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ARTICLE

Remote FEV1 Monitoring in Asthma Patients: A Pilot Study

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Forced expiratory volume in one second (FEV_1) is a critical parameter for the assessment of lung function for both clinical care and research in patients with asthma. While asthma is defined by variable airflow obstruction, FEV_1 is typically assessed during clinic visits. Mobile spirometry (mSpirometry) allows more frequent measurements of FEV_1, resulting in a more continuous assessment of lung function over time and its variability. Twelve patients with moderate asthma were recruited in a single-center study and were instructed to perform pulmonary function tests at home twice daily for 28 days and weekly in the clinic. Daily and mean subject compliances were summarized. The agreement between clinic and mobile FEV_1 was assessed using correlation and Bland-Altman analyses. The test-retest reliability for clinic and mSpirometry was assessed by interclass correlation coefficient (ICC). Simulation was conducted to explore if mSpirometry could improve statistical power over clinic counterparts. The mean subject compliance with mSpirometry was 70% for twice-daily and 85% for at least once-daily. The mSpirometry FEV1 were highly correlated and agreed with clinic ones from the same morning (r = 0.993) and the same afternoon (r = 0.988) with smaller mean difference for the afternoon (0.0019 L) than morning (0.0126 L) measurements. The test-retest reliability of mobile (ICC = 0.932) and clinic (ICC = 0.942) spirometry were comparable. Our simulation analysis indicated greater power using dense mSpirometry than sparse clinic measurements. Overall, we have demonstrated good compliance for repeated at-home mSpirometry, high agreement and comparable test-retest reliability with clinic counterparts, greater statistical power, suggesting a potential for use in asthma clinical research.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Forced expiratory volume in one second (FEV1) is the gold standard in clinical care and research practice for assessing patients with asthma. Mobile spirometry (mSpirometry) provides an opportunity to collect frequent repeated measures remotely with minimum disruption to everyday life.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We sought to estimate concordance of mobile and clinic measures, establish patient compliance, assess diurnal variation of FEV_1, and explore whether at-home repeated FEV1 measures would improve statistical power over traditional clinic measures.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The mSpirometry FEV1 measurements were strongly correlated with clinic FEV1 from both the same morning (r = 0.993) and same afternoon/evening (r = 0.988). The mean subject compliance with mSpirometry was 85.3%. Our simulation analysis indicated a higher power using dense mSpirometry measurements.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Deploying mSpirometry in clinical trials is likely to improve statistical power.

Asthma is characterized by airway inflammation, airway hyper-responsiveness, and variable airflow obstruction.[1] Despite advances in our understanding of its pathophysiology, biomarker identification, and phenotyping, many patients remain poorly controlled. Asthma displays a strong circadian rhythm, which can cause symptom variability throughout a 24-hour period.[2,3] Clinical trials of novel drugs in asthma are faced with the challenge of measuring changes in lung function in this condition, which displays variable airflow obstruction, including diurnal fluctuations.

Forced expiratory volume in 1 second (FEV_1) is the gold standard for monitoring lung function in clinical care and research.[4] Traditionally, measurements of lung function are performed during clinic visits. However, the frequency of measurements is often limited in clinical trials due to feasibility considerations for patients and cost. Asthma is characterized by airflow obstruction, which displays a

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diurnal pattern. Diurnal variation is observed in lung function in healthy individuals[5] and is greater in patients with asthma.[6] The lowest FEV_1 measurements are observed in early morning hours coinciding with increased symptoms and airway inflammation.[7] The requirement for clinic visits limits the ability to capture this variability. These limitations impose requirements of a relatively large sample size for drug development clinical trials to control for measurement variability. Furthermore, frequent clinic visits can limit patient participation.

It is well known that multiple measures improve the accuracy of a measurement and therefore provide greater statistical power to detect a treatment difference in a measure with fewer patients.[8] The ability to monitor FEV_1 frequently may therefore be of benefit in clinical trials that evaluate treatment interventions in asthma. Frequent FEV_1 assessments can also help to account for diurnal variation. FEV_1 monitoring using mobile spirometers (mSpirometers) provides an opportunity to do at-home monitoring, collect dense data, and minimize the effect of random anomalous tests results that may occur during sparse clinic visits. Although mSpirometers provide convenient means for collecting lung function data at home, a concern about this modality is related to patient compliance and willingness to put the best effort to perform expiratory maneuvers while unsupervised.

The recent advances in remote FEV_1 monitoring demonstrated high correlation and small mean differences between at-home mobile handheld and clinic-based FEV_1 measurements in the context of randomized clinical trials in asthma[9] and chronic obstructive pulmonary disease (COPD).[10] However, the studies describing a comparison of clinic and mSpirometry data are limited, and study findings may be device-specific. Moreover, patient compliance with mSpirometry was reported only in patients with COPD,[10] indicating a need to establish compliance data in different populations, including asthma. Additionally, to our knowledge, no study has investigated if FEV_1 repeated measurements at home can improve statistical power to detect a treatment effect. The aim of our study was to build on previous findings, by verifying agreement between clinic and mobile FEV_1 measurements using a different spirometer device, establishing patient compliance in patients with moderate asthma. Furthermore, we used the data to perform power simulation to estimate the effect sizes that can be detected from either weekly clinic measurements or daily measurements at home in clinical trials.

METHODS

Patients

This was a single-center study performed at the Medicines Evaluation Unit based at the Manchester University Hospitals Trust, UK. Twelve patients with moderate asthma for at least a period of 2 years were recruited. The sample size was determined based on practical considerations and is typical for pilot studies investigating repeated measures.[11–13] No formal statistical sample size determination was performed.

Study subjects were enrolled if they met the following inclusion criteria: were male or female aged between 18 and 55 years; had body mass index 18–32 mg/m^2; used inhaled corticosteroid at doses equivalent to 400–1,000 µg/day beclomethasone dipropionate; demonstrated ability to perform satisfactory clinic and mSpirometry; possessed a smartphone and demonstrated the ability to use a mobile application; were nonsmokers or exsmokers with a cumulative tobacco exposure < 5 pack-years and have stopped smoking more than 1 year ago. Concomitant use of long acting β2 agonists (LABAs) was permitted. At screening, subjects were required to demonstrate a pre-bronchodilator FEV1 of 65–80% predicted together with an improvement in FEV1 of ≥ 12% and ≥ 200 mL following the inhalation of 400 µg salbutamol. The exclusion criteria included a history of life-threatening asthma, occurrence of asthma exacerbations or respiratory tract infections within 4 weeks prior to screening; diagnosis of any other airway pulmonary diseases, such as COPD; a history of clinically significant neurologic; endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, or other clinically significant organ system disease; a history of neoplastic disease; and patients who were treated with oral or parenteral corticosteroids in previous 8 weeks. The study was approved by the London Bromley Research Ethics Committee (16/LO/1474) and all subjects provided written informed consent.

Study design

Following screening, eligible subjects were issued and trained in the use of the mSpirometer and had to demonstrate at least two successful forced expiratory maneuvers. Data from the screening clinic visits were not used in subsequent analysis.

Subjects were instructed to use the mSpirometer at home for the next 28 days, performing measurements twice daily (06:00–10:00 and 18:00–22:00); subjects could also perform an optional third set of measurements between 11:00 and 13:00. At each timepoint, the subject was required to perform three forced expiratory maneuvers and the highest value of the three maneuvers were used for subsequent analyses. Subjects also attended the clinic at weekly intervals (every 7 days) for spirometry to be performed. Subjects attended clinic visits at the same time of day for the duration of the study during normal business hours for most of the clinic visits. During these visits, subjects performed forced expiratory maneuvers using the clinic spirometer. Subjects were required to withhold short acting β2 agonists for 6 hours prior to screening; LABAs were withheld for 12 hours prior to screening. Subjects were allowed to do their mobile or clinic spirometry at any time in relation to the last use of their bronchodilator.

Spirometry

Clinic spirometry was performed in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using either microlab or microloop spirometers (Care Fusion, Basingstoke, UK). Patients had to perform at least three technically acceptable maneuvers with the two highest FEV_1 and forced vital capacity values being ≤ 150 mL apart. The highest values of the three maneuvers were used for subsequent analyses.

The ambulatory mSpirometer device (Cohero Health, New York, NY, USA) is a Bluetooth enabled device that synchronizes with the BreatheSmart (Cohero Health) smartphone application. This application confirms with the patient that satisfactory forced expiratory maneuvers have been performed and electronically records the spirometry data obtained; the latter feature enabling determination of subject compliance.

