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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. Introduction

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

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

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

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

CFHealthHub centers have access to the cloud-based CFHealthHub digital platform which continuously captures and displays adherence data from 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 deliver a 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 607-participant randomized controlled trial (RCT) (15). CFHealthHub is now active in over 50% of adult CF centers in England, as an evidence-based digital platform and behavioural intervention, which empowers 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 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 nebulizer devices with electronic data capture (EDC) capability. The CFHealthHub digital platform is device agnostic, and compatible with both of the EDC-capable nebulizer devices used in the UK, the I-neb Adaptive Aerosol Delivery (AAD) System (Philips Respironics, Chichester, UK) and eFlow Technology nebulizers with an eTrack data-logging Controller (PARI Pharma GmbH, Starnberg, Germany), subsequently referred to as “eTrack 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 nebulizer, do not have this functionality and therefore require data processing algorithms to determine completeness of the dose delivery with accuracy. Therefore, this work focuses on data from eTrack nebulizers only. The component parts of the eTrack nebulizer, referred to throughout this article, are shown in Figure 1.

To ensure accurate calculation of percent adherence, the nebulizer data must be processed to count the number of doses of medicine which have been delivered ‘completely’ each day. This figure, produced for each day, is referred to as the ‘‘daily complete dose count’’. Each time a dose of medicine is initiated via an

eTrack nebulizer, a log is created with the timestamp, duration of the dose, and a numeric code (known as an interruption code) recording whether the dose was considered 'complete' or not (Table 1). An interruption code of "4" denotes a 'complete' dose. Alternative interruption codes suggest the dose may have been 'incomplete'. For example, an interruption code of "1" suggests the dose was interrupted due to loss of power supply to the eTrack nebulizer controller. Most medicines delivered via an eTrack nebulizer are expected to take between 2-8 minutes to complete, therefore, all doses with a very short duration (<60s) are likely 'incomplete' (Personal Communication, Dr C Fuchs, PARI GmbH, Email, Jan 2021).

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

- all duplicate doses, based on start time, duration, and interruption code,
- all doses of duration less than 60 seconds,
- all doses with interruption code 3 (suggesting there was no medicine in the device at the initiation of the dose),
- all doses conducted in the *EasyCare* cleaning mode (identified by an interruption code >100),
- all doses with a date of "01JAN2015' (suggesting device corruption).

After exclusions, the following doses are combined in calculating the "daily complete dose count".

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

There is ongoing, real-world learning in the CFHealthHub Learning Health System, where many more adults are using eTrack nebulizers. Approximately 6% of all doses recorded on the CFHealthHub digital platform had a duration of <60s and 24.5% were potentially 'incomplete', as per the interruption code, in the 12 months prior to this work. The most accurate method of processing data from these doses is uncertain and requires stronger evidence than advice from the manufacturer.

The objectives of this sub-analysis within CFHealthHub were: first, to understand how doses could be identified as 'complete' based on their duration and interruption code. Second, by triangulating eTrack nebulizer data with participants' records of taking each dose, to develop and validate a data processing algorithm to optimize the accuracy of the "daily complete dose count" used in percent adherence calculations. These objectives align with the key aim of developing the CFHealthHub digital platform as one which maximizes the salience of adherence data and may also serve as an exemplar for other platforms capturing digital adherence data remotely.

## 2. Participants and Methods

In this sub-analysis, data collected from eTrack nebulizers were triangulated against real-world records, created by adults with CF, of what happened during each dose. Participants were all eTrack nebulizer users who had consented to the CFHealthHub Learning Health System. Regulatory approval was provided by the London-Brent Research Ethics Committee (Reference number: 17/LO/0032).

This analysis included adults with CF who had ≥20 nebulizer doses that were either <60s in duration or potentially 'incomplete', as per their interruption code. There were no previous data to inform a target sample size. Since approximately 30% of doses were expected to be of short duration or potentially 'incomplete', 300 doses was chosen as a pragmatic target to provide 100 doses of interest, which should encompass an adequate range of different interruption codes. Due to constraints in clinical resources, the plan was to enrich the sample with the doses of interest (short duration and/or potentially 'incomplete') so that an adequate range of different interruption codes can be covered over a short time duration. Therefore, purposive sampling was used to identify participants with a particularly high number of doses of interest (≥20 doses of interest per week), such that 10 participant-weeks of data each for derivation and validation datasets was determined as sufficient.

Participants were included from three centers which are part of the CFHealthHub Learning Health System. These centers were selected due to the relatively high prevalence of eligible participants and the availability of clinicians to complete this work. Approximately 8,000 doses from the CFHealthHub digital platform were screened between 15th October 2021 and 31st October 2021 (two weeks prior to the sub-analysis start date). Data collection was between 1st November 2021 and 15th December 2021.

Local clinicians approached eligible adults with CF from these three centers using a standardized script to facilitate the initial discussion (Appendix B). In the first telephone call, participants were informed about this work and invited to provide verbal consent to participation. If they agreed, a longer call was arranged at a future time to discuss their nebulizer data.

*2.1 Phase 1 (data calibration)*

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

preceding week, extracted from the CFHealthHub digital platform. These data included the timestamp, duration, and interruption code for each recorded dose. To mitigate recall bias, clinicians used these data to help prompt participant recall of 1) the time the dose was started, 2) the medicine used for each dose, 3) if they considered the dose 'complete' or not, and 4) if relevant, a reason why the dose was considered '(in)complete'. Discussions around nebulizer usage are part of routine clinical care in CF and the data used to inform these discussions is available to all clinicians providing care to adults with CF enrolled in the CFHealthHub Learning Health System on request.

