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The Feasibility and Efficacy of Telespirometry for Pulmonary Monitoring of Cystic Fibrosis: A Systematic Review

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Abstract

Background: Spirometry via telehealth (telespirometry) involves remote monitoring of lung function, which is useful to detect pulmonary changes and increase continuity of care for patients with cystic fibrosis (CF). Purpose: This systematic review aims to evaluate the feasibility and efficacy of telespirometry assessments for paediatric and adult CF patients. Method: A comprehensive search of health-related databases (CINAHL, Emcare (Ovid), Medline (Ovid), PEDRo and Scopus) was conducted. For inclusion, patients had to be clinically diagnosed with CF and studies could be of any study design or level according to the National Health and Medical Research Council (NHMRC) evidence hierarchy, had to use telespirometry devices for lung function tests, and be written or translated into English. The Crowe Critical Appraisal Tool (CCAT) was used to assess study quality, while also accounting for potential sources of bias encountered during the review process. Data was exported and summarised using the population, intervention, comparators, and outcomes (PICO) framework in Microsoft excel, to provide clinical recommendations. Results: Fourteen studies were included, with participants ranging from 5 to 44-years-old. Thirteen trials were performed domestically, while sample sizes and baseline patient characteristics varied. Nine studies analysed a control and intervention group. All studies varied in the intervention regime and clinical support provided. Collectively, the literature indicated poor patient adherence to telespirometry, which acted as a barrier to gauging its efficacy. Although appearing to be effective in detecting pulmonary deterioration, inconsistencies in pulmonary exacerbation (PEx) criteria were identified and lack of significant improvements in pulmonary outcomes were observed. Conclusion: Poor quality literature and small sample sizes increased risk of bias and restricted the application of the results to clinical practice. The current evidence base is limited by minimal experimental studies, lack of standardised telespirometry protocols, and criteria for PExs and poor patient compliance. Recommendations: At this stage, telespirometry for CF monitoring should be used by motivated and rurally/remotely located patients to complement in-person consults until its uptake is improved and accuracy and clinically efficacy can be ascertained.

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ABSTRACT

Background: Spirometry via telehealth (telespirometry) involves remote monitoring of lung function, which is useful to detect pulmonary changes and increase continuity of care for patients with cystic fibrosis (CF). **Purpose:** This systematic review aims to evaluate the feasibility and efficacy of telespirometry assessments for paediatric and adult CF patients. **Method:** A comprehensive search of health-related databases (CINAHL, Emcare (Ovid), Medline (Ovid), PEDRo and Scopus) was conducted. For inclusion, patients had to be clinically diagnosed with CF and studies could be of any study design or level according to the National Health and Medical Research Council (NHMRC) evidence hierarchy, had to use telespirometry devices for lung function tests, and be written or translated into English. The Crowe Critical Appraisal Tool (CCAT) was used to assess study quality, while also accounting for potential sources of bias encountered during the review process. Data was exported and summarised using the population, intervention, comparators, and outcomes (PICO) framework in Microsoft excel, to provide clinical recommendations. **Results:** Fourteen studies were included, with participants ranging from 5 to 44-years-old. Thirteen trials were performed domestically, while sample sizes and baseline patient characteristics varied. Nine studies analysed a control and intervention group. All studies varied in the intervention regime and clinical support provided. Collectively, the literature indicated poor patient adherence to telespirometry, which acted as a barrier to gauging its efficacy. Although appearing to be effective in detecting pulmonary deterioration, inconsistencies in pulmonary exacerbation (PEx) criteria were identified and lack of significant improvements in pulmonary outcomes were observed. **Conclusion:** Poor quality literature and small sample sizes increased risk of bias and restricted the application of the results to clinical practice. The current evidence base is limited by minimal experimental studies, lack of standardised telespirometry protocols, and criteria for PExs and poor patient compliance. **Recommendations:** At this stage, telespirometry for CF monitoring should be used by motivated and rurally/remotely located patients to complement in-person consults until its uptake is improved and accuracy and clinically efficacy can be ascertained.