Comparison of the mSpirometry and clinic FEV_1 measurements

To analyze the full set of mobile and clinic FEV_1 measurements, we used the residuals from a linear mixed model, which fit the subject as a random effect and the indicator to separate mSpirometry and clinic FEV_1 as a fixed effect. The residual indicates the deviation of each FEV_1 value from that subject's mSpirometry or clinic average FEV_1 value. Model residuals, instead of absolute FEV_1 values, were used because of a higher number of mSpirometry measurements than clinic measurements (~ 8 times), requiring an adjustment for subject averages. These residuals were grouped into morning (6:00–10:00) mSpirometry, evening (18:00–22:00) mSpirometry, before noon clinic, and afternoon clinic, and tested for pairwise differences using *t*-tests.

To further explore the relationship between mobile and clinic measurements in absolute values (not model residuals), mSpirometry FEV_1 measures were matched to the clinic FEV_1 with the smallest absolute difference in measurement time on the same day and stratified by morning and afternoon/evening measurement groups. We then used correlation and Bland–Altman analysis[14] to establish agreement. The 95% limits of agreement between the matched mSpirometry and clinic measurements were estimated as $d \pm 1.96s$ where d and s denote the mean and SD of the difference between mSpirometry and clinic FEV_1, respectively.

Test-retest reliability

Test-retest reliability or repeatability was estimated using the intraclass correlation (ICC). The ICC was estimated as the percentage of total variance that was between subjects. The between-subject and within-subject variances were estimated using a linear mixed model with FEV_1 as dependent variable and subject as random effect independent variable for mSpirometry and clinic FEV_1, respectively.

Power simulation

To assess whether densely collected mSpirometry data could improve power to detect the treatment effect in FEV_1, we used simulated interventional studies based on the following four datasets to mimic potential clinical trial design scenarios.

1. "Standard" using only the FEV_1 measurements from the first and last clinic visits per subject. This scenario intends to follow a standard analysis approach often deployed in asthma clinical trials. Linear regression model was used to estimate the treatment effect with FEV_1 values from the treatment period as dependent variable, the control/treatment group as independent variable, and average FEV_1 from the baseline period as regression offset.
2. "Multi-visit" using FEV_1 measurements from all five clinic visits after screening per subject. This scenario intends to maximize the use of clinic spirometry data. Linear mixed model (LMM) was used to estimate the treatment effect with FEV_1 values from the treatment period as dependent variable, control/treatment group as fixed effect independent variable, subject as random effect independent variable, and average FEV_1 from the baseline period as regression offset.
3. "Once-daily" using only one morning (6:00–10:00) mSpirometry FEV_1 measurement per subject per day, as described elsewhere.[6] This scenario intends to strike a balance between maximizing the use of dense mSpirometry measurements and minimizing the patient burden. A similar LMM as "multi-visit" was used. However, given a larger amount of data and increased degrees of freedom, this LMM accounts for one additional factor compared to the "multi-visit": time of day, accounting for the impact of disease diurnal variation.
4. "Dense" using all available mSpirometry FEV_1 measurements. This scenario intends to maximize the use of dense mSpirometry measurements. The same LMM as "once-daily" was used to estimate the treatment effect.

For all four simulation scenarios we divided our 4-week study into "baseline period" (first 2 weeks) and "treatment period" (last 2 weeks). The following steps were performed and repeated 500 times (i.e., 500 simulations):

1. We randomly assigned six subjects to be in the "control group" and the rest of the six subjects to be in the "treatment group."
2. For each of the four simulation scenarios, respectively, we calculated the average FEV_1 during the baseline period for each dataset, which was used as the offset in each respective regression model.
3. The four respective regression models for the scenarios described above were fitted; the estimated treatment effect recorded as the regression coefficient corresponding to the control/treatment group.

We recorded the estimated treatment effects from 500 simulations to form our null distribution. Using this empirical null distribution, we obtained the empirical critical values as the top and bottom 2.5th percentile, corresponding to a two-sided test of 5% significance.

We then used the simulation process above but added a simulated effect to FEV_1 values for the treatment group during the treatment period only. The simulated treatment effect or group mean difference is formulated as various values of effect size times the pooled SD for subjects from both the control and treatment groups. The pooled SD of FEV_1 in this study is 0.7 L. For a number of different values of effect size ranging from 0.05 to 0.2, empirical power was calculated as the percentage of simulations out of 500 simulations

in which the estimated treatment effect exceeded the previously established empirical critical values.

RESULTS

The study participants (n = 12) were predominantly male, mean age of 41 years, and were all nonsmokers. Five participants used LABA. The subjects had a mean post-bronchodilator FEV_1 of 69.7 % predicted with reversibility of 19.8% (**Table 1**).

Compliance

The mSpirometry compliance ranged from 33.9% to 98.2% across the study subjects; the number of measurements performed within the 2 prespecified morning/evening windows also varied. The mean compliance for all subjects was 69.9% with 468 observed of 670 expected combined morning and evening measurements being completed (**Table 2**). A total of 115 additional mSpirometry measurements occurred outside of the prespecified time windows. Subjects contributed at least one mSpirometry measurement per day on 85.3% of study days (**Table 3**). There was a slight decline in subject compliance as the study progressed (1.6 readings/day during week 1 and 1.3 readings/day during week 4).

Comparison of the mSpirometry and clinic FEV1 measurements

We compared the model residuals of FEV_1 measurements done at home and during clinic visits (**Figure 1**). The data set consisted of 245 morning (6:00–10:00) and 238 evening (18:00–22:00) mSpirometry measurements, and 27 clinic measurements done before noon and 33 clinic measurements in the afternoon. The morning mSpirometry FEV_1 measurements were statistically significantly lower than the evening mSpirometry FEV_1 ($P < 0.0001$). The morning mSpirometry FEV_1 measurements were numerically lower than, but not statistically different from, the clinic measurements done before noon ($P = 0.099$). There was no statistically significant difference between clinic FEV_1 measurements done in the morning and in the afternoon; likewise, there was no significant difference in the mean between clinic FEV_1 measurements done in the afternoon and evening mSpirometry.

We studied the correlations between matched measurements in absolute values (not model residuals) stratifying by morning and afternoon/evening measurement groups. The absolute time difference between the matched measurements were < 20 minutes for all except 2 pairs. The matched mSpirometry FEV_1 measurements were highly correlated with clinic FEV_1 from the same morning ($r = 0.993$; $P < 0.0001$) and the same afternoon ($r = 0.988$; $P < 0.0001$) as shown in **Figure 2a,b**.

Bland–Altman analyses between mSpirometry and clinic measurements were performed. The matched mSpirometry

Table 1 Demographic details of study participants

Characteristics	Mean (SD)
N	12
Age	41.1 (9.9)
Sex (F:M)	4:8
Pre-bronchodilator FEV_1, L	2.7 (0.6)
Pre-bronchodilator FEV_1, % predicted	69.7 (6.9)
Pre-bronchodilator FEV_1/FVC, %	61.3 (4.3)
Bronchodilator reversibility, mLs	513.3 (147.5)
Bronchodilator reversibility, %	19.8 (6.2)
Pack years smoked	0
Total ICS dosage, μg[a]	600 (400–1,000)
LABA (n/12)	5/12

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long acting bronchodilator.
[a]Data is shown as median (range).

Table 2 Subject mSpirometry compliance of twice daily measurements within specified time windows (06:00–10:00 and 18:00–22:00)

		FEV_1 measurement count			
Subject	Days on study	Expected (twice daily)	Observed (all measurements)	Observed (measurements within specified windows)	Compliance rate, %
1	29	56	73	52	92.9
2	29	56	52	46	82.1
3	28	54	45	39	72.2
4	29	56	51	45	80.4
5	29	56	54	43	76.8
6	29	56	45	33	58.9
7	29	56	46	30	53.6
8	28	54	36	33	61.1
9	29	56	62	55	98.2
10	29	56	33	19	33.9
11	30	58	28	22	37.9
12	29	56	58	51	91.1
Total	347	670	583	468	69.9

FEV_1, forced expiratory volume in 1 second; mSpirometry, mobile spirometry.

Table 3 Subject mSpirometry compliance of once daily measurements at any time

Subject	Number of clinics visits after screening	Days on study	Days with any measurement	Daily compliance rate, %
1	5	29	29	100.0
2	5	29	26	89.7
3	5	28	26	92.9
4	5	29	24	82.8
5	5	29	28	96.6
6	5	29	24	82.8
7	5	29	23	79.3
8	5	28	20	71.4
9	5	29	29	100.0
10	5	29	19	65.5
11	5	30	19	63.3
12	5	29	29	100.0
Total	60	347	296	85.3

mSpirometry, mobile spirometry.

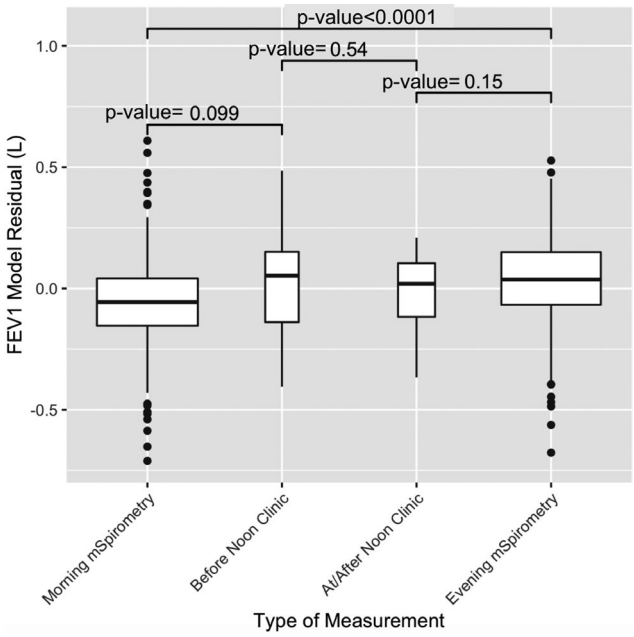

Figure 1 Comparison of forced expiratory volume in one second (FEV_1) model residual between mobile spirometry (mSpirometry), and clinical measurements. The FEV_1 model residual is the deviation of each FEV_1 value from the subject's mSpirometry or clinic average FEV_1 value.

and clinic FEV_1 from the same morning had a mean difference of 0.0126 L (SD = 0.1003 L, median = 0.0088 L, interquartile range = 0.1202 L) and 95% limits of agreement of (–0.1840 L, 0.2092 L); **Figure 2c**. The matched evening mSpirometry and clinic FEV_1 from the same day afternoon had a smaller mean difference of 0.0019 L (SD = 0.1000 L, median = 0.0156 L, interquartile range = 0.1412 L) and 95% limits of agreement of (–0.1940 L, 0.1979 L); **Figure 2d**.

Test-retest reliability assessment

The test-retest reliability or repeatability was assessed by ICC, which estimates consistency of measurements within the same study subjects. We compared the ICC for both mSpirometry and measurements done in the clinic. ICC values were comparable between mSpirometry (ICC = 0.932) and clinic spirometry (ICC = 0.942), indicating high repeatability.

Power simulation

To assess the statistical power afforded by conventional clinic FEV_1 measurements and mSpirometry, we performed power simulations using both measurements done in the clinic and mSpirometry data. We compared several scenarios of both clinic and mobile measurements. The results from 500 simulations suggested that the empirical power using sparse clinic data is lower compared with using dense mSpirometry data: the maximum power under effect size of 0.2 are 35.2% for a "standard" scenario (using clinic FEV_1 data from the first and last clinic visits), 44.2% for a "multi-visit" scenario (using data from 5 clinic visits), 75.6% for a "once-daily" scenario (using once daily morning mSpirometry data) and 94.2% for a "dense" scenario (using all available mSpirometry data), respectively (**Figure 3**).

DISCUSSION

Our results indicate that it is feasible to collect mSpirometry measurements in patients with asthma. Patients showed a reasonably high level of compliance, delivering 69.9% of the expected twice-daily measurements within prespecified windows, while 85.3% performed at least one measurement per day. The mSpirometry data were highly correlated with clinic spirometry. Our results concur with previous data[9] generated with other spirometry devices showing concordance between clinic and home spirometry. Furthermore, mSpirometry showed excellent repeatability over time. Modeling these data, we show how the collection of dense mSpirometry allowed increased statistical power. These findings demonstrate how mSpirometry can be used to design clinical trials with small subject numbers to measure the effects of pharmacological interventions.

A potential concern with mSpirometry is poor compliance, with patients being less able to perform adequate quality spirometric maneuvers while unsupervised. We observed that although some readings were missed, the multiple opportunities to record data allowed 12 subjects to provide over 500 mSpirometry measurements over 1 month. Furthermore, we confirmed a high correlation between the mSpirometry and clinic FEV_1 measurements, indicating that patients with asthma can perform adequate remote spirometry if trained properly. Our compliance results are similar to the home spirometry data reported in patients with COPD participating in a 52-week clinical trial,[10] indicating that achieving a relatively high compliance rate in a longer duration study is feasible. Additionally, high test-retest reliability of both assessments (ICC = 0.932 for mSpirometry and ICC = 0.942 for clinic spirometry), suggests that mSpirometry can supplement or even supplant clinic spirometry, reducing the number of site visits during a clinical trial.