The clinician and participant reached consensus as to whether each nebulizer dose was likely to have been 'complete'. For example, the participant recognising an appropriate residual volume of the medicine in the medication reservoir suggests the dose was 'complete' even though the eTrack nebulizer had not recognized the dose as complete. Clinicians then asked participants to keep a record of their nebulizer usage for prospective data collection in Phase 2. Participants were asked to record the name of the medicine being nebulized and the date and time the dose was started. They were also asked to note anything remarkable about that dose, for example if they experienced a power failure or disruption, and if they considered the dose to be 'complete'. A follow-up call was then arranged with each participant to review their prospective record.

The purpose of Phase 1 was to familiarize participants with the process of discussing their nebulizer usage and to consider ways of determining whether a dose was 'complete', in preparation for the prospective data collection. Data from Phase 1 were not used in the analysis.

*Phase 2 (prospective data collection)*

Clinicians contacted participants at the agreed time to review 1-2 weeks of nebulizer data, extracted from the CFHealthHub digital platform, as described in Phase 1. These data were discussed with the participant and triangulated with their record of the corresponding doses, which the clinicians then cross-checked

against the nebulizer data. Clinicians completed a data collection form using Microsoft Excel (version 16.62). As in Phase 1, the clinician and participant reached consensus as to whether each recorded dose was considered 'complete' or not, along with a brief description, e.g., "participant reported their device timed-out after 20 minutes". An example of a completed data collection form is shown in Figure 2.

Following collection, the prospective data were divided into derivation and validation sets, prior to any analysis being undertaken. Therefore, clinicians were not aware of the resultant algorithm at the time of data collection. For participants providing two separate weeks of data, one week of data was allocated to derivation and the other week's data to validation. This was done to ensure both datasets contained an adequate range of interruption codes, given the small number of participants (n=12) and doses (approximately 300 in each data set).

Researchers reviewed the derivation dataset, consisting of nebulizer data (date & time, duration, and interruption code for each dose), and whether the dose was considered 'complete' by the clinician-participant consensus, with associated free text comments where available. First, all doses with duration of <60s were reviewed. Next, all doses with duration ≥60s were stratified by the interruption code listed in Table 1, and each resultant group was reviewed separately. With this information, an algorithm to calculate a "daily complete dose count" from the nebulizer data was developed, which used dose start time, duration, and interruption code only, to determine if a dose was likely to be 'complete'. Appendix C contains a full description of the number of doses in each combination of duration and interruption code, with a justification for how the algorithm would process these combinations, based on the triangulated nebulizer data and consensus "daily complete dose count". If a dose was likely to be 'complete', then it would be included and counted as a 'complete' dose, however if it was likely to be 'incomplete', it would be excluded or combined with another dose to create a single 'complete' dose.

The agreement between algorithm-derived "daily complete dose count" and consensus-derived "daily complete dose count" in the derivation dataset were determined using both percent accuracy and kappa values. In view of the clustered nature of the dataset, bootstrapping was used to calculate kappa and agreement values (17). This involved bootstrapping of 1000 samples from the original dataset, calculation of kappa and agreement values for each sample (i.e. 1000 values were calculated for each participant) and then ascending re-order of those values to provide a median, 2.5$^{th}$ and 97.5$^{th}$ centile as measures of central tendency and dispersion. In addition, the extent to which the algorithm under- or over-estimated the consensus-derived "daily complete dose counts" were quantified with absolute differences in both "daily complete dose counts" and percent adherence between the two measures.

An a-priori target was to proceed to validation if the algorithm-derived "daily complete dose count" was ≥80% accurate in comparison to the consensus-derived "daily complete dose count", which was considered as the 'reference standard'. If the accuracy was <80%, then the derivation dataset would be re-reviewed to refine the algorithm.

## 3. Results

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

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

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

each provided two weeks of data, compared to the four other participants, contributing one week of data each who were assigned to either the derivation or validation datasets in a 1:1 ratio. A total of 74 patient days (with 295 doses) from 10 patients were used in the derivation dataset and 69 patient days (with 309 doses) from 10 patients in the validation dataset. Dose durations and interruption codes for the derivation dataset were reviewed and results are reported in Table 3.

*3.1 Proposed screening algorithm*

We proposed the following process for identifying 'complete' doses from the nebulizer data.

1) Initially screen out:

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

2) Combine

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

3) Finally screen out:

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

*3.2 Accuracy of the proposed screening algorithm*

In the derivation dataset, there was a high level of agreement between the algorithm-derived "daily complete dose count" and the consensus-derived "daily complete dose count". The kappa co-efficient was 0.85 with 95% confidence interval of 0.71-0.91 and accuracy was 87.5% (77.0-95.7). Similar agreement and accuracy were seen in the validation dataset (kappa co-efficient 0.86 [0.77-0.94], accuracy 89.9% [84.3-95.5]). These results along with the total numbers of doses considered 'complete' by both the algorithm and consensus are reported in Table

4. The absolute differences in "daily complete dose count" between these two measures were 10 (out of 266 'complete' doses by consensus) in the derivation dataset and 7 (out of 267 'complete' doses by consensus) in the validation dataset. The absolute differences in mean percent adherence calculated using the "daily complete dose count" from these two measures were 3.2% and 2.8% respectively, as reported in Table 5.

## 4. Discussion

Through examination of nebulizer data and triangulation of these data with participant records, we have developed an algorithm to generate a "daily complete dose count". This algorithm involved excluding all doses of <60s, combining doses which start within 120s of each other and then using a combination of the interruption code and dose duration to determine which other doses are likely to be 'complete'. The resultant "daily complete dose count" was 87.5% accurate in the derivation dataset and 89.9% accurate in an internal validation dataset.

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

An erroneously high "daily complete dose count" risks overestimating adherence, which risks then falsely reassuring both adults with CF and clinicians that adherence is higher than it is. The consequence of this is that some people may be under-served by the health care system by not being offered adherence support when they could benefit from it. Furthermore, overestimating adherence may result in unnecessary treatment escalation in the event of clinical deterioration.

Conversely, underestimating adherence could create conflict between adults with CF and their clinicians and lead to both parties losing faith in the adherence data available on the CFHealthHub digital platform.

We recognize that the algorithm produced a marginally higher "daily complete dose count" than the participant-clinician consensus, which was considered the 'reference standard' in this project. However, the difference in percent adherence derived from the "daily complete dose count" (around 3% against an average adherence exceeding 90%) was clinically negligible. It is worth noting that a participant-clinician consensus for whether each dose of treatment is 'complete' is not feasible outside of a dedicated research project. It would be unreasonably burdensome for all participants on CFHealthHub to keep a detailed daily dairy of all their nebulizer doses. Therefore, we are reassured by the small differences noted in this study.

Within a Learning Health System where data used to generate knowledge which drives and measures improvement work, optimising data quality is critical (12). Previous quality improvement work, underpinned by large datasets, has focussed on measures of completeness, conformance and plausibility, through the production of automated functions with statistical software (19). In this work, we have developed an algorithm to improve calculation of "daily complete dose counts". This was strengthened by working alongside adults with CF to gain a qualitative understanding of circumstances of doses, from which quantitative data were produced.

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

There are however some limitations. To minimize the burden of adults with CF, there is a need to use a parsimonious study design enriching the cohort with participants with relatively high numbers of short or "potentially incomplete" nebulizer doses. By applying a purposive sampling strategy within three of the 15 CFHealthHub centers, the sample of participants could be criticized as being less generalizable. For example, the mean adherence of the sample exceeded 90% when real-world median adherence is only around 30% (9). However, this study design allowed us to capture an adequate range of short and/or 'potentially incomplete' doses to enhance the applicability of the resultant algorithm in a larger population.

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

Another limitation was reliance on patient self-report as to which medicine was being administered for each dose, and circumstances around doses which were considered potentially 'incomplete'. Currently, eTrack nebulizers lack the technology to identify the specific medicine being administered. We also cannot identify, from data alone, whether prolonged nebulisation duration is due to equipment malfunction or patient factors. We mitigated potential recall bias by prospectively asking participants to keep contemporaneous records for data collection during the study period, rather than relying on retrospective recall. We also cross-referenced their records against the nebulizer data. An alternate approach of direct observation of nebulizer usage in a controlled environment

would have allowed the gold standard data collection around whether a dose was 'complete' or not. This was considered unfeasible given the time and resource burden for clinicians and participants, which is a known barrier to participation in research within CF (23). Our chosen methods were parsimonious and better captured the real-world experience of adults with CF using eTrack nebulizers where factors such as consumable wear and dose interruptions come into play.

Finally, this study was limited to adults with CF who were using eTrack nebulizer devices, which represents 88% of the approximately 1400 adults with CF who are enrolled in CFHealthHub. At the time of this study, only two data-logging nebulizer devices are used in the UK: eTrack nebulizer and the I-neb. As an adaptive aerosol delivery device, the I-neb already provides dose completeness information in the following scale: "Full"; ">12.5%; <100%"; "<12.5%" and "none". Therefore, such an algorithm is not required for I-neb users.

This data processing algorithm will now be embedded within the CFHealthHub digital platform, where further validation in larger and more diverse cohort is recommended. These data are used to support adherence in the real-world setting (24). CFHealthHub also has a research arm, currently undertaking a large observational study, exploring the role of co-adherence to inhaled therapy for adults with CF who are taking novel oral treatments (25). Digital endpoints may present unique challenges in the value assessment of pharmaceuticals or cost evaluation of consumed medications. Recognising this, CFHealthHub adherence data are also used to optimize medicines supply by aligning supply with actual usage, with the potential to realize significant cost savings (26, 27). For both of these workstreams to be effective, data accuracy, which is strengthened by this work, is critical.

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

attention to data from digital measures can have real-world benefits for people with long-term conditions.

## 5. Conclusion

We have developed a data processing algorithm by triangulating nebulizer usage data with participants' real-world records, which was then tested in a multi-center dataset. The algorithm has high levels of accuracy. Co-designing and validating this algorithm helps optimize the accuracy of, and trust in, adherence data from the CFHealthHub digital platform. These data can be used to optimize clinical interactions at a patient-level, underpin quality improvement work at an organisation-level and facilitate national benchmarking at a system-level. The methods we use could also be applied by other platforms capturing digital adherence data remotely. Publication of data processing algorithms encourages confidence in Learning Health Systems embedded within routine clinical care.

**Declaration of Interest**

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**Article Highlights**

- Supporting adherence to medicine regimens in long-term conditions requires accurate measurement of adherence.

- The CFHealthHub Learning Health System offers a digital platform which can collect inhaled medicine usage data from nebuliser devices capable of electronic data capture.
- Clinicians and people with cystic fibrosis collaborated to develop a data processing algorithm for these usage data to calculate the number of complete doses taken each day (''daily complete dose count'').
- The resultant data processing algorithm was considered highly accurate for calculating the ''daily complete dose count''.
- Accurate nebuliser usage data processing allows for calculation of accurate adherence measurement, which can be used as both a digital study endpoint in but also as part of optimising routine care.

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*11 Eakin et al. Study demonstrating the importance of adherence in clinical outcomes for people with CF

**13. Sandler et al. An editorial describing the development journey and functions of CFHealthHub Learning Health System, since inception in 2014

**15. Wildman et al. RCT demonstrating that CFHealthHub increases adherence compared to usual 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

(dose A and dose B) on a single day. If the reality was that dose A was complete and dose B was incomplete, but the algorithm determined dose A was incomplete, but dose B was complete, the "daily complete dose count" would still, correctly, be 1.

## 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

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

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

## 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.*

Three individual doses from two participants were identified.

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.
2) One was the second attempt of the aforementioned dose.
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 ≥60s and an interruption code of 4 as 'complete'.

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

One dose was identified. The dose was considered complete as the participant manually disconnected the main power supply as the dose had already taken 590 seconds and they could see that the appropriate volume of liquid medicine has been administered.