Keywords: telehealth, spirometry, pulmonary function

INTRODUCTION

Cystic fibrosis (CF) is an inherited chronic disease caused by an autosomal recessive mutation of the cystic fibrosis transmembrane regulator (CFTR) gene, responsible for coding the CFTR protein. Dysfunction of this protein results in the accumulation of thick, highly concentrated mucus causing harmful blockages in organs such as the lungs, liver, pancreas, and intestines.[1] Within the respiratory system, these altered secretions can harbour bacteria, increasing the frequency of respiratory infection and subsequent pulmonary exacerbations (PExs). The progressive nature of CF unfortunately means this respiratory dysfunction is cyclic and damage to the airways is irreversible, resulting in bronchiectactic-like changes which inhibit mucociliary clearance and further increase infection risk. Pulmonary decline combined with other pathological organ changes limit the life expectancy of those with CF and diminish aspects such as quality of life (QoL).[2]

Health professionals (HPs) provide ongoing assessments and treatments often in specialised CF centres.[3] As there are currently no curative treatments for CF, close monitoring of signs and symptoms alongside therapies such as airway clearance techniques, ventilation, exercise, antibiotic treatment, and nutritional intervention are used to optimise patient outcomes.[4] Physiotherapy has a key role in CF care, providing interventions such as airway clearance techniques and exercise prescription and undertaking spirometry as a pulmonary function test (PFT). Spirometry is an essential tool for monitoring different aspects of lung function, which include anticipating and assessing responses to interventions, determining patient prognoses, and predicting PExs. Moreover, the readings can often change before the presentation of clinical symptoms, preventing avoidable hospitalisations.[5] Changes particularly in FEV1 are used to assist in the diagnosis of a PEx, which is usually indicated by a decrease of more than 10% from baseline.[5, 6]

Telehealth is a promising emerging health care platform. Through the use of information communication technologies (ICT), health services usually offered in-person can be delivered remotely to diagnose, assess, and treat acute and chronic conditions.[7,8] Technologies can take different forms such as via video conferencing, telephone, mobile phone and alert systems, and web-based applications, all allowing easy access to and exchange of professional health advice and patient information.[7,9] Telehealth can be divided into two categories: synchronous and asynchronous. The transmission of data or patient-clinician interaction in real-time is referred to as synchronous, while asynchronous telehealth involves receival and storage of data.[10]

Initially acting as a way to overcome geographical barriers, telehealth has evolved to serve many purposes, including home-telemonitoring of chronic conditions such as CF.[9] As an asynchronous form of telehealth, home-telemonitoring involves the rapid transmission of patient data from home settings to respective health facilities.[11] The process requires patients or caregivers to electronically transmit health information, allowing remote interpretation by HPs to prescribe assessments and treatments as needed.[6,10,11] As technology has advanced, so has the uptake and establishment of telehealth, encouraging more frequent and efficient occasions of service to benefit both patients and clinicians. The integration of ICT allows the delivery of higher quality health care through increased service availability and instant exchange of data, while having minimal disruption to patients' daily life and lowering costs incurred by travel.[7,8,10] This upskilling of HPs also significantly benefits the health care system, allowing maintenance of patient-clinician rapport, more effective collaboration within multi-disciplinary teams (MDTs), and potentially reduced workloads.[10]

Recent evidence suggests that spirometry performed using telehealth (telespirometry) is viable for assessing paediatric and adult CF patients for improving continuity of care, detecting pulmonary deterioration, and encouraging patient self-monitoring.[5,6] Telespirometry devices usually connect to computer and record and transmit results to be accessed remotely by clinicians.[6] It allows for more frequent and closer monitoring of symptoms, triggering prompt intervention and lessening the severity of PExs or potentially avoiding them entirely. These personal devices can also promote self-management, providing CF patients with a visual representation of their lung function and potentially improving patient education, with the aim to increase intrinsic motivation and self-efficacy. Furthermore, telespirometers often have attachments to additional tools such as pulse oximeters and electronic symptom diaries and can be further enhanced by other forms of telehealth (e.g., electronic reminders and telephone or video calling) to improve health care delivery.[6,12-15]

Where infection risk is high for CF populations, telespirometry may overcome these barriers by offering an alternative platform for frequent monitoring.[16] Especially in the climate of the ongoing the COVID-19 pandemic where the manifestations of the virus pose serious danger to those with CF, telespirometry could be an ideal and suitable substitute to in-person reviews, reducing risk of infection while providing frequent high-quality care. Due to its convenience and versatility, telespirometry can be easily used across different contexts such as home-based admissions and outpatient monitoring.[16] It can also be integrated into existing therapeutic regimes with minimal disruption, while decreasing the burden and risk which accompany frequent hospital visits.[13]

Current evidence has largely evaluated the feasibility, acceptability, and effectiveness of using general telehealth for CF management; however, a gap in the research exists relative to analysing telespirometry in a CF-only population. Telespirometry has the potential to support CF management, but as it is relatively new and relies on patient compliance, further research into its performance, usability, and uptake is required. Therefore, as telehealth is a growing platform for health care, this warrants the completion of this systematic review, which aims to summarise and evaluate the feasibility and efficacy of telespirometry to remotely monitor children and adults with CF.