The mean difference between morning mSpirometry and before noon clinic FEV_1 (0.0126 L) was higher than the mean difference observed between the evening mSpirometry and afternoon clinic FEV_1 (0.0019 L). This finding is consistent with asthma diurnal variation and should be taken into consideration when defining the time of at-home measurements. Circadian variation in asthma causes lower spirometry measurements in the early morning hours when the disease is at its nadir.[6] A larger difference between mSpirometry and clinic measurements observed in the morning compared with afternoon/evening suggests the impact of FEV_1 diurnal variation rather than suboptimal efforts by study subjects accounts for lower values collected at home. This is an important finding as it indicates the need to control for the time of the day when the pulmonary function tests are performed, and it requires a larger number of data points. This can be achieved by increasing the number of study subjects or number of measurements per subject. Deploying mSpirometry measurements at home gives an option of collecting more data from the same subject without an increase in sample size or number of site clinic visits. Our limits of agreement are narrower than the previously reported results.[9]

mSpirometry can be a useful tool for early phase development clinical trials when the efficacy and safety profiles of an investigational agent are not well-established. Having

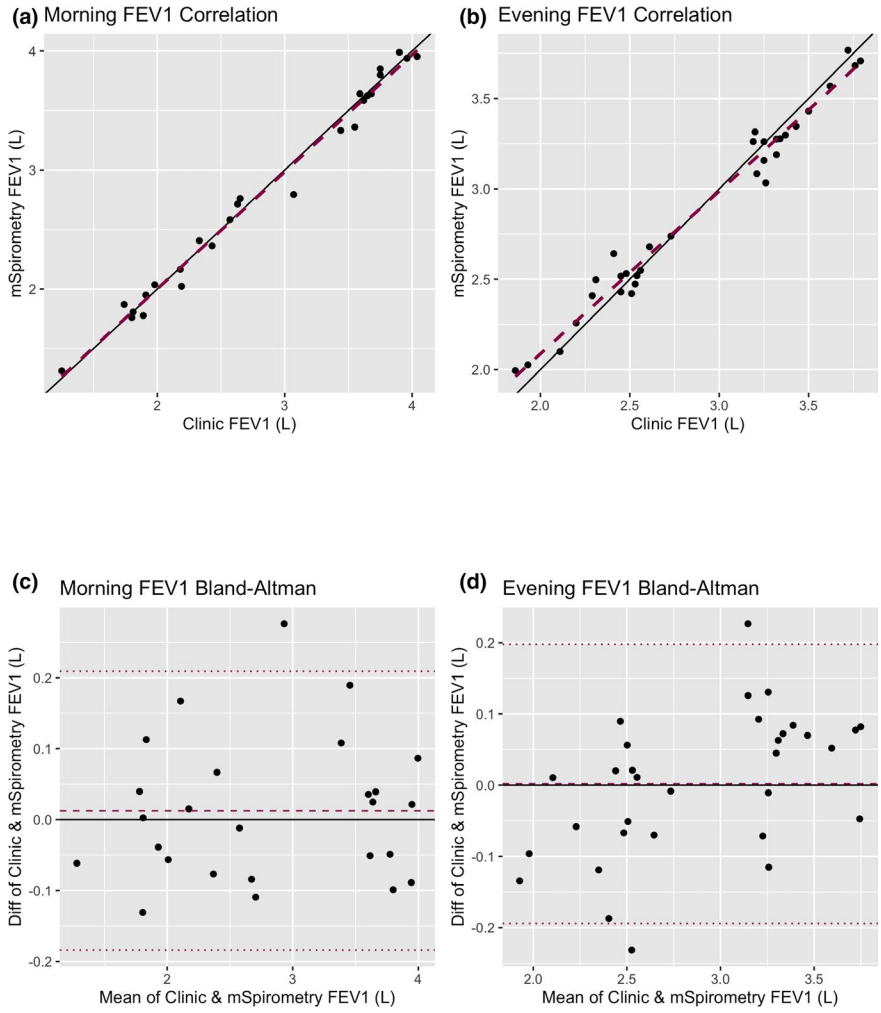

Figure 2 The comparison of mobile spirometry (mSpirometry) and clinic forced expiratory volume in one second (FEV_1) measurements in terms of correlation (**a, b**) and Bland–Altman (**c, d**) analyses. Panels **a** and **c** describe the morning FEV_1 values and panels **b** and **d** describe the afternoon/evening FEV_1 values. The black solid line on panels **a** and **b** is the 45-degree diagonal line that crosses the origin denoting perfect agreement; the dashed purple line indicates the observed linear relationship between mSpirometry and clinic FEV_1 measurements. The solid black line on panels **c** and **d** is the zero horizontal line denoting no mean difference; the dashed purple line indicates the observed mean difference between mSpirometry and clinic FEV_1 measurements; and the dotted purple lines indicate the upper and lower bounds of 95% limits of agreement between mSpirometry and clinic FEV_1 measurements.