We propose screening including doses which have an interruption code 1 and above a duration threshold which is likely to represent a 'complete' dose. This duration threshold will be discussed in section xxx. We recognize that this may inaccurately increase the "daily complete dose count" in certain circumstances.

*Doses with duration ≥60s and interruption code 2 (disconnection of handset from eTrack Controller)*

Seventy-nine doses from six participants were identified. Three were considered 'incomplete', and seventy-six were considered 'complete'. Two of the incomplete doses were from one participant. On one occasion, this participant felt the dose was taking too long and terminated it manually, recognising that the residual volume of non-aerosolized medicine left in the medication reservoir was greater than usual. On the second occasion, the dose was manually terminated again as the participant felt the medicine was not aerosolizing. For the third dose in this

category, the participant also terminated the dose early as they felt it was not aerosolising correctly.

In view of this, we do not propose screening out doses which have an interruption code of 2 and duration ≥60s.

*Doses with interruption code 3 (dose started without medicine in reservoir)*

No doses with interruption code 3 were identified. By definition, all doses with interruption code 3 would be <60s duration and would be screened out by 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 recognize 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)*

Eighteen doses from six participants were identified. Of these, five were considered 'complete' and 13 'incomplete'. 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 13/18 (72%) 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=21), six (28%) were considered 'complete' and 15 (71%) 'incomplete'. Applying a duration threshold

of <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.

We therefore propose screening out doses with interruption code 1 and interruption code 6 and duration <480s.

*Doses with interruption code 7 (timeout during inhalation mode)*

Three doses from one participant was identified. All three doses were considered 'complete'. The duration of a dose with interruption code 7 will always be 1201s, as the eTrack Controller times out at this time during inhalation mode. Prolonged dose durations may suggest the handset, through which the liquid medicine is aerosolized, is worn, or clogged.

We do not propose screening out doses with interruption code 7, as after 20 minutes of nebulisation, we would expect a 'complete' dose to have been administered, though this is not a certainty and is a recognized limitation of this algorithm.

*Doses with interruption code 8 (timeout during pause mode)*

No doses were identified. As interruption code 8 denotes a dose which has timed out during pause mode, we would expect that, by virtue of the dose being paused (rather than terminated) by the patient, then the dose would not be considered 'complete'. The eTrack nebulizer will generate an interruption code of 8 if the device is paused for >600s without being un-paused.

We propose screening out doses with interruption code 8.

*Doses with interruption code 101-108*

One dose was identified. As these doses refer to the "*easycare*" cleaning mode, we do not expect any therapeutic doses to be administered with this interruption code. We propose screening out all doses with interruption code 101-108.

**Multiple doses starting within 120s.**

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.

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

## 1. Introduction

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

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

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

CFHealthHub is a UK-based multi-~~centre~~center Llearning H~~h~~ealth S~~s~~ystem. A Learning Health System is described as "a health system in which outcomes and experience are continually improved by applying science, informatics, incentives and culture to generate and use knowledge in the delivery of care"(12) ~~m, which~~

~~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 randomi~~z~~sed 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 recogni~~z~~sed 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 aerosoli~~z~~sed 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 delivery~~determine completeness of the dose delivery with accuracy.

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

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

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

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

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

After exclusions, the following doses are combined in calculating the "daily complete dose count".

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

There is ongoing, real-world learning in the CFHealthHub ~~learning health system~~Learning Health System, where many more adults are using ~~the~~ eTrack ~~nebuliser~~nebulizers. Approximately 6% of all doses recorded on the CFHealthHub digital platform had a duration of <60s and 24.5% were potentially 'incomplete', ~~(~~as per the interruption code,~~)~~ ~~over~~ in the 12 months prior to this work. The most accurate method of processing data from these doses is uncertain and requires stronger evidence than ~~just expert~~ advice from the manufacturer.

The objectives of this sub-analysis within CFHealthHub were: first, to understand how doses could be identified as 'complete' based on their duration and interruption code. Second, by triangulating eTrack ~~nebuliser~~nebulizer ~~usage~~ data with participants' ~~experiences~~records of taking each dose, to develop and validate a data processing algorithm to optimi~~z~~se the accuracy of the "~~'complete~~ daily complete dose count"~~'~~ used in percent adherence calculations. ~~It is possible for a singular dose to be misclassified, but the algorithm still yield an accurate 'daily complete dose count' as explained in Appendix 1.~~ These objectives align with the key aim of developing the CFHealthHub digital platform ~~as a platform~~as one which

maximiseizes the salience of adherence data and may also serve as an exemplar for other platforms capturing digital adherence data remotely.

## 2. Participants and Methods

In this sub-analysis, data collected from eTrack nebulisernebulizers were triangulated against the real-world experiences records, created by adults with CF, of what happened during each doseof adults with CF. Participants were all eTrack nebulisernebulizer users who had consented to the CFHealthHub learning health systemLearning Health System. Regulatory approval was provided by the London-Brent Research Ethics Committee (Reference number: 17/LO/0032).

This analysis included people adults with CF who had ≥20 nebulisenebulizer d medication dosesdoses that were either <60s in duration or potentially 'incomplete', (as per their interruption code). There were no previous data to inform a target sample size. Since approximately 30% of doses were expected to be of short duration or potentially 'incomplete', 300 doses was chosen as a pragmatic target to provide 100 doses of interest, which should encompass an adequate range of different interruption codes. Due to constraints in clinical resources, the plan was to enrich the sample with the doses of interest (short duration and/or potentially 'incomplete') so that an adequate range of different interruption codes can be covered over a short time duration. Therefore, pPurposive sampling was used to identify participants with a particularly high number of doses of interests of relevant (short duration or potentially 'incomplete' doses (≥20 doses of interest per week), hence such that 10 participant-weeks' of data each for each derivation and validation datasets was determined as sufficient.