METHOD

Search Strategy

This systematic review was written with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17] The overarching research question, "What is the feasibility and efficacy of performing telespirometry for a CF population?" was formatted according to the Population, Intervention, Comparators, and Outcomes (PICO) structure, as recommended by the PRISMA statement.

Population

Both adult and paediatric patients with CF were included to reflect the common use of spirometry testing over the course of a CF patient's lifespan.[18] Spirometry technical standards and recommendations have also been developed for children and adults, underlining its suitability for use across wide age range.[19, 20]

Intervention

The intervention of interest was spirometry performed via telehealth (telespirometry) as spirometry is the mostly widely used lung function test in CF management and is useful for monitoring the course of the condition.[21,22] Tests could be performed independently or with the assistance of a HP through communication platforms such as phone call or video conferencing.

Comparators

As the feasibility and efficacy of telespirometry were being evaluated in isolation with no comparison to other assessments, no set comparators were required to be included in this review.

Outcomes

A preliminary literature search was completed to identify common objective and subjective outcomes measures amongst the studies which assessed the feasibility and efficacy of telespirometry for CF monitoring. These quantitative and qualitative outcomes were then applied to the systematic review, whereby corresponding data was included for analysis and comparison.

Feasibility within this review described the practicality and capability of undertaking telespirometry assessments in a CF population. This was measured quantitatively in terms of average patient adherence (total number of transmissions in relation to the number of days the study was conducted over), total number of transmissions, duration taken to conduct the assessments, and proportion of subjects requiring operational assistance.[5,6,12-16,22,23-27]

Efficacy was indicated by the objective success of the telespirometry tests to accurately and reliably detect PExs, initiate medical intervention, as well as its subjective ability to improve quality of life.[5,6,12-16,22,23-28]

Design

A systematic review was deemed to be a suitable design at the time of writing, as no systematic reviews addressing this research question were in the process of or had been completed. This was confirmed by searching the International Prospective Register of Systematic Reviews (PROSPERO).

Protocol and Registration

This systematic review protocol (CRD42020209225) was registered with PROSPERO on 2nd December 2020.

Funding and supports

No financial or non-financial supports were sourced for this review.

Eligibility criteria

Eligibility criteria were based on the elements of the PICO framework and research characteristics including language and publication status.[17] Studies were included if participants (paediatric and adult) were clinically diagnosed with CF and used a telespirometry device for assessing lung function. Additionally, the research had to be published or able to be translated into

English and could be of any study design. Studies were excluded if they were study protocols or prototypes or non-research studies. Research was also excluded if the intervention combined telespirometry assessments with other assessment types, due to difficulty incurred with determining the effect of the telespirometry in isolation. Systematic reviews were also not included for analysis but were used to hand-search for relevant literature using reference lists.

Information Sources

Health-related online databases including CINAHL, Emcare (Ovid), Medline (Ovid), PEDro, and Scopus were searched on the 30 December 2020. These databases were selected due to the availability of a wide range of well-accredited journals from fields of allied health, medicine, nursing, and science. A search strategy was created by the primary researcher with guidance of a James Cook University (JCU) librarian.

Hand-searching of reference lists of key studies was performed manually to identify additional relevant literature. Literature citing was also completed to ensure complete study selection. Google Scholar was used to identify grey literature sources not yet published in the databases on the 27th January 2021. Search phrases used were similar to those of the database searches.

Search strategy

Database searches were constructed on the basis of the PICO outline (see Table 1). Due to the recency of telehealth, no database limits or search filters were applied. Full search strategies are outlined in the Appendix. Due to the alternate formatting of PEDro and Scopus searches, singular Boolean phrases were used. The final search strategy was reviewed and approved by both authors and the assisting librarian.

Table 1. Search Phrases

"cystic fibrosis" or "CF"
AND
"mobile health" OR telehealth OR telemedicine OR telemonitoring OR ehealth OR mhealth
AND
spirometry OR spirometer OR "pulmonary function test" OR "lung function test" OR "respiratory function test" OR "lung volume measurements"

Data Collection and Extraction

The PRISMA statement encompassing of the inclusion and exclusion criteria was used by the authors to screen and select suitable literature for this review (see Figure 1).[17] Search records were exported into EndNote X9 to remove duplicates and store and organise the data obtained. Titles, abstracts, and keywords were then surveyed with reference to the eligibility criteria, discarding unