithm.

274

275 1.3. Results

276

277 Twenty-two adults with CF receiving care in ~~Centre~~Center 1 (n=8), ~~Centre~~Center
278 2 (n=8) and ~~Centre~~Center 3 (n=6) were identified as potentially eligible for
279 inclusion.

280

281 Eight of these 22 ~~people~~-adults were excluded after approach, and two excluded
282 after review of their nebulisation data prior to Phase 2. Twelve participants were
283 included in the analysis. Their baseline characteristics are shown in Table 2. The
284 flow of recruitment, reasons for exclusion and allocation are shown in Figure 3.

285

286 One week of data from ~~101~~ participants ~~comprise~~ized the derivation dataset, with
287 one week of data from 10 participants comprising the validation dataset. ~~Nine~~
288 Eight of the 12 participants contributed data to both derivation and validation
289 sets, as they each provided two weeks of data, compared to the ~~three~~-four other
290 participants, contributing one week of data each who were assigned to either the
291 derivation or validation datasets in a 1:1 ratio. A total of ~~80~~-74 patient days (with
292 ~~337~~-295 doses) from ~~101~~ patients were used in the derivation dataset and 69
293 patient days (with 309 doses) from 10 patients in the validation dataset. Dose

294 durations and interruption codes for the derivation dataset were reviewed and
 295 results are reported in Table 3.

296

297 *3.1 Proposed screening algorithm*

298 We proposed the following process for identifying ‘complete’ doses from the
 299 ~~CFHealthHub~~nebulizer ~~nebulisation~~ data.

300

301 1) Initially screen out:

- 302 • All doses with duration <60s.
- 303 • All doses that had a timeout during pause mode (interruption code = 8).
- 304 • All doses in cleaning mode (interruption code = 101--108).

305

306 2) Combine

- 307 • Any 2 or more doses starting within 120s of each other.

308

309 3) Finally screen out:

- 310 • Doses with duration <480s due to loss of supply voltage or battery power
 311 to the eTrack ~~nebuliser~~nebulizer (interruption code = 1 or 6).

312

313

314 *3.2 Accuracy of the proposed screening algorithm*

315 In the derivation dataset, there was a high level of agreement between the
 316 algorithm-generated ~~derived~~ “daily complete dose count” ~~‘complete daily dose~~
 317 ~~count’~~ and the consensus-derived “daily complete dose count”. The ~~κ~~ (kappa
 318 co-efficient was 0.85 with 95% confidence interval of 0.71-0.91 and 6, accuracy
 319 was 87.5% (77.0-95.7)7%). Similar agreement and accuracy were seen in the
 320 validation dataset (kappa co-efficient 0.86 [0.77-0.94], accuracy 89.9% [84.3-
 321 95.5]). These results along with the total numbers of doses considered ‘complete’
 322 by both the algorithm and consensus are comparison of daily counts are reported
 323 in Table 4. The absolute differences in “daily complete dose count” between these
 324 two measures were 10 (out of 266 ‘complete’ doses by consensus) in the
 325 derivation dataset and 7 (out of 267 ‘complete’ doses by consensus) in the
 326 validation dataset. The absolute differences in mean percent adherence calculated

327 using the “daily complete dose count” from these two measures were 3.2% and
 328 2.8% respectively, as reported in Table 5.

329

330 4. Discussion

331 2.

332 Through examination of nebulizer data ~~from the CFHealthHub learning health~~
 333 ~~system~~ and triangulation of these data with participant records-experiences, we
 334 have developed an algorithm ~~to count daily ‘complete’ nebulised medicine doses to~~
 335 generate a “daily complete dose count”. This algorithm involved excluding all
 336 doses of <60s, combining doses which start within 120s of each other and then
 337 using a combination of the interruption code and dose duration to determine
 338 which other doses are likely to be ‘complete’. The resultant “daily complete dose
 339 count” ~~‘complete daily dose count’~~ was 8788.57% accurate in the derivation
 340 dataset and 89.9% accurate in an internal validation dataset.

341

342 By outlining the process for designing and validating a data processing algorithm
 343 in collaboration with adultsPwCF with CF, we aim to inspire trust in adherence
 344 data from the CFHealthHub digital platform as a digital measure. At a patient-level,
 345 adherence data from the CFHealthHub digital platform is central to the
 346 development of personaliseized care plans, an essential part of caring for people
 347 with long term conditions (18). A tangible benefit of the greater objectivity is that
 348 actual pattern of ~~nebuliser~~nebulizer use can be understood by clinicians, who can
 349 then provide personaliseized advice on how to fit ~~nebuliser~~nebulizer use within
 350 the other routines of the adult-person with CF.

351

352 ~~Over~~An erroneously high-counting “daily complete dose count” ~~daily ‘complete’~~
 353 ~~doses~~ risks overestimating adherence, which may-risks then falsely reassuringe
 354 both people-adults with CF and clinicians that adherence is higher than it is. ~~This~~
 355 ~~may mean~~The consequence of this is that ~~those people-some people may with CF~~
 356 ~~who may benefit from adherence support may not be identified, and they would~~
 357 ~~be at risk of~~be being under-served by the health care system by not being offered
 358 adherence support when they could benefit from it. Furthermore, overestimating
 359 adherence may result in unnecessary treatment escalation in the event of clinical

1
2
3 360 deterioration. ~~Conversely~~, underestimating adherence could create conflict
4 361 between ~~people-adults~~ with CF and their clinicians and lead to both parties losing
5 362 faith in the ~~adherence~~ data ~~provided by available on the~~ CFHealthHub ~~digital~~
6 363 ~~platform~~.

