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Unsupervised home spirometry is not equivalent to supervised clinic spirometry in children and young people with cystic fibrosis: Results from the CLIMB-CF study

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Abstract

Background: Handheld spirometry allows monitoring of lung function at home, of particular importance during the COVID-19 pandemic. Pediatric studies are unclear on whether values are interchangeable with traditional, clinic-based spirometry. We aimed to assess differences between contemporaneous, home (unsupervised) and clinic (supervised) spirometry and the variability of the former. The accuracy of the commercially available spirometer used in the study was also tested.

Methods: Data from participants in the Clinical Monitoring and Biomarkers to stratify severity and predict outcomes in children with cystic fibrosisc (CLIMB-CF) Study aged ≥ 6 years who had paired (±1 day) clinic and home forced expiratory volume in 1 s (FEV_1) readings were analyzed. Variability during clinical stability over 6-months was assessed. Four devices from Vitalograph were tested using 1 and 3 L calibration syringes.

Results: Sixty-seven participants (median [interquartile range] age 10.7 [7.6–13.9] years) provided home and clinic FEV_1 data pairs. The mean (SD) FEV_1% bias was 6.5% [±8.2%]) with wide limits of agreement (−9.6% to +22.7%); 76.2% of participants recorded lower results at home. Coefficient of variation of home FEV_1% during stable periods was 9.9%. Data from the testing of the handheld device used in CLIMB-CF showed a potential underread.

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Conclusion: In children and adolescents, home spirometry using hand-held equipment cannot be used interchangeably with clinic spirometry. Home spirometry is moderately variable during clinical stability. New handheld devices underread, particularly at lower volumes of potential clinical significance for smaller patients; this suggests that supervision does not account fully for the discrepancy. Opportunities should be taken to obtain dual device measurements in clinic, so that trend data from home can be utilized more accurately.

KEYWORDS
cystic fibrosis, remote monitoring, remote spirometry, unsupervised spirometry

1 | INTRODUCTION

Spirometry-derived volumes, in particular forced expiratory volume in 1 s (FEV_1), have been routinely used in cystic fibrosis (CF) clinics for decades.[1] Serial spirometry measurements based on technical and quality standards[2] are used longitudinally to monitor disease progression[3,4] and to detect periods of exacerbation. Over recent years there has been an increase in the number of handheld spirometers available commercially and in the possibilities of monitoring lung function remotely at home. This was especially important during the coronavirus 19 (COVID-19) pandemic when many CF centers moved to virtual clinics, providing handheld spirometers to patients.

Studies in adults (healthy and a range of lung diseases) comparing handheld spirometers with conventional hospital spirometers, have reported good agreement between the devices.[5–9] The majority of these compared one specific handheld spirometer with a conventional hospital spirometer under the direct supervision of a trained medical professional. Comparison of unsupervised handheld and supervised hospital spirometry in patients who had undergone allogenic hematopoietic cell transplant showed a mean FEV_1 under-read of −0.24 L (95% confidence interval −0.32 to −0.17 L) in the handheld devices.[7] A recent publication from the Early intervention in CF exacerbation (eICE) study compared home and clinic spirometry readings and estimated that FEV_1 readings from the former were an average of 2 (95% confience interval [CI]: 0.3–3.5) percentage points lower than the latter.[10]

The data from pediatric studies is less clear. One recent study concluded the Nuvoair Air Next device was technically valid for children over 6 years of age using a mixed cohort of asthma and CF (mean age 10.2 years). They compared the handheld device with a conventional clinic spirometer, both used under supervision. There was a mean overread of +40 mL for FEV_1 for the handheld spirometer, although the 95% limits of agreement were wide (−270 to 352 mL).[11] In contrast, another study concluded that hand-held spirometers could not be used interchangeably with conventional hospital spirometers, reporting a bias of −65 mL with 95% limits of agreement of +189 to −319 mL for FEV_1 (L).[12] Shakkottai et al reported intra-class correlations between handheld devices and clinic spirometers ranging from 0.69 to 0.95 at different time points during the year-long study of 39 young people with CF (mean age 15.9 years).[13] Another study explored the relationship between unsupervised home spirometry and supervised hospital spirometry in children with CF and asthma. The home spirometer underread in the 23 children with CF, and of interest, this discrepancy increased significantly with age.[14]

We have recently completed Clinical Monitoring and Biomarkers to stratify severity and predict outcomes in children with cystic fibrosis (CLIMB-CF), a study exploring the feasibility of home monitoring of children and young people with CF. CLIMB-CF started enrolling in 2017 adopting one of the first completely Bluetooth handheld spirometers available in the market and demonstrated adherence to home twice weekly spirometry to be 58% over a 6 month study period.[15] The data from the study provides opportunity to address other research questions of relevance to this group of patients. In this study, based on a hypothesis that home spirometry could be used interchangeably with clinic measurements, we aimed to answer three research questions:

1. Were there differences between readings obtained unsupervised at home during the study period and those achieved in CF clinic with encouragement and supervision, and if so, did differences decrease (due to practice) over the course of the CLIMB-CF study?
2. How variable were unsupervised home spirometry readings during periods of clinical stability in participants from the CLIMB-CF study?
3. How accurate was the Vitalograph lung monitor BT Smart spirometer when tested using syringes of a known volume?

2 | METHODS

2.1 | CLIMB-CF study design

CLIMB-CF was a multicentre study assessing feasibility and acceptability of home monitoring for children with CF. Full methodology has been previously published[16] but in summary participants aged between 2 and 16 years were enrolled at six sites in the UK and two sites in Canada. Over 6 months they were asked to collect multiple measures at home at the same time of day (Supporting Information: Methods). Participants aged $\geq$ 5 years were asked to provide lung function measures twice a week via a Vitalograph lung monitor BT Smart. Participants and their parents were trained in the use of the handheld spirometer face to face

by a member of the study team and videos were also provided. The members of the study team at each site had received training on the device by the lead study team during their site set up and the videos were produced by the lead site trainer. Each participant was provided with a nose clip, although consistency of use was not documented. Participants were asked to repeat spirometry three times during each reading. The CLIMB-CF app automatically selected the highest valid lung function result as determined by the internal software on the handheld spirometer. This value was then uploaded to a web-based study database. The study design also included an acceptability and feasibility questionnaire to be completed by parents and participants aged ≥ 12 years at the end of the study.

2.2 | Comparison of unsupervised home spirometry readings with supervised lung function readings obtained in clinic

Data from participants aged ≥ 6 who had paired supervised routine clinic and unsupervised home FEV_1 readings (±1 day apart) were included. This age cut-off was used as guidelines for spirometry in children aged less than 6 years recommend supervision by experienced professionals.[17] If participants had more than one reading meeting these criteria during the study period, their first was used for this initial analysis. In a subsequent analysis, participants with at least three such episodes had their first, second and last paired measures analyzed to seek temporal trends suggestive of either learning or fatigue. Supervised clinic spirometry was carried out as per the individual site's standard operating procedure.

2.3 | Variability of unsupervised home spirometry readings during periods of clinical stability

All participants aged 6 or over who provided home spirometry readings were included in this analysis. Any readings obtained within a month of a pulmonary exacerbation (defined by the start date of antibiotics for increased respiratory symptoms) were excluded from the analysis (these data are being analyzed separately in a sub-study). Recorded height was updated for each participant after their documented clinic visits.

2.4 | Testing the hand-held device with calibration syringes

Two syringes were used: a 1 L fixed volume syringe (CareFusion calibration pump) and a 1L-3L adjustable volume syringe (Series 5530; Hans Rudolph inc.) set to 3 L. Volumes of both syringes were recorded in triplicate on a calibrated Jaeger Vyntus Pneumo Spirometer (Vyaire Medical Illinois) at the Lung Function Department at the Royal Brompton Hospital. These syringes were subsequently used to test 4 new, unused hand-held Vitalograph lung monitor BT Smart spirometer (Vitalograph, Buckingham). Each device was tested in triplicate on four separate occasions in a random order.

2.5 | Statistics

This was a pragmatic feasibility study and therefore no formal sample size calculations were performed. All raw data were converted using global lung function initiative normative data to obtain percent predicted values using height documented at the clinic visit. GraphPad Prism 9.0.2 and SPSS 28.0.0 were used to generate Bland–Altman plots to determine agreement between the supervised clinic spirometry readings and the unsupervised home spirometry readings. The bias (mean difference between the devices) and standard deviation (SD) for FEV_1 percent predicted (% predicted) was calculated by subtracting the unsupervised home measurement from the clinic measurement. Correlation coefficients were calculated for the clinic and home measurement data sets. Simple linear regression was used for age and differences in litres and percent predicted analysis. Nonparametric paired data were compared using Wilcoxon signed rank test and non-parametric unpaired data were compared using Mann–Whitney *U* test. The Kruskal–Wallis test was used for nonparametric multiple comparisons data sets. Coefficient of variation (CoV) was calculated per individual to assess variability during stability. Means and SD for each device were calculated by combining every replicate for each device.

3 | RESULTS

3.1 | Clinical data

CLIMB-CF recruited 144 participants, of whom 98 provided home spirometry data. 67 participants had readings that met the criteria for matched clinic and home readings; 18 participants met the criteria to provide three matched clinic and home readings during the study (Table 1, Figure 1).

3.2 | Comparison of unsupervised home spirometry readings with spirometry readings obtained under supervision in clinic

Unsupervised home spirometry readings were compared with supervised clinic spirometry readings for 67 participants with a median (interquartile range [IQR]) age of 10.7 years (7.6–13.9). We analyzed data from the cohort, as well as separately for 6–11 and ≥12 years of age (Supporting Information: Table 1). There was a significant difference between the values obtained at home vs those obtained in clinic ($p = <0.001$) with lower home spirometry values seen in 51/67 (76.2%) of participants. The bias (mean [SD] for FEV_1 percent predicted was 6.5% [±8.2%]). Limits of agreement were wide, −9.6% to +22.7% (Figure 2). These bias and wide limits of agreement were similar in both age subgroups. The same pattern was seen in the bias and limits of agreement for absolute (L) FEV_1 readings (Supporting Information: Table 1).

The differences between unsupervised home spirometry and supervised clinic readings for both FEV1 in litres and FEV1% predicted by age analyzed using linear regression are shown in Figure 3. There was

TABLE 1 Summary table of the demographics of participants in each of the three groups reported in this paper.

		Participants with paired clinic and home spirometry reading ($n = 67$)	Participants with three paired clinic and home spirometry reading ($n = 18$)	Participants providing home spirometry readings during periods of stability ($n = 74$)
Gender		36 (54%) female	7 (39%) female	45 (61%) female
Age (years); median (IQR)		10.7 years (7.6–13.9)	11.3 years (7.6–13.87)	10 years (7.8–12.7)
Weight z scores; median (IQR)		0.12 (−0.58 to 0.73)	0.08 (−0.52 to 0.86)	0.12 (−0.59 to 0.55)
Ethnicity	White	63 (94%)	17 (94%)	71 (96%)
	Minority ethnic groups	4 (6%)	1 (6%)	3 (4%)
Genotype	F508del/F508del	44 (66%)	11 (61%)	47 (64%)
	F508del/Other	20 (30%)	5 (28%)	23 (31%)
	Other/Other	3 (4%)	2 (11%)	4 (5%)
$ppFEV_1$; median (IQR)		92.8% (81.9–97.1%)	92.1% (80.3–100.9%)	90.9% (83.4–96.3%)
Pancreatic insufficient		61 (91%)	16 (89%)	69 (93%)
Cystic Fibrosis related diabetes		8 (12%)	2 (11%)	8 (11%)
Liver disease (including fatty liver)		4 (6%)	2 (11%)	7 (95%)
Previous* *Pseudomonas aeruginosa*		43 (64%)	13 (72%)	45 (61%)
Previous* *Mycobacterium abscessus*		3 (45%)	1 (5%)	3 (4%)
Previous[+] ABPA		6 (9%)	4 (22%)	4 (5%)
Intravenous courses of antibiotics in previous 6 months Median (IQR)		0 (0–1)	0.5 (0–1)	0 (0–1)
Oral courses of antibiotics in previous 6 months Median (IQR)		1 (1–2.75)	1 (1–2.25)	1 (1–2)

Note: *Defined as any sputum culture positive documented in medical notes by the site and not cultured during the study period. [+]Participants could be included in more than one group.

Abbreviations: IQR, interquartile range, ppFEV1, percent predicted Forced expiratory volume over 1 s.

no relationship with age in the absolute (L) discrepancy between readings, but the impact in terms of % predicted was significantly age-related, being greater at younger ages (p 0.005 r^2 0.116). When looking specifically at measures with a difference ≥ 10% (19 (28.4%) of participants) this was seen more commonly in the younger participants aged 6–11 (35.5%) than the older (13.6%), although this did not meet statistical significance.

We wondered whether the wide limits of agreement could have reflected the 1-day window allowed between home and clinic measurements, so we looked separately at paired measures obtained on the same day versus 1 day apart. 29 subjects (43%) had same day measurements; neither equipment differences nor limits of agreement were significantly different from the 37 subjects who had measures on different days (Supporting Information: table 2).

We also explored whether agreement of home measures and those in clinic would change with the time subjects had been in the study. Eighteen participants, median (IQR) age of 11.3 years (7.6–13.87), had three paired clinic and home spirometry readings which met the inclusion criteria (Table 2). Over a median period of 17.5 (15.7–23.1) weeks, neither a learning effect, nor any worsening in the agreement was apparent (Figure 4, Supporting Information: Table 3).

3.3 | Home spirometry readings during periods of clinical stability

Spirometry had been requested twice weekly by participants in CLIMB-CF; during the 6 month study period subjects completed a median (IQR) of 58.3% (29.2–100%) of requested spirometry measures. 74 participants with a median (IQR) age of 10 years (7.8–12.7) provided a median (IQR) of 20 (8–35) serial measures during periods of protocol-defined clinical stability. Median (IQR) CoV of FEV_1% predicted was 9.9% (5.8–14.2%). There was no difference

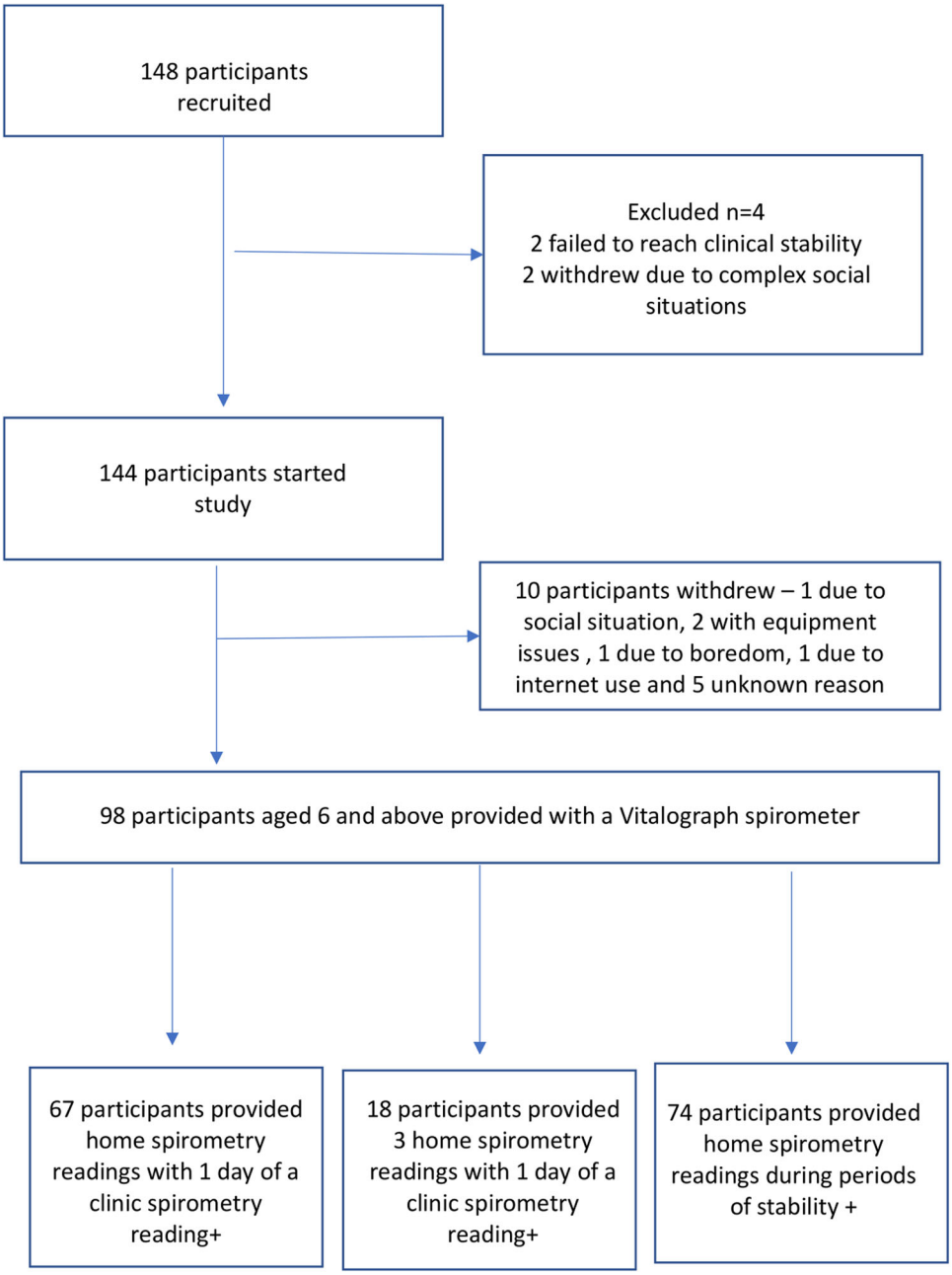

FIGURE 1 CLIMB-CF spirometry Consolidated Standards of Reporting Trials diagram + participants could be included in more than one group. [Color figure can be viewed at wileyonlinelibrary.com]

in the CoV between age groups (6–11 years 11% [6.2–14.4%] compared to 9.1% [4.5–14%] in those aged ≥ 12) ($p = 0.31$).

3.4 | Results of the acceptability questionnaire for home spirometry

When parents and participants ≥ 12 years were asked at the end of CLIMB-CF to rank the requested measures by acceptability, spirometry was the least acceptable measure for participants aged ≥ 12 years and one of the three least acceptable measures as ranked by parents of 6–11 year olds.

3.5 | Documenting the accuracy of four different hand-held devices

The home spirometer selected for the CLIMB study, the vitalograph BT, was the only Bluetooth enabled device at the time. Having demonstrated that its use in "the field" provided measures (a) with ~10% CoV during clinical stability and (b) with bias and wide limits of agreement with standard, clinic spirometers, we sought to document the device's accuracy against calibration syringes.

The 1 and 3 L syringes, tested in triplicate, on Jaeger Vyntus Pneumo Spirometer recorded mean (SD) FEV_1 of 1.01(0) and 3.06(0) L with coefficients of variation of 0% and 0.19% respectively.

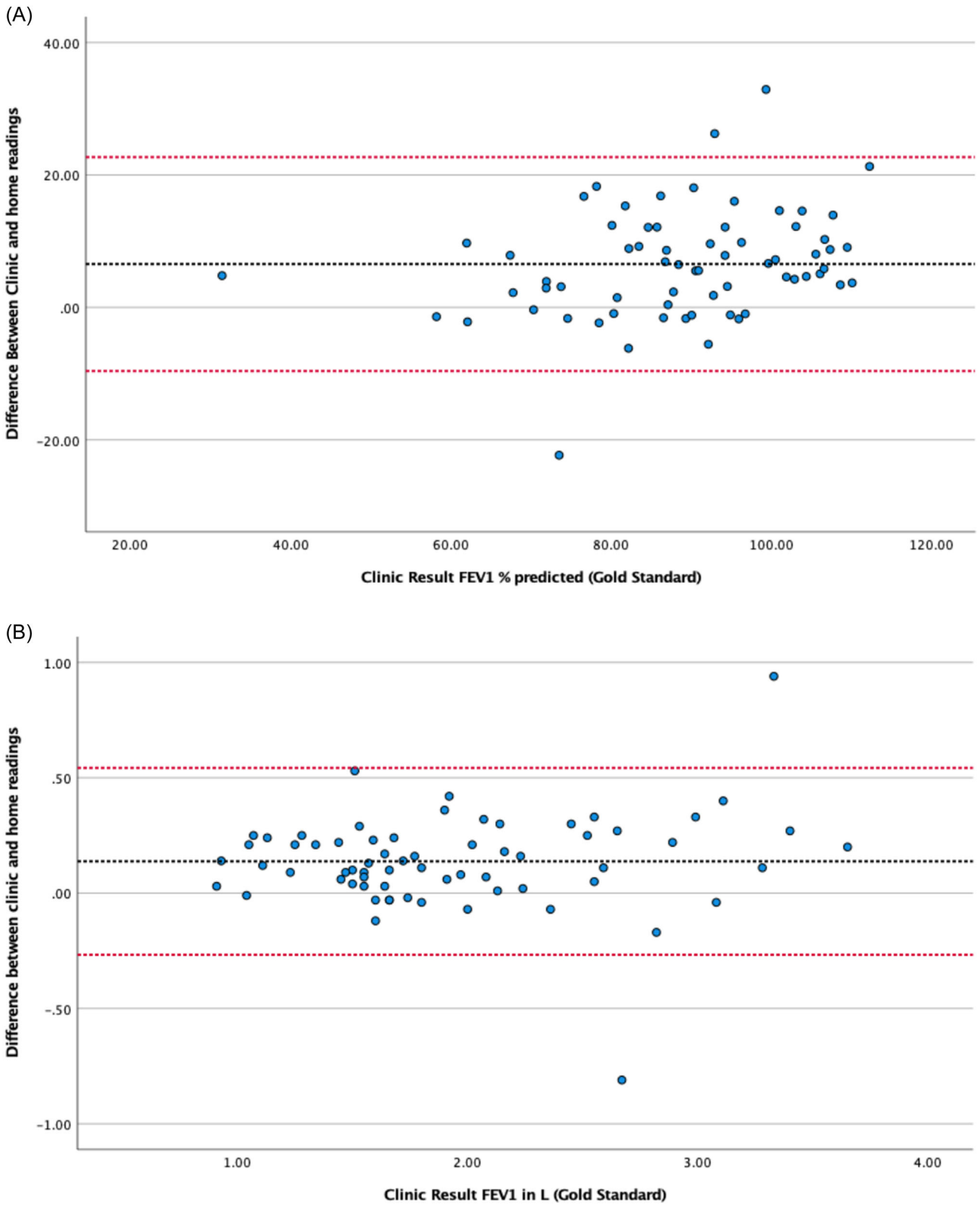

FIGURE 2 Panel a Bland–Altman plot for all participants aged 6 years and over with paired first clinic (Gold standard) and home spirometry measurements in FEV_1 percent predicted. The red dotted lines indicate the 95% limits of agreement, and the dotted black line is the mean difference (bias). Panel b Bland–Altman plot for all participants aged 6 years and over with first paired clinic (Gold standard) and home spirometry measurements in FEV_1 in litres. The red dotted lines indicate the 95% limits of agreement, and the dotted black line is the mean difference (bias). FEV_1, Forced expiratory volume over 1 s; L, litres. [Color figure can be viewed at wileyonlinelibrary.com]

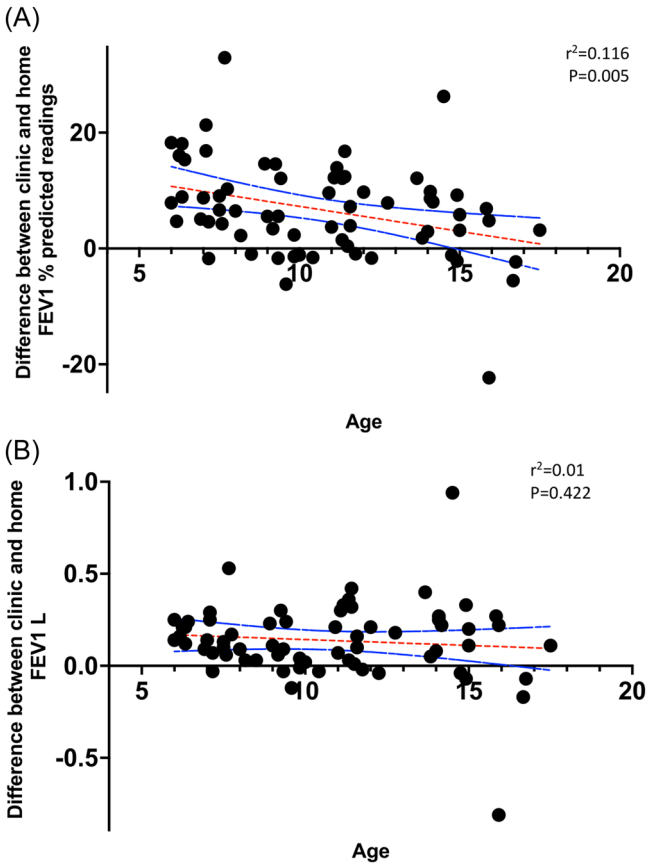

FIGURE 3 Panel a Difference between first paired supervised clinic and unsupervised home recorded shown as FEV_1% predicted shown by age of participant (blue lines represent the 95% confidence interval). Panel b Difference between first paired supervised clinic and unsupervised home spirometry readings shown as FEV_1 in litres shown by age (blue lines represent the 95% confidence interval). FEV_1, Forced expiratory volume over 1 s. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Days into the study for readings 1, 2, and 3 with differences between clinic and home spirometry in 18 participants and FEV_1 percent predicted and FEV_1 in litres.

	Days into the study Median (IQR)	Difference in clinic versus home FEV_1% predicted Median (IQR)	Difference in clinic versus home FEV_1 L Median (IQR)
Reading 1	0.5 (0–39)	5.7% (0.9–9.5%)	0.12 L (0–0.23 L)
Reading 2	66.5 (39–100)	7.5% (−1.1 to 11.6%)	0.2 L (0–0.27 L)
Reading 3	123 (110–162)	7.1% (0.9–13.7%)	0.13 L (0–0.5 L)

Abbreviations: FEV_1, forced expiratory volume over 1 s; IQR, interquartile range; L, litres.

Four devices from Vitalograph were tested in triplicate on 4 separate occasions. The Vitalograph lung monitor BT Smart underread by a mean (SD) of 65.6 (21.1) mL at 1 L ($p = 0.004$) and 30 (50) mL at 3 L (ns).

The ranges of coefficients of variation of the four devices were 1 L 0–2.3%, 3 L 0.2-1.4% (Supporting Information: Tables 4-5). The readings for each individual device and trial are provided in the Supporting Information Material (Supporting Information: Table 6).

4 | DISCUSSION

Our study has shown that unsupervised home spirometry readings using the Vitalograph lung monitor BT Smart are significantly lower than those from supervised hospital spirometry; in younger children the difference is as great as 35%. Variability of home measurements was close to 10% during periods of protocol-defined clinical stability and limits of agreement with contemporaneous supervised, clinic spirometry were wide, confirming that these measures cannot be used interchangeably. In part, this appears to be related to the device itself, as we have demonstrated a statistically significant under-read with this device at the one litre volume when tested with known volume calibration syringes. These findings are of particular importance to our pediatric population whose total lung volumes are lower than the adult population and the underread could translate to an assumed clinical drop in lung function and may cause the initiation of unnecessary treatment. The underread could also have a consequence for those people with CF who have significant respiratory disease and subsequent lower lung volumes.

To our knowledge this is the largest pediatric CF study exploring unsupervised home spirometry readings compared to supervised hospital readings and variations within unsupervised home spirometry readings during periods of stability.

One of the strengths of our study was that as participants were regularly attending their routine clinic appointments, we were able to obtain regular height measurements to ensure the home spirometry FEV_1% predicted readings were as accurate as possible. Only readings obtained within a day of the clinic visit were used for this comparison as opposed to other studies which allowed up to 7 days.[10] Despite this, when comparing the unsupervised spirometry readings at home with the supervised clinic readings, there are wide limits of agreement between the readings, with the unsupervised home spirometry readings being up to 35% lower. These limits of agreement between the two sets of readings would not satisfy the ATS/ERS standards for within test repeatability.[2] A lack of awareness of this could lead to clinical decisions being made erroneously. Our data shows that supervised measurements and unsupervised measurements are clearly not able to be used interchangeably, this contrasts with some previous findings documented in an older cohort of CF patients (mean age 15.89 ± 2.18 years).[13] Interestingly we also found that the difference in percent predicted values was greater in younger children. This contrasts with Gerzon et al.[14] one possible reason for this could be our larger sample size.

These differences between home and clinic readings did not decrease with time, suggesting that lack of familiarity with the hand-held device was not responsible. This is consistent with results seen by Paynter et al.[10] although both sets of analysis were limited by low sample numbers. Our data also demonstrate that even when participants were clinically stable there was an approximate 10%

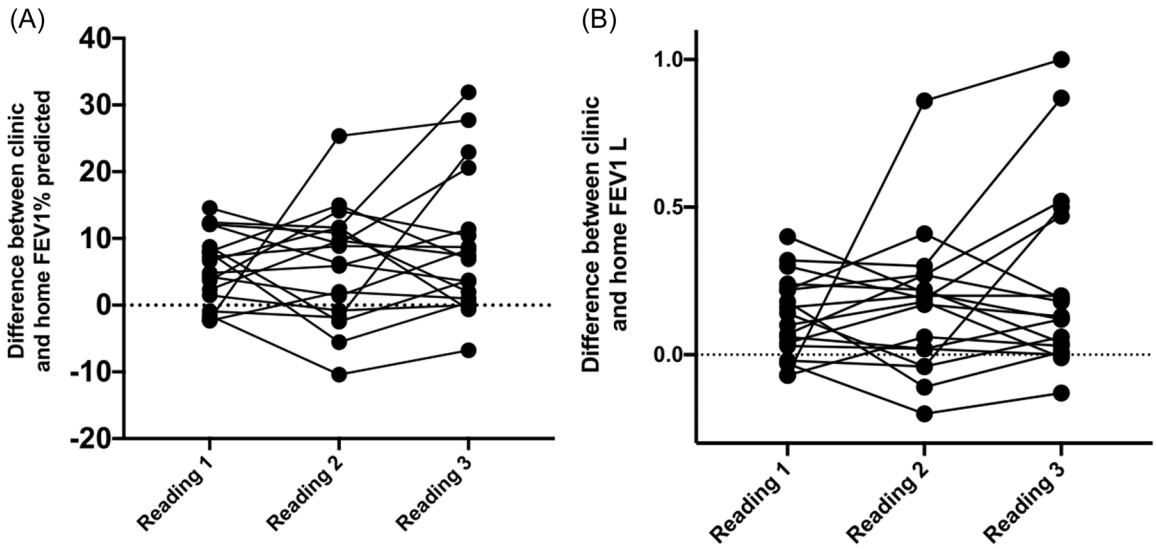

FIGURE 4 Differences between clinic and home spirometry readings for 18 participants. Panel A shows FEV_1 percent predicted, and panel B shows FEV_1 in litres. FEV_1, Forced expiratory volume over 1 s; L, litres.

variability in their home spirometry readings. Previous supervised spirometry studies reporting variation in FEV_1% predicted suggest 'normal' variation during periods of clinical stability is between 5.3 and 6.3% [18–20] in CF and that this variation does not differ significantly during a pulmonary exacerbation.[21] There is no clear definition of a pulmonary exacerbation in CF, however a 10% drop in FEV_1% predicted is considered clinically significant in the presence of other signs and/or symptoms.[22] We have shown variation meeting these criteria in stable participants measuring their lung function at home. The variation we have seen during stable periods of home monitoring suggest currently that even unsupervised trends at home are unreliable and further work needs to be carried out looking at technique or devices as well as trends during stability if home spirometry is useful to predict or identify early pulmonary exacerbations as previously suggested.[23]

It is also important to note that participants ≥ 12 years in CLIMB-CF found home spirometry one of the least acceptable measures to carry out, which may impact ongoing engagement. Home spirometry has been used for over 20 years in patients who have undergone lung transplantation and has been shown to lead to earlier detection of bronchiolitis obliterans but has not been reliably shown to affect survival.[24] In one study only 65% of adults surveyed who had undergone a lung transplant thought their home spirometer was reliable.[25] In a year long cohort study assessing adherence to home spirometry in lung transplant recipients, only 35.7% were satisfied with the spirometer.[26] CLIMB-CF was a feasibility study—we did not act on the home monitoring results. It is possible that if families were aware that home monitoring influenced clinical decisions, this may have increase adherence and improved technique, leading to less variation during periods of stability. Currently the required amount of data needed from home monitoring to make clinical decisions has not been determined and this warrants further exploration.

With regard to study limitations, development of the CLIMB-CF app started in 2016 and was based on a hand-held spirometer which does not easily display flow volume loops. This precluded any professional validation of the readings (allowing only the internal validation of the hand-held device) or review of technique. Since 2016 technology has advanced rapidly and visualization of individual flow volume loops has become more of a standard. However, one London pediatric CF Center recently published their experience of trying to establish home spirometry in their patients during the COVID pandemic and found some patients known to have good technique in clinic continued to struggle to provide satisfactory spirometry data at home.[27] Supervised real time home spirometry readings have been shown to satisfy ATS/ERS criteria in up to 93% of participants; however, no data were provided comparing these home spirometry readings with readings obtained in clinic.[28,29] Another limitation is that we could not standardize for the use of noseclips. Although for most children whether a nose clip is used or not does not introduce bias, in a few there are significant differences (>190 mL).[30]

The COVID-19 pandemic has required teams to rapidly change the way in which care is delivered to their pediatric patients; the provision of home spirometry has been a significant part of that. Based on our findings we would advocate several precautions: first, using virtual platforms to allow health care professionals to supervise home spirometry readings in these early stages of device implementation—this was not possible during the time of the CLIMB-CF study; second, whenever possible directly compare same-day results to those taken in clinic using a gold standard calibrated hospital spirometer at every opportunity. Third, variability during periods of stability may be greater than expected, and particularly if measurements are being made only infrequently, could mislead. Rather than monthly measures, or those obtained to coincide with clinical review, more frequent measures may enable

an individualized "usual range" and would be required for these longitudinal data to then be used to aid potential pulmonary exacerbation algorithms. However, this needs to be balanced against patient willingness to perform this measure. At the very least, when an abnormal value is being considered to trigger a management change, a series of repeat measurements may be more useful to identify a true trend. And finally, as home and clinic-based measurements may not be used interchangeably, device and setting should be recorded in clinical notes whenever a measurement is recorded, and trends only interpreted from same-device measures.

AUTHOR CONTRIBUTIONS

Claire Edmondson: Conceptualization; investigation; writing—original draft; writing—review and editing; methodology; project administration; data curation. **Nicole Westrupp**: Investigation, project administration; data curation. **Christopher Short**: Investigation, project administration; data curation. **Paul Seddon:** Investigation, project administration; data curation. **Catherine Olden**: Investigation, project administration; data curation. **Colin Wallis**: Investigation, project administration; data curation. **Malcolm Brodlie**: Investigation, project administration; data curation. **Francis Baxter**: Investigation, project administration; data curation. **Jonathan McCormick:** Investigation, project administration; data curation. **Susan MacFarlane**: Investigation, project administration; data curation. **Richard Brooker**: Investigation, project administration; data curation. **Margaret Connon**: Investigation, project administration; data curation. **Salim Ghayyda**: Investigation, project administration; data curation. **Lesley Blaikie:** Investigation, project administration; data curation. **Rebecca Thursfield**: Investigation, project administration; data curation. **Lynsey Brown**: Investigation, project administration; data curation. **April Price**: Investigation, project administration; data curation. **Erin Fleischer**: Investigation, project administration; data curation. **Daniel Hughes**: Investigation, project administration; data curation. **Christine Donnelly**: Investigation, project administration; data curation. **Mark Rosenthal**: Data curation. **John Wallenburg**: Conceptualization. **Keith Brownlee**: Conceptualization. **Eric W. F. W. Alton**: Conceptualization; investigation; supervision; writing—review and editing; methodology; curation. **Andrew Bush**: Conceptualization; investigation; supervision; writing—review and editing; methodology; curation. **Jane C. Davies**: Conceptualization; investigation; supervision; writing—review and editing; methodology; project administration; data curation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval for the CLIMB-CF study was granted by London Research Committee—Queen's Square, UK (16/LO/1987), Western University HSREB, London, Ontario, Canada (109185) and IWK Research Ethics Board, Halifax, Nova Scotia, Canada (1022312). Written informed consent (and where appropriate assent from the child) was obtained from participant's parents or legal guardians. Participants aged over 16 years provided their own consent. The study was also adopted by the NIHR Clinical Research Network Portfolio.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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