frequent home mSpirometry measurement may provide very useful early information about both proof of concept (e.g., lung function change in response to treatment), or a potential safety signal (e.g., disease exacerbation). We therefore explored opportunities of reducing a clinical trial sample size using mSpirometry measurements. It is well known that multiple measures are able to improve accuracy of a measurement and decrease the sample size needed in clinical trials to demonstrate a treatment effect.[8] Here, we propose a way to characterize and reduce natural variability of a key clinical trial outcome, FEV_1, without increasing the sample sizes and hence the cost of such a trial. Collecting dense data minimizes the effect of random anomalous test results and corrects for factors that inherently increase variability, such as time of the day when the FEV_1 measurement is taken and seasonal effects, accounting for daily and seasonal allergen exposure variability. We provide an example of how increased measurements from home mSpirometry can reduce the number of subjects required for clinical trials in patients with moderate asthma.

Our study has certain limitations. This is a small, single center study with a limited number of study subjects enrolled. The small sample size may limit the representativeness of the study population and generalizability of the study results. The other limitation is a short study duration of 4 weeks. The results of this study would have to be confirmed in a larger, longer, multicenter interventional study that involves a treatment with well-defined efficacy and safety profiles.

Overall, our results indicate that mSpirometry data are in high agreement with clinic spirometry. We confirmed that both mSpirometry and clinic spirometry are impacted by diurnal variation, indicating the need for correcting for its effect. Moreover, we demonstrated that studies that assess

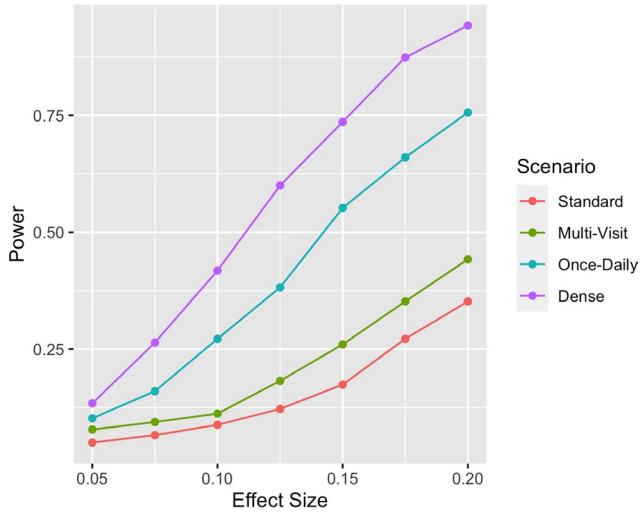

Figure 3 Empirical power to detect a treatment effect on forced expiratory volume in one second (FEV_1) with two-sided significance level of 0.05 from 500 simulations under four simulation scenarios (indicated by four colors). The red line shows the power of the "standard" scenario using only one baseline and one treatment period clinic measurements. The green line shows the power of the "multi-visit" scenario using measurements from all clinic visits after screening. The blue line shows the power of the "once-daily" scenario using all of the morning (6–10) mobile spirometry (mSpirometry) measurements. The purple line demonstrates the power of the "dense" scenario using all available mSpirometry measurements.

change in FEV_1 using dense home mSpirometry are likely to benefit from increased statistical power as well as the ability to account for a number of exogenous factors that impact FEV_1, such as time of the day.

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Author Contributions. C.H., E.S.I., R.E., G.B., D.S., and M.R. wrote the manuscript. G.B., N.J., M.R., and D.S. designed the research. N.J. and D.S. performed the research. C.H., E.S.I., R.E., and G.B. analyzed the data.

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