7 364
8 365 We recognize that the algorithm produced a marginally higher “daily complete
9 366 dose count” than the participant-clinician consensus, which was considered the
10 367 ‘reference standard’ in this project. However, the difference in percent adherence
11 368 derived from the “daily complete dose count” (around 3% against an average
12 369 adherence exceeding 90%) was clinically negligible. It is worth noting that a
13 370 participant-clinician consensus for whether each dose of treatment is ‘complete’
14 371 is not feasible outside of a dedicated research project. It would be unreasonably
15 372 burdensome for all participants on CFHealthHub to keep a detailed daily dairy of
16 373 all their nebulizer doses. Therefore, we are reassured by the small differences
17 374 noted in this study.

18 375
19 376 Within a ~~learning health system~~ Learning Health System where data used to
20 377 generate knowledge which drives and measures improvement work, optimising
21 378 data quality is critical (12). Previous quality improvement work, underpinned by
22 379 large datasets, has focussed on measures of completeness, conformance and
23 380 plausibility, through the production of automated functions with statistical
24 381 software (19). In this work, we have developed an algorithm to improve
25 382 calculation of “daily complete dose counts”~~e-daily-dose-count accuracy~~. This was
26 383 strengthened by working alongside ~~people-adults~~ with CF to gain a qualitative
27 384 understanding of circumstances of doses, from which ~~the quantitative data were~~
28 385 produced and allow accurate counting of the number of ‘complete’ nebulised
29 386 medicine doses taken each day.

30 387
31 388 A key strength is that this is the first report triangulating nebulizer objective data
32 389 from CFHealthHub with ~~data with~~ the real-world experiences of ~~people-adults~~ with
33 390 CF using eTrack ~~nebuliser~~ nebulizers within the CFHealthHub Learning Health
34 391 System, using a parsimonious study design to minimize the burden of adults with
35 392 CF. Putting people at the center of research into their condition is a key priority

1
2
3 393 for improving care in long-term conditions (18). Continuous patient engagement
4
5 394 is recommended during the evaluation phase of digital measures such as this (20,
6
7 395 21).

8
9 396

10 397 There are however some limitations. To minimize the burden of adults with CF,
11 there is a need to use a parsimonious study design ~~Due to the need to enriching~~
12 398 the cohort with participants with relatively high numbers of short or “potentially
13 incomplete” nebulizer doses. ~~By applying a~~
14 399 purposive sampling strategy within three of the 15 CFHealthHub centers, the
15 400 sample of participants could be criticized as being less generalizable. For example,
16 401 the mean adherence of the sample exceeded 90% when real-world median
17 402 adherence is only around 30% (9). However, this study design allowed us to
18 403 capture an adequate range of short and/or ‘potentially incomplete’ doses to
19 404 enhance the applicability of the resultant algorithm in a larger population.
20 405 ~~Therefore, the sample was not randomly generated, which means confidence in~~
21 406 ~~generalisability is reduced.~~
22 407
23 408
24 409

25 410 Due to the limited number of participants imposed by scarce resources, data from
26 411 different weeks by the same participant were included in both the derivation and
27 412 validation datasets. ~~This to ensured~~ an adequate range of interruption codes in
28 413 both datasets. Whilst no individual dose appeared in both datasets, the inclusion
29 414 of the same participant in both datasets meant that the validation dataset is not
30 415 external to to that of the derivation dataset. ~~Reassuringly, for the one participant~~
31 416 ~~contributed to only the validation dataset, there was perfect agreement between~~
32 417 ~~the consensus- and algorithm-derived ‘complete daily dose counts’.~~ Further
33 418 validation of this algorithm in other CFHealthHub centers would be useful. The
34 419 fact that CF is a rare disease, with approximately 7,000 adults with CF in the UK
35 420 and the relative infrequency of potentially incomplete doses (<25% of all doses on
36 421 the CFHealthHub digital platform) contributed to the small sample size of 12
37 422 participants and 604 doses (22).

38 423

39 424 Another limitation was reliance on patient self-report as to which medicine was
40 425 being administered for each dose, and circumstances around doses ~~recorded~~

1
2
3
4 426 ~~which were considered as~~ potentially ‘incomplete’. Currently, ~~CFHealthHub~~
5 427 ~~eTrack nebulizers~~ lacks the technology to identify the specific medicine being
6
7 428 administered. We also cannot identify, from data alone, whether prolonged
8
9 429 nebulisation duration is due to equipment malfunction or patient factors. We
10
11 430 mitigated potential recall bias by prospectively asking participants to keep
12
13 431 contemporaneous ~~logs-records~~ for data collection ~~during the study period~~, rather
14
15 432 than relying on retrospective recall. We also cross-referenced their ~~logs-records~~
16
17 433 against the ~~CFHealthHub-nebulizer~~ data. An alternate approach of direct
18
19 434 observation of ~~nebulisernebulizer~~ usage in a controlled environment would have
20
21 435 allowed the gold standard data collection around whether a dose was ‘complete’
22
23 436 or not. This was considered unfeasible given the time and resource burden for
24
25 437 clinicians and participants, which is a known barrier to participation in research
26
27 438 within CF (23). Our chosen ~~methodology-methods were parsimonious and~~ better
28
29 439 captured the real-world experience of ~~people-adults with CF~~ using eTrack
30
31 440 ~~nebulisernebulizers~~ where factors such as consumable wear and dose
32
33 441 interruptions come into play.

34
35 442
36 443 ~~Finally, this study was limited to adults with CF who were using eTrack nebulizer~~
37
38 444 ~~devices, which represents 88% of the approximately 1400 adults with CF who are~~
39
40 445 ~~enrolled in CFHealthHub. At the time of this study, only two data-logging nebulizer~~
41
42 446 ~~devices are used in the UK: eTrack nebulizer and the I-neb. As an adaptive aerosol~~
43
44 447 ~~delivery device, the I-neb already provides dose completeness information in the~~
45
46 448 ~~following scale: “Full”; “>12.5%; <100%”; “<12.5%” and “none”. Therefore, such~~
47
48 449 ~~an algorithm is not required for I-neb users.~~

49
50 450
51 451 This data processing algorithm will now be embedded within ~~the~~ CFHealthHub
52
53 452 ~~digital platform, where further validation in larger and more diverse cohort is~~
54
55 453 ~~recommended. There are currently approximately 1400 patients across 14 UK~~
56
57 454 ~~Adult CF Centres enrolled in CFHealthHub, where T~~hese data are used to support
58
59 455 adherence in the real-world setting (24). CFHealthHub also has a research arm,
60
61 456 currently undertaking a large observational study, exploring the role of co-
62
63 457 adherence to inhaled therapy for ~~PwCF-adults with CF~~ who are taking novel oral
64
65 458 treatments (25). Digital endpoints may present unique challenges in the value

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3 459 assessment of pharmaceuticals or cost evaluation of consumed medications.
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5 460 Recognising this, CFHealthHub adherence data ~~is-are~~ also used to optimiseize
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7 461 medicines supply by aligning supply with actual usage, with the potential to
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9 462 realiseize significant cost savings (26, 27). For both of these workstreams to be
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11 463 effective, ~~data accuracy~~the accuracy of CFHealthHub data, which is strengthened
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13 464 by this work, is critical.

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15 466 Inspired by information uncovered during this work, we have since completed a
16
17 467 formal study of how ~~these CFHealthHub~~ data can identify PwCF adults with CF
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19 468 who are having frequently prolonged ~~nebuliser~~nebulizer durations.
20
21 469 Troubleshooting and replacement of consumable parts led to mean 37%
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23 470 reduction in the time PwCF adults with CF spent on ~~nebuliser~~nebulizer treatment
24
25 471 each day (28). This is a further demonstration of how paying attention to data
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27 472 from digital measures can have real-world benefits for people with long-term
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29 473 conditions.

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31 32 475 5. Conclusion

33 476 ~~3.~~

34
35 477 We have developed a data processing algorithm by triangulating ~~CFHealthHub~~
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37 478 ~~nebuliser~~nebulizer usage data with participants' real-world ~~experie~~ncerecords,
38
39 479 which was then tested in a multi-center dataset. The algorithm has high levels of
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41 480 accuracy. Co-designing and validating this algorithm helps optimiseize the
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43 481 accuracy of, and trust in, ~~adherence data from the objective nebuliser usage data~~
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45 482 ~~within~~CFHealthHub digital platform. These data can be used to optimiseize
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47 483 clinical interactions at a patient-level, underpin quality improvement work at an
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49 484 organisation-level and facilitate national benchmarking at a system-level. The
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51 485 methods we use could also be applied by other platforms capturing digital
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53 486 adherence data remotely. Publication of data processing algorithms encourages
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55 487 confidence in ~~learning health system~~Learning Health Systems embedded within
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57 488 routine clinical care.

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60 491 Declaration of Interest

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3 492 RDS has been a sponsored delegate at conferences by Lilly & UCB and has also
4
5 493 received an educational bursary supported by Chiesi and the European Cystic
6
7 494 Fibrosis Charity. SC has undertaken consultant work with Gilead. MJW declares
8
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10
11 496 no other relevant affiliations or financial involvement with any organization or
12
13 497 entity with a financial interest in or financial conflict with the subject matter or
14
15 498 materials discussed in the manuscript apart from those disclosed.
16

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20
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22
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24

25 504

26 505 **Article Highlights**

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28 506 • Supporting adherence to medicine regimens in long-term conditions requires
29
30 507 accurate measurement of adherence.
31
32 508 • The CFHealthHub Learning Health System offers a digital platform which can
33
34 509 collect inhaled medicine usage data from nebuliser devices capable of
35
36 510 electronic data capture.
37
38 511 • Clinicians and people with cystic fibrosis collaborated to develop a data
39
40 512 processing algorithm for these usage data to calculate the number of complete
41
42 513 doses taken each day (“daily complete dose count”).
43
44 514 • The resultant data processing algorithm was considered highly accurate for
45
46 515 calculating the “daily complete dose count”.
47
48 516 • Accurate nebuliser usage data processing allows for calculation of accurate
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50 517 adherence measurement, which can be used as both a digital study endpoint
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52 518 in but also as part of optimising routine care
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Appendix A

An example of how different data processing methods can yield different “complete daily complete daily dose counts”.

Date	Start Time	Duration (seconds)	Interruption Code
26/05/2021	10:44:15	366	2
26/05/2021	11:00:13	69	4
26/05/2021	11:24:45	49	4
26/05/2021	19:27:14	13	3
26/05/2021	19:28:04	102	2
26/05/2021	20:24:26	250	2
26/05/2021	21:02:04	61	2
26/05/2021	21:32:01	46	2

These are data from one CFHealthHub participant (not involved in this sub-analysis). To create a 24-hour “daily complete dose count” ~~daily ‘complete’ dose count~~, there needs to be a data processing algorithm. If every recorded dose were considered complete, the “daily complete dose count” ~~daily count~~ would be eight. By combining the 19:27:14 and 19:28:04 doses (on the assumption that two doses starting in such quick succession were likely to be two attempts to administer the same dose of nebulized medicine), the “daily complete dose count” ~~daily count~~ would be seven. Excluding the three doses with duration <60s (too short to be a ‘complete’ dose) would give a “daily complete dose count” ~~daily count~~ of five. Including only those marked with an interruption code of 4 (indicating a dose was completed as expected) and excluding doses with duration <60s would give a “daily complete dose counts” ~~daily count~~ of one. This example demonstrates that the data processing algorithm must be carefully considered to accurately reflect the true “daily complete dose count” ~~complete daily dose count~~.

It must be emphasized that the ‘outcome’ of interest is the number of nebulizer doses taken each day, i.e. the “daily complete dose count”. It may be possible that certain complete doses are inaccurately identified but the “daily complete dose

1
2
3 count” remains correct. For example, take someone with two recorded doses
4 (dose A and dose B) on a single day. If the reality was that dose A was complete
5 and dose B was incomplete, but the algorithm determined dose A was incomplete,
6 but dose B was complete, the “daily complete dose count” would still, correctly, be
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Appendix B

A script to guide the initial approach of eligible people with CF to participate in the sub-analysis.

At the start of the call

"I am ringing to see if now might be a convenient time to have a quick chat? I wondered if you may be happy to help us with a small project, we are conducting to improve the quality of the data on CFHealthHub.

[If yes, continue. If no, see if you can arrange to speak with participant at a more convenient time.]

As part of a bigger piece of work, CFHealthHub aims to improve the medicines supply process, by ensuring that people with CF get the right amount of their nebulizer treatments when they need them. It's therefore really important that the data on CFHealthHub is as accurate as possible.

As you (may) know, CFHealthHub displays the days and the times that treatments are taken but it doesn't show which treatment has been taken at a given time. To ensure the data is as accurate as possible on CFHealthHub and provides a true reflection of the treatments taken at a given time, some things are screened out and don't appear on CFHealthHub. E.g., if you ever use "easycare" mode on your eTrack to clean your mesh (or aerosol head), this doesn't show on CFHealthHub as a treatment (it is screened out because it's not a treatment).

Sometimes people experience technical issues with their devices (e.g. cable issues, batteries lose power), which means they experience interruptions mid-treatment. This can sometimes show as two treatments on CFHealthHub (e.g., if you've had to turn your eTrack on again to deliver the remainder of the treatment), even though it is actually just a split dose. We are carrying out a small project to see if we can understand more about where treatments have been taken and where some have been screened out, along with the reasons for these.

I am ringing to see if we could have a look at your nebulizer data for the past week. It might take around 10 minutes in total – is now a good time to do that?

[If yes, continue. If no, see if you can arrange to speak with participant at a more convenient time.]

I've got a list of the times and days in front of me here. It would be great if we could have a look at the doses recorded on a given day and if you could say which treatments you think were taken on that day (some of these might have been screened out and so don't appear on CFHealthHub). Does that make sense? Have you any questions?"

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4 *[Go through times and dates provided by LL with the participant and ask the participant to*
5 *recall what they think happened at each time point e.g. did they take a treatment, and if so,*
6 *which treatment? Ask participant to try to recall anything out of the ordinary too, to identify*
7 *any split doses, and reasons for these etc.]*
8

9
10 **At the end of the call**

11 “Thank you very much for your time today. Please can I give you a ring in another week
12 to do the same thing again? It would be great if we could do this for another week to help
13 us see if we can understand these in more detail. Would that be ok?”

14 *[If yes, arrange time to call again in a week. Ask participant if they might be happy to keep*
15 *a log of the times and days they do a treatment for the next week (e.g. on their phone, or a*
16 *piece of paper). Ask them to note the: 1) date; 2) time; 3) name of treatment; 4) and anything*
17 *to note with each treatment or the eTrack in general e.g. Did they see two ticks – one when*
18 *the treatment had finished and one when the data had transferred? Did the device lose*
19 *power? Did they do an “easycare” clean? Did the grey cable disconnect? Did they pause their*
20 *treatment? Did they turn the device off or did it turn off itself? etc.]*
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Appendix C

Detailed explanation of how doses with different combinations of durations and interruption codes were triangulated with experiences of participants taking these doses and the participant-clinician consensus decision on completeness. This also describes and how decisions were reached on which doses to screen out from the calculator of the “daily complete dose count” in the algorithm.

Doses with duration <60s (not likely to be ‘complete’, as per the manufacturer’s recommendation)

Dose <60s and interruption code = 4

Four ~~Two~~ individual doses from ~~three~~ two participants were identified. Of these, one ~~three~~ (75%) ~~werewas~~ considered ‘incomplete doses’ by the clinician-participant consensus.

1) Three ~~One~~ doses ~~wasere~~ considered ‘incomplete’ and ~~werewas~~ immediately followed by a dose of the same medicine lasting >60s with interruption code 4, indicating a ‘complete’ dose.

2) One ~~One~~ dose was considered ‘complete’ and had interruption code 4, despite being <60s duration.

2)

Dose <60s and interruption code ≠ 4

Twenty-five individual doses from eight participants were identified. Of these, 23 (92%) were considered ‘incomplete doses’ . ~~Of the two doses considered as ‘complete’:~~

1) One dose was felt to be ‘complete’ by the participant.

2) One dose reflected an ‘incomplete’ dose followed by a ‘complete’ dose within one minute.

~~*Dose <60s and interruption code = 4*~~

~~Four individual doses from three participants were identified. Of these three (75%) were considered ‘incomplete doses’.~~

~~3) Three doses were considered ‘incomplete’ and were immediately followed by a dose of the same medicine lasting >60s with interruption code 4, indicating a ‘complete’ dose.~~

~~4) One dose was considered 'complete' and had interruption code 4, despite being <60s duration.~~

Given the low likelihood of doses <60s being genuinely 'complete', and the manufacturer's recommendation that no nebulised medicine dose should be delivered in <60s, we proposed screening out all doses that were <60s duration, irrespective of interruption code.

Doses with duration ≥ 60 s and interruption code 4 but considered incomplete.

~~Nine-Three individual doses from five-two participants were identified. Three of these doses have been discussed above. Of the remaining six:~~

~~1) One dose was considered incomplete and was immediately followed by a dose of the same medicine lasting >60s with interruption code 7.~~

~~2) One dose lasted 709s, but as the participant did not put the full volume of the salbutamol ampoule into the medicine reservoir, it was an 'incomplete' dose.~~

3)1) One dose was complicated by technical issues with the power cable (despite the interruption code not recognising this), and this was followed by a second attempt by the patient to administer the medicine.

4)2) One was the second attempt of the aforementioned dose.

5)3) One dose was interrupted, as the eTrack Controller seemed to lose power, though this was not reflected in the interruption code. It was followed by another dose of duration >60s and interruption code 4 which resulted in 'complete' delivery of the same medicine as this dose.

We propose considering doses of duration ≥ 60 s and an interruption code of 4 as 'complete'.

Doses with duration ≥ 60 s and interruption code 1 (mains supply power failure)

~~Two-One doses from two participants werewas identified. For one dose, the participant did not recall an electrical supply problem occurring with that dose, and as the dose had run for 770s, it was considered 'complete'. The other dose was considered incomplete complete due to there being an excessive residual~~

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3 ~~medicine volume in the medicine reservoir, but this was immediately followed by~~
4 ~~another dose to deliver the remainder of the nebulised medicine dose, which was~~
5 ~~then considered ‘complete’ as the participant manually disconnected the main~~
6 ~~power supply as the dose had already taken 590 seconds and they could see that~~
7 ~~the appropriate volume of liquid medicine has been administered.~~
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17 ~~Despite one of these doses being considered incomplete, given the whole context~~
18 ~~around that dose and how the algorithm would process the ‘complete daily dose~~
19 ~~count’, we do not~~We propose screening ~~out doses~~including doses which have an
20 interruption code 1 and ~~duration ≥ 60 s~~above a duration threshold which is likely
21 to represent a ‘complete’ dose. This duration threshold will be discussed in section
22 xxx. We ~~therefore~~ recognise that this ~~would~~ may inaccurately increase the
23 “daily complete dose count” ‘complete daily dose count’ in certain circumstances.
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31 *Doses with duration ≥ 60 s and interruption code 2 (disconnection of handset from*
32 *eTrack Controller)*
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35 ~~Eighty-one~~Seventy-nine doses from six participants were identified. ~~Two~~ Three
36 were considered ‘incomplete’, ~~three~~ ‘indeterminate’ and ~~seventy-six~~ six were
37 considered ‘complete’. ~~The~~ Two of the incomplete doses were from one
38 participant. On one occasion, ~~the~~ this participant felt the dose was taking too long
39 and terminated it manually, recognising that the residual volume of non-
40 aerosoliseized medicine left in the medication reservoir was greater than usual.
41 On the second occasion, the dose was manually terminated again as the
42 participant felt the medicine was not aerosolizing. For the third dose in this
43 category, the participant also terminated the dose early as they felt it was not
44 aerosolising correctly.
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54 In view of this, we do not propose screening out doses which have an interruption
55 code of 2 and duration ≥ 60 s.
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59 *Doses with interruption code 3 (dose started without medicine in reservoir)*
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No doses with interruption code 3 were identified. By definition, aAll doses with interruption code 3 would always be <60s duration and would be screened out by our the proposed algorithm.

Doses with interruption code 5 (manual shutdown of eTrack Controller)

Two doses from one participant were identified. Of these:

- 1) One dose was considered complete, with a duration of 1079s.
- 2) One dose followed a preceding dose which had been considered incomplete, in an attempt by the participant to deliver one 'complete dose'.

The combination of these two doses made for one 'complete' dose.

We do not propose screening out doses with interruption code 5. However, we recognise that, in situations such as number two described above there is a risk of an additional 'complete' dose being counted using this algorithm.

Doses with interruption code 6 (battery empty)

Nineteen Eighteen doses from seven six participants were identified. Of these, five were considered 'complete' and, 13 'incomplete' and the completeness of one dose could not be determined. As an interruption code 6 denotes a non-user-initiated early interruption, we can be confident, but not certain that it is unlikely that a 'complete' dose has been delivered, as seen in 13/189 (7268%) of examples.

Doses with non-user-initiated early termination (interruption code 1 and interruption code 6) and duration >60s

When analysing all doses with interruption code 1 or 6 (n=~~1121~~), six (28%) were considered 'complete' and 15 (71%) 'incomplete', four incomplete and one indeterminate. Screening Applying a duration threshold of out doses of duration <=480s (eight minutes) for exclusion left three remaining doses, all of which were considered complete and had durations of 590s, 606s and 707s respectively. Applying lower duration thresholds captured a combination of doses which were considered 'complete' and 'incomplete', hence the decision to apply the duration threshold of 480s.

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3 We therefore propose screening out doses with interruption code 1 and
4 interruption code 6 and duration <480s.
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8 Doses with interruption code 7 (timeout during inhalation mode)
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10 ~~Eighteen-Three~~ doses from ~~two-one~~ participants ~~were-was~~ identified. All three
11 doses were considered 'complete'. The duration of a dose with interruption code
12 7 will always be 1201s, as the eTrack Controller times out at this time during
13 inhalation mode. Prolonged dose durations may suggest the handset, through
14 which the liquid medicine is aerosoliseized, is worn, or clogged. ~~One of the~~
15 ~~participants, who recorded 15 of the 18 doses with interruption code 7 was not~~
16 ~~able to reliably determine if these doses were 'complete' or not. The other~~
17 ~~participant considered each of their interruption code 7 doses 'complete'.~~
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26 We do not propose screening out doses with interruption code 7, as after 20
27 minutes of nebulisation, we would expect a 'complete' dose to have been
28 administered, though this is not a certainty and is a recogniseized limitation of this
29 algorithm.
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35 Doses with interruption code 8 (timeout during pause mode)
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37 No doses were identified. As interruption code 8 denotes a dose which has timed
38 out during pause mode, we would expect that, by virtue of the dose being paused
39 (rather than terminated) by the patient, then the dose would not be considered
40 'complete'. The eTrack nebuliseizer will generate an interruption code of 8 if the
41 device is paused for >600s without being un-paused.
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47 We propose screening out doses with interruption code 8.
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50 Doses with interruption code 101-108
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52 ~~No One~~ doses ~~were-was~~ identified. As these doses refer to the "easycare" cleaning
53 mode, we do not expect any therapeutic doses to be administered with this
54 interruption code. We propose screening out all doses with interruption code 101-
55 108.
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Multiple doses starting within 120s.

~~55~~ Forty-three doses were identified across all participants. In most cases, they resulted from multiple attempts (recorded as individual doses) to deliver one 'complete' dose. We propose that all doses starting within 120s of the preceding dose start time should be combined with the preceding dose into a single dose and then processed as per the algorithm with respect to duration and interruption code.

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Table 1: Explanation of interruption code, adapted from “Interruption criteria explanations” (PARI GmbH, 2021).

Code	Definition	Complete dose
1	Loss of supply voltage to eTrack Controller	No
2	Disconnection of handset from eTrack Controller	No
3	Dose started without medicine in medication reservoir	No
4	Inhalation finished as expected	Yes
5	Manual shutdown of eTrack Controller	No
6	Battery empty	No
7	Timeout during inhalation mode (triggered at 120s)	No
8	Timeout during pause mode (triggered at 801s)	No
101-108	As above, but during the “ <i>easycare</i> ” (cleaning) mode	No

Table 2: Baseline characteristics of participants and datasets

	Derivation dataset	Validation dataset
<u>Characteristics of participants</u>	<i>N</i> = 10*	<i>N</i> = 10*
Age in years, median (range)	38 (23-62)	41 (23-49)
Female, n (%)	6 (60%)	7 (70%)
Chronic Pseudomonas, n (%)	7 (70%)	8 (80%)
Pancreatic insufficient, n (%)	8 (80%)	9 (90%)
CF related diabetes, n (%)	5 (50%)	6 (60%)
BMI, median (range)	23.5 (18-29.5)	23.5 (18-29.5)
%FEV ₁ , median (range)	82 (39-111)	73 (32-111)
<u>Characteristics of nebuliser doses</u>	<i>N</i> = 295 doses over 74 days	<i>N</i> = 309 doses over 69 days
Duration in seconds, median (IQR)	209 (134-409)	251 (149-403)
<60s, n (%)	26 (8.8)	30 (9.7)
60 to 600s, n (%)	232 (78.6)	229 (74.1)
>600s, n (%)	43 (14.6)	50 (16.2)
Multiple doses within 120s of each other, n (%)	50 (16.9)	56 (18.1)
Doses with interruption code		
"4", n (%) (<i>dose completed as expected</i>)	184 (62.4)	203 (65.7)
"1", n (%) (<i>loss of supply voltage</i>)	3 (1.0)	10 (3.3)
"6", n (%) (<i>battery empty</i>)	18 (6.1)	0 (0.0)
"8", n (%) (<i>device timeout during pause mode >600s</i>)	0 (0.0)	0 (0.0)
"101" to "108", n (%) (<i>easycare cleaning mode</i>)	1 (0.3)	5 (1.6)

Others	91 (29.4)
	89 (30.2)

*Note – Eight participants contributed data to both derivation and validation datasets and are included separately, with four participants only contributing data to either dataset. The total sample size for this project was 12.

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Table 3: Distributions of combinations of dose duration and interruption codes (IC) in the derivation dataset, with decisions of how to use these in the data processing algorithm

	Number of doses identified	Number (%) considered 'complete' by consensus	Algorithm formulation decision
<u>Dose duration <60s</u>			
Dose completed as expected (<i>IC = 4</i>)	2	1 (50%)	Exclude
Dose not completed as expected (<i>IC ≠ 4</i>)	25	2 (8%)	Exclude
<u>Dose Duration ≥60s</u>			
Loss of supply voltage (<i>IC = 1</i>)	1	1 (100%)	Include*
Disconnection of handset from eTrack Controller (<i>IC = 2</i>)	76	74 (97%)	Include
Dose started without medicine in chamber (<i>IC = 3</i>)	0		Exclude
Dose completed as expected (<i>IC = 4</i>)	178	175 (98%)	Include
Manual shutdown of eTrack Controller (<i>IC = 5</i>)	2	1 (50%)	Include
Battery empty (<i>IC = 6</i>)	18	5 (28%)	Include*
Device timeout at 1201s (<i>IC = 7</i>)	3	3 (100%)	Include
Device timeout at 601s during pause mode (<i>IC = 8</i>)	0	-	Exclude
<i>easycare</i> cleaning mode (<i>IC = 101-108</i>)	1	0 (0%)	Exclude

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* Include only if duration >480s. See Appendix C for detailed justification.

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Table 4: Kappa and accuracy scores for the algorithm-derived “daily complete dose count” against the gold standard consensus-derived “daily complete dose count” in the derivation and validation datasets.

	Derivation	Validation
Total ‘complete’ doses by algorithm	268	272
Total ‘complete’ doses by consensus	266	267
Accuracy (per day), %, (95% CI)	87.5 (77.0-95.7)	89.9 (84.3-95.5)
Kappa (95% CI)	0.85 (0.71-0.91)	0.86 (0.77-0.94)

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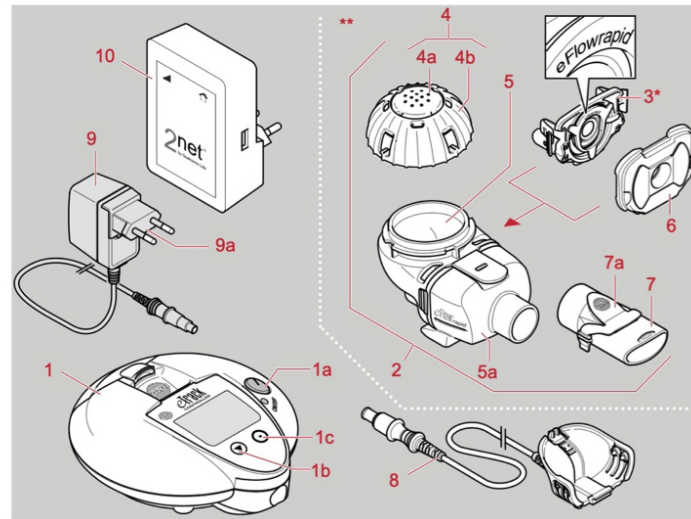
Table 5: Differences in total ‘complete’ doses and mean adherence calculations when using the algorithm-derived and consensus-derived “daily complete dose counts”

	Total ‘complete’ doses by algorithm	Total ‘complete’ doses by consensus	Absolute difference in ‘complete’ doses between algorithm and consensus	Mean adherence by algorithm	Mean adherence by consensus	Mean of all absolute differences in adherence between algorithm and consensus
Derivation dataset (295 doses, 74 days)	268	266	10 ^α	91.2%	90.7%	3.1%
Validation dataset (309 doses, 69 days)	272	267	7 ^β	92.3%	90.5%	2.8%

^α Among the 74 days of data, there were 66 days (89%) with identical “daily complete dose counts” by both algorithm & consensus, 4 days (5%) with a higher count by consensus and 4 days (5%) with a higher count by algorithm.

^β Among the 69 days of data, there were 62 days (90%) with identical “daily complete dose counts” by both algorithm & consensus, 1 day (1%) with a higher count by consensus and 6 days (9%) with a higher count by algorithm.

2 PRODUCT DESCRIPTION



1 Controller	7 Mouthpiece with 7a Expiratory valve (preassembled)
1a ON/OFF button	8 Connection cord (connection between the controller and the nebuliser handset)
1b Scroll button	9 Power adapter
1c Selection button	9a Interchangeable adapter (3 items)
2 Nebuliser handset (incl. aerosol head)**	10 Hub
3 Aerosol head	- <i>easycare</i> cleaning aid for backwashing the aerosol head
4 Medication cap (preassembled), consisting of:	- Batteries (4x)
4a Cap seal	
4b Cap	
5 Medication reservoir and	Check that all components are contained in the package. If anything is missing, tell the study coordinator.
5a Aerosol chamber (preassembled)	
6 Inspiratory valve	

* TouchSpray® Technology made under licence from the Technology Partnership PLC
 ** The nebuliser handset with aerosol head is not included in the package as supplied.

38

eFlow®*rapid* & eTrack®- 2018-12

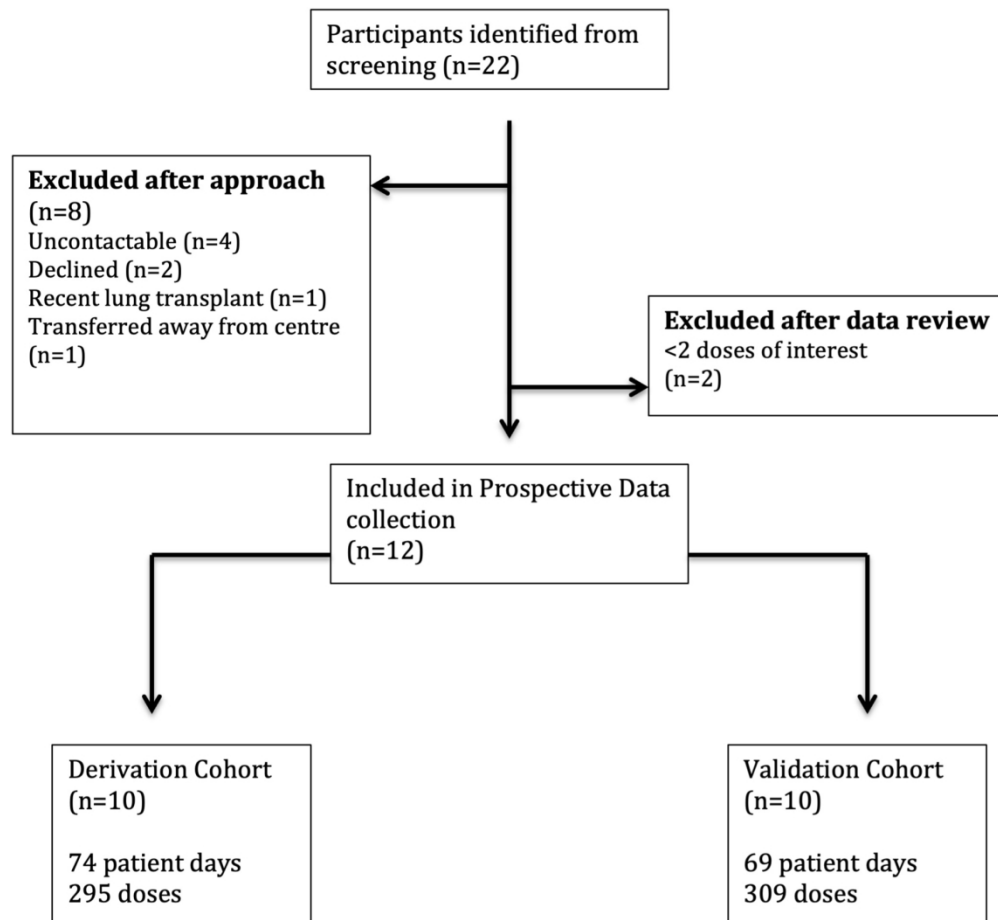
Diagram of the components of an eTrack nebuliser (from "Gebrauchsanweisung - Instructions for use. eFlow rapid nebuliser system & eTrack Controller, PARI, 2018-12).

146x207mm (150 x 150 DPI)

	A	B	C	D	E	F
1	Date & Time	Treatment Duration (seconds)	Interruption Code	Retrospective or Prospective	Dose 'complete' Y(1) N(0)	Description
57	14/11/2021 08:27	734	5	Prospective	1	HTS - power disconnected 8:39 had to restart, turned off at end as it kept going, only two drops left
58	14/11/2021 09:23	1201	7	Prospective	1	Colomycin - timed out and turned itself off as over 20 mins
59	14/11/2021 21:16	932	5	Prospective	1	HTS - finished at 21:31 had to turn off as kept running, made noise as if empty, worried about overheating
60	14/11/2021 21:50	1201	7	Prospective	1	Colomycin - went over 20 mins, displayed a 'I' and then turned itself off
61	14/11/2021 22:11	309	4	Prospective	0	Doesn't recall this extra treatment but when prompted, he suspects he may have put eTrack on again to get rest of the treatment if some left in chamber
62	14/11/2021 22:22	382	4	Prospective	1	Dnase turned off, no breaks and no restarts
63	15/11/2021 10:26	862	5	Prospective	1	HTS - patient says eTrack turned itself off
64	15/11/2021 11:05	1201	7	Prospective	1	Colomycin - timed out - displayed a 'I'
65	15/11/2021 20:55	819	5	Prospective	1	HTS
66	15/11/2021 21:59	1201	7	Prospective	1	Colomycin
67	15/11/2021 22:23	269	4	Prospective	1	Dnase

Example of a completed data collection form for a single participant.

146x36mm (150 x 150 DPI)



Recruitment and allocation flow diagram

159x147mm (300 x 300 DPI)