Participants were included from three centers which are part of the CFHealthHub learning health systemLearning Health System. These centers were selected due to the relatively high prevalence of eligible participants and the availability of clinicians to complete this work. Approximately 8,000 doses within from the CFHealthHub digital platform were screened between 15th October 2021 and 31st

October 2021 (two weeks prior to the sub-analysis start date). Data collection was between 1st November 2021 and 15th December 2021.

Local clinicians approached eligible ~~people~~ adults with CF from these three centers using a standard~~ise~~ized script to facilitate the initial discussion (Appendix B). In the first telephone call, participants were informed about this work and invited to provide verbal consent to participation. If they agreed, a longer call was arranged at a future time to discuss their ~~nebuliser~~nebulizer ~~usage~~ data.

2.1

*Phase 1 (data calibration)*

~~1.~~

Once relevant participants were identified for inclusion in this analysis local clinicians were provided with a log of each participant's ~~nebuliser~~nebulizer ~~usage~~ data for the preceding week, extracted from the CFHealthHub digital platform. These data included the timestamp, duration, and interruption code for each recorded dose. To mitigate recall bias, clinicians used these data to help prompt participant recall of 1) the time the dose was started, 2) the ~~medication~~ medicine used for each dose, 3) if they considered the dose 'complete' or not, and 4) if relevant, a reason why the dose was considered '(in)complete'. Discussions around ~~nebuliser~~nebulizer usage are part of routine clinical care in CF and the data used to inform these discussions is available to all clinicians providing care to ~~people~~ adults with CF enrolled in the CFHealthHub ~~learning health system~~Learning Health System on request.

The ~~participant and clinicians~~clinician and participant reached consensus as to whether each ~~logged~~ nebulizer dose was likely to have been 'complete'. For example, the participant recognising ~~that~~ an appropriate residual volume of the medicine in the medication reservoir suggests the dose was 'complete' even though the eTrack nebulizer~~Controller~~ had not recogn~~ise~~ized the dose as complete. Clinicians then asked participants to keep a ~~log~~ record of their ~~nebuliser~~nebulizer usage for prospective data collection in Phase 2. Participants were asked to record the name of the medicine being nebul~~ise~~ized and the date

and time the dose was started. They were also asked to note anything remarkable about that dose, for example if they experienced a power failure or disruption, and if they considered the dose to be 'complete'. A follow-up call was then arranged with each participant to review their prospective ~~log~~record.

The purpose of Phase 1 was to familiar~~ise~~ize participants with the process of discussing their ~~nebulisation experiences~~nebulizer usage and to consider ways of determining whether a dose ~~of nebulised medicine~~ was 'complete', in preparation for the prospective data collection. ~~T~~D~~he d~~ata from Phase 1 ~~was~~ were not used in the analysis.

### ~~2.2~~ *Phase 2 (prospective data collection)*

Clinicians contacted participants at the agreed time to review 1-2 weeks of ~~objective nebulisation~~ nebulizer data, extracted from the CFHealthHub digital platform, ~~(~~as described in Phase 1~~)~~. These data were discussed with the participant and triangulated with ~~using~~ their ~~contemporaneous~~ record ~~records~~ of the corresponding ~~nebulisations~~ doses, which the clinicians then cross-checked against the nebulizer ~~CFHealthHub~~ data. Clinicians completed a data collection form using Microsoft Excel (version 16.62). As in Phase 1, the ~~participant and clinician reached~~clinician and participant reached consensus as to whether each recorded dose was considered 'complete' or not, along with a brief description, e.g., "participant reported their device timed-out after 20 minutes". An example of a completed data collection form is shown in Figure 2.

Following collection, the~~The~~ prospective data were divided into derivation and validation sets, prior to any analysis being undertaken. Therefore, clinicians were not aware of the resultant algorithm at the time of data collection. ~~To ensure both datasets comprised an adequate range of interruption codes and considering the small number of participants, F~~for participants providing two separate weeks of data, one week of data was allocated to derivation and the other week's ~~weeks'~~ data to validation. This was done to ensure both datasets contained an adequate

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

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

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

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

quantified with absolute differences in both "daily complete dose counts" and percent adherence between the two measures.

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

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

## ~~1.~~3. Results

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

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

One week of data from 1~~0~~1 participants compr~~ise~~ized the derivation dataset, with one week of data from 10 participants comprising the validation dataset. ~~Nine~~ Eight of the 12 participants contributed data to both derivation and validation sets, as they each provided two weeks of data, compared to the ~~three~~ four other participants, contributing one week of data each who were assigned to either the derivation or validation datasets in a 1:1 ratio. A total of ~~80~~ 74 patient days (with ~~337~~ 295 doses) from 1~~0~~1 patients were used in the derivation dataset and 69 patient days (with 309 doses) from 10 patients in the validation dataset. Dose

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

*3.1 Proposed screening algorithm*

We proposed the following process for identifying 'complete' doses from the ~~CFHealthHub~~nebulizer ~~nebulisation~~ data.

1) Initially screen out:

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

2) Combine

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

3) Finally screen out:

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

*3.2 Accuracy of the proposed screening algorithm*

In the derivation dataset, there was a high level of agreement between the algorithm-~~generated~~derived "daily complete dose count" ~~'complete daily dose count'~~ and the consensus-derived "daily complete dose ~~coun~~count". The ~~t (~~kappa co-efficient was 0.85 with 95% confidence interval of 0.71-0.91 and~~6,~~ accuracy was 8~~78~~.5% (77.0-95.7)~~7%)~~. Similar agreement and accuracy were seen in the validation dataset (kappa co-efficient 0.86 [0.77-0.94], accuracy 89.9~~%~~% [84.3-95.5]). These results along with the total numbers of doses considered 'complete' by both the algorithm and consensus are ~~comparison of daily counts are~~ reported in Table 4. The absolute differences in "daily complete dose count" between these two measures were 10 (out of 266 'complete' doses by consensus) in the derivation dataset and 7 (out of 267 'complete' doses by consensus) in the validation dataset. The absolute differences in mean percent adherence calculated

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

## 4. Discussion

~~2.~~

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

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

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

deterioration. ~~–~~Conversely, underestimating adherence could create conflict between ~~people~~ adults with CF and their clinicians and lead to both parties losing faith in the adherence data ~~provided by~~ available on the CFHealthHub digital platform.

We recognize that the algorithm produced a marginally higher "daily complete dose count" than the participant-clinician consensus, which was considered the 'reference standard' in this project. However, the difference in percent adherence derived from the "daily complete dose count" (around 3% against an average adherence exceeding 90%) was clinically negligible. It is worth noting that a participant-clinician consensus for whether each dose of treatment is 'complete' is not feasible outside of a dedicated research project. It would be unreasonably burdensome for all participants on CFHealthHub to keep a detailed daily dairy of all their nebulizer doses. Therefore, we are reassured by the small differences noted in this study.

Within a ~~learning health system~~Learning Health System where data used to generate knowledge which drives and measures improvement work, optimising data quality is critical (12). Previous quality improvement work, underpinned by large datasets, has focussed on measures of completeness, conformance and plausibility, through the production of automated functions with statistical software (19). In this work, we have developed an algorithm to improve calculation of "daily complete dose counts"~~e daily dose count accuracy~~. This was strengthened by working alongside ~~people~~ adults with CF to gain a qualitative understanding of circumstances of doses, from which ~~the~~ quantitative data were produced ~~and allow accurate counting of the number of 'complete' nebulised medicine doses taken each day.~~

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

for improving care in long-term conditions (18). Continuous patient engagement is recommended during the evaluation phase of digital measures such as this (20, 21).

There are however some limitations. To minimize the burden of adults with CF, there is a need to use a parsimonious study design ~~Due to the need to~~ enrich~~ing~~ the cohort with participants with relatively high numbers of short or "potentially incomplete" nebulizer doses. ~~of nebulised medicine, we applied~~By applying a purposive sampling strategy within three of the 15 CFHealthHub centers, the sample of participants could be criticized as being less generalizable. For example, the mean adherence of the sample exceeded 90% when real-world median adherence is only around 30% (9). However, this study design allowed us to capture an adequate range of short and/or 'potentially incomplete' doses to enhance the applicability of the resultant algorithm in a larger population. ~~Therefore, the sample was not randomly generated, which means confidence in generalisability is reduced.~~

Due to the limited number of participants imposed by scarce resources, data from different weeks by the same participant were included in both the derivation and validation datasets. This ~~to~~ ensured an adequate range of interruption codes in both datasets. Whilst no individual dose appeared in both datasets, the inclusion of the same participant in both datasets meant that the validation dataset is not external to ~~to that of~~ the derivation dataset. ~~Reassuringly, for the one participant contributed to only the validation dataset, there was perfect agreement between the consensus- and algorithm-derived 'complete daily dose counts'.~~ Further validation of this algorithm in other CFHealthHub centers would be useful. The fact that CF is a rare disease, with approximately 7,000 adults with CF in the UK and the relative infrequency of potentially incomplete doses (<25% of all doses on the CFHealthHub digital platform) contributed to the small sample size of 12 participants and 604 doses (22).

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

which were considered ~~as~~ potentially 'incomplete'. Currently, ~~CFHealthHub~~ eTrack nebulizers lack~~s~~ the technology to identify the specific medicine being administered. We also cannot identify, from data alone, whether prolonged nebulisation duration is due to equipment malfunction or patient factors. We mitigated potential recall bias by prospectively asking participants to keep contemporaneous ~~logs~~ records for data collection during the study period, rather than relying on retrospective recall. We also cross-referenced their ~~logs~~ records against the ~~CFHealthHub~~ nebulizer data. An alternate approach of direct observation of ~~nebuliser~~nebulizer usage in a controlled environment would have allowed the gold standard data collection around whether a dose was 'complete' or not. This was considered unfeasible given the time and resource burden for clinicians and participants, which is a known barrier to participation in research within CF (23). Our chosen ~~methodology~~ methods were parsimonious and better capture~~d~~s the real-world experience of ~~people~~ adults with CF using eTrack ~~nebuliser~~nebulizers where factors such as consumable wear and dose interruptions come into play.

Finally, this study was limited to adults with CF who were using eTrack nebulizer devices, which represents 88% of the approximately 1400 adults with CF who are enrolled in CFHealthHub. At the time of this study, only two data-logging nebulizer devices are used in the UK: eTrack nebulizer and the I-neb. As an adaptive aerosol delivery device, the I-neb already provides dose completeness information in the following scale: "Full"; ">12.5%; <100%"; "<12.5%" and "none". Therefore, such an algorithm is not required for I-neb users.

This data processing algorithm will now be embedded within the CFHealthHub digital platform, where further validation in larger and more diverse cohort is recommended. ~~There are currently approximately 1400 patients across 14 UK Adult CF Centres enrolled in CFHealthHub, where~~ T~~t~~hese data are used to support adherence in the real-world setting (24). CFHealthHub also has a research arm, currently undertaking a large observational study, exploring the role of co-adherence to inhaled therapy for ~~PwCF~~ adults with CF who are taking novel oral treatments (25). Digital endpoints may present unique challenges in the value

assessment of pharmaceuticals or cost evaluation of consumed medications. Recognising this, CFHealthHub adherence data ~~is~~ are also used to optim~~ise~~ize medicines supply by align~~ing~~ supply with actual usage, with the potential to real~~ise~~ize significant cost savings (26, 27). For both of these workstreams to be effective, data accuracy~~the accuracy of CFHealthHub data~~, which is strengthened by this work, is critical.

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

## 5. Conclusion

~~3.~~

We have developed a data processing algorithm by triangulating ~~CFHealthHub nebuliser~~nebulizer usage data with participants' real-world ~~experience~~records, which was then tested in a multi-center dataset. The algorithm has high levels of accuracy. Co-designing and validating this algorithm helps optim~~ise~~ize the accuracy of, and trust in, adherence data from the ~~objective nebuliser usage data within~~ CFHealthHub digital platform. These data can be used to optim~~ise~~ize clinical interactions at a patient-level, underpin quality improvement work at an organisation-level and facilitate national benchmarking at a system-level. The methods we use could also be applied by other platforms capturing digital adherence data remotely. Publication of data processing algorithms encourages confidence in ~~learning health system~~Learning Health Systems embedded within routine clinical care.

**Declaration of Interest**

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**Article Highlights**

- Supporting adherence to medicine regimens in long-term conditions requires accurate measurement of adherence.
- The CFHealthHub Learning Health System offers a digital platform which can collect inhaled medicine usage data from nebuliser devices capable of electronic data capture.
- Clinicians and people with cystic fibrosis collaborated to develop a data processing algorithm for these usage data to calculate the number of complete doses taken each day ("daily complete dose count").
- The resultant data processing algorithm was considered highly accurate for calculating the "daily complete dose count".
- Accurate nebuliser usage data processing allows for calculation of accurate adherence measurement, which can be used as both a digital study endpoint in but also as part of optimising routine care

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*11 Eakin et al. Study demonstrating the importance of adherence in clinical outcomes for people with CF

**13. Sandler et al. An editorial describing the development journey and functions of CFHealthHub Learning Health System, since inception in 2014

**15. Wildman et al. RCT demonstrating that CFHealthHub increases adherence compared to usual 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 nebul~~ise~~ized 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

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

## 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 nebul~~ise~~izer 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 nebul~~ise~~izer 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**

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

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

## 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*

FourTwo individual doses from threetwo participants were identified. Of these, one three (750%) werewas considered 'incomplete doses' by the clinician-participant consensus.

1) ThreeOne 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 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 nebul~~ise~~ized 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.*

~~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 ≥60s and an interruption code of 4 as 'complete'.

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

~~Two~~ One doses ~~from two participants were~~was 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~~

~~medicine volume in the medicine reservoir, but this was immediately followed by another dose to deliver the remainder of the nebulised medicine dose, which was then considered 'complete'.~~as the participant manually disconnected the main power supply as the dose had already taken 590 seconds and they could see that the appropriate volume of liquid medicine has been administered.

~~Despite one of these doses being considered incomplete, given the whole context around that dose and how the algorithm would process the 'complete daily dose count', we do not~~We propose screening ~~out doses~~including doses which have an interruption code 1 and ~~duration ≥60s~~above a duration threshold which is likely to represent a 'complete' dose. This duration threshold will be discussed in section xxx. We ~~therefore~~ recogn~~ise~~ize that this ~~would~~ may inaccurately increase the "daily complete dose count" ~~'complete daily dose count'~~ in certain circumstances.

*Doses with duration ≥60s and interruption code 2 (disconnection of handset from eTrack Controller)*

~~Eighty-one~~Seventy-nine doses from six participants were identified. ~~Two~~ Three were considered 'incomplete', ~~three 'indeterminate'~~ and seventy-six~~six~~ were considered 'complete'. ~~The~~ T~~t~~wo of the incomplete doses were from one participant. On one occasion, ~~the~~ this participant felt the dose was taking too long and terminated it manually, recognising that the residual volume of non-aerosol~~ise~~ized medicine left in the medication reservoir was greater than usual. On the second occasion, the dose was manually terminated again as the participant felt the medicine was not aerosolizing. For the third dose in this category, the participant also terminated the dose early as they felt it was not aerosolising correctly.

In view of this, we do not propose screening out doses which have an interruption code of 2 and duration ≥60s.

*Doses with interruption code 3 (dose started without medicine in reservoir)*

No doses with interruption code 3 were identified. By definition, a~~A~~ll 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 recogn~~ise~~ize 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 13/1~~8~~9 (72~~68~~%) 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=~~11~~21), 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.

We therefore propose screening out doses with interruption code 1 and interruption code 6 and duration <480s.

*Doses with interruption code 7 (timeout during inhalation mode)*

~~Eighteen~~ Three doses from ~~two~~ one participants ~~were~~ was identified. All three doses were considered 'complete'. The duration of a dose with interruption code 7 will always be 1201s, as the eTrack Controller times out at this time during inhalation mode. Prolonged dose durations may suggest the handset, through which the liquid medicine is aerosol~~ise~~ized, is worn, or clogged. ~~One of the participants, who recorded 15 of the 18 doses with interruption code 7 was not able to reliably determine if these doses were 'complete' or not. The other participant considered each of their interruption code 7 doses 'complete'.~~

We do not propose screening out doses with interruption code 7, as after 20 minutes of nebulisation, we would expect a 'complete' dose to have been administered, though this is not a certainty and is a recogn~~ise~~ized limitation of this algorithm.

*Doses with interruption code 8 (timeout during pause mode)*

No doses were identified. As interruption code 8 denotes a dose which has timed out during pause mode, we would expect that, by virtue of the dose being paused (rather than terminated) by the patient, then the dose would not be considered 'complete'. The eTrack nebul~~ise~~izer will generate an interruption code of 8 if the device is paused for >600s without being un-paused.

We propose screening out doses with interruption code 8.

*Doses with interruption code 101-108*

~~No~~ One doses ~~were~~ was identified. As these doses refer to the "*easycare*" cleaning mode, we do not expect any therapeutic doses to be administered with this interruption code. We propose screening out all doses with interruption code 101-108.

**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.

**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 "*easycare*" (cleaning) mode | No |

**Table 2:** Baseline characteristics of participants and datasets

| | Derivation dataset | Validation dataset |
|---|---|---|
| Characteristics of participants | *N* = 10* | *N* = 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) |
| Characteristics of nebuliser doses | *N* = 295 doses over 74 days | *N* = 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 (%) (*dose completed as expected*) | 184 (62.4) | 203 (65.7) |
| "1", n (%) (*loss of supply voltage)* | 3 (1.0) | 10 (3.3) |
| "6", n (%) (*battery empty*) | 18 (6.1) | 0 (0.0) |
| "8", n (%) (*device timeout during pause mode >600s*) | 0 (0.0) | 0 (0.0) |
| "101" to "108", n (%) (*easycare cleaning mode)* | 1 (0.3) | 5 (1.6) |

| | |
|---|---|
| Others | 91 (29.4)<br>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.

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

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

**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) |

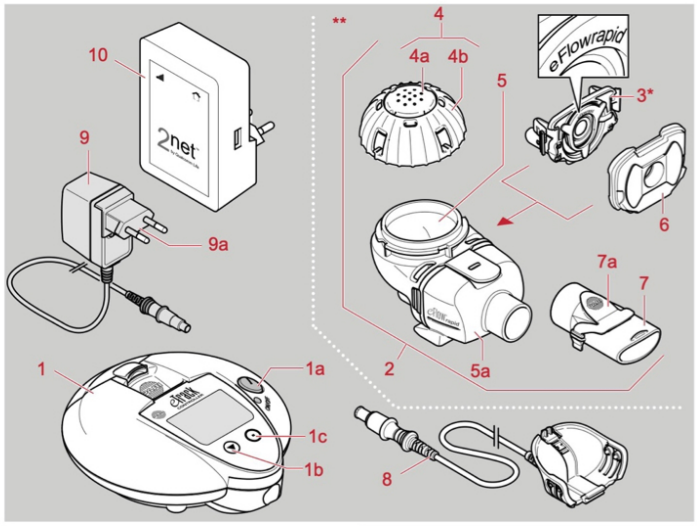
**Table 5:** Differences in total 'complete' doses and mean adherence calculations when using the algorithm-derived and consensus-derived "daily complete dose counts"

| | 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 |
| 1a | ON/OFF button |
| 1b | Scroll button |
| 1c | Selection button |
| 2 | Nebuliser handset (incl. aerosol head)** |
| 3 | Aerosol head |
| 4 | Medication cap (preassembled), consisting of: |
| 4a | Cap seal |
| 4b | Cap |
| 5 | Medication reservoir and |
| 5a | Aerosol chamber (preassembled) |
| 6 | Inspiratory valve |
| 7 | Mouthpiece with |
| 7a | Expiratory valve (preassembled) |
| 8 | Connection cord (connection between the controller and the nebuliser handset) |
| 9 | Power adapter |
| 9a | Interchangeable adapter (3 items) |
| 10 | Hub |
| – | *easycare* cleaning aid for backwashing the aerosol head |
| – | Batteries (4x) |

Check that all components are contained in the package. If anything is missing, tell the study coordinator.

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



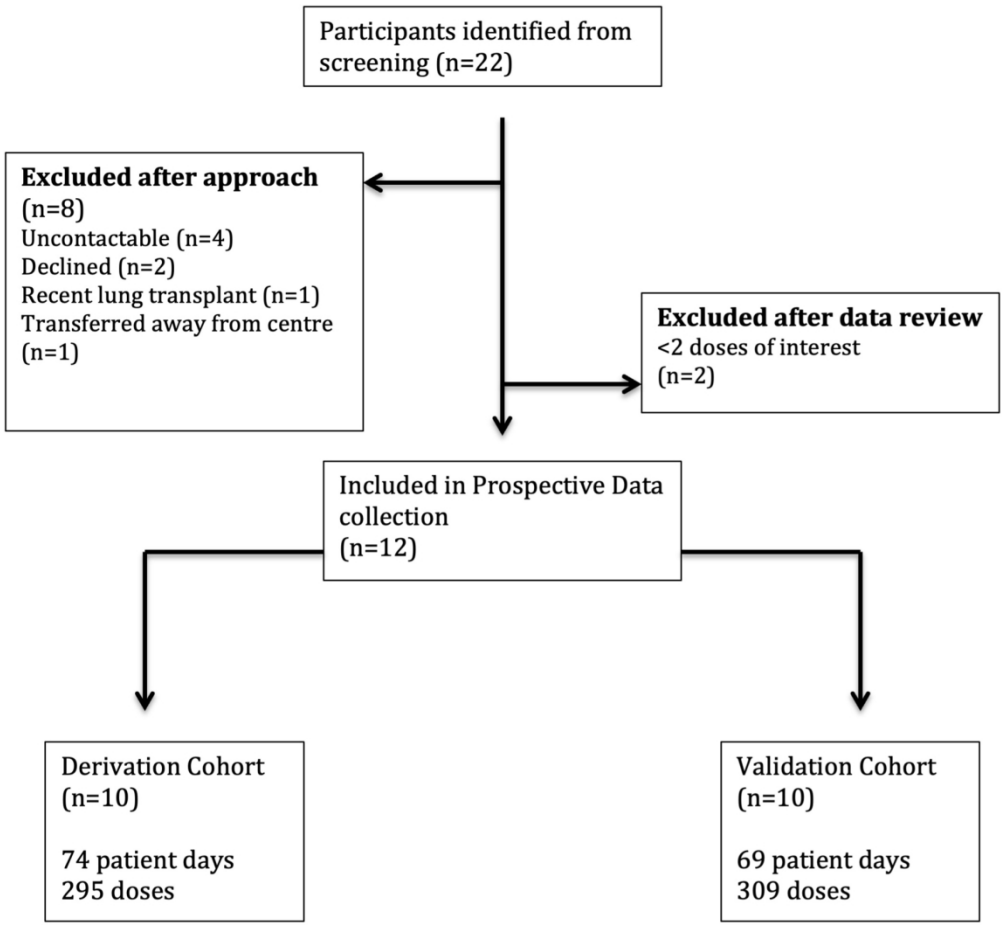
Diagram of the components of an eTrack nebuliser (from "Gebrauchsanweisung - Instructions for use. eFlow rapid nebuliser system & eTrack Controller, PARI, 2018-12).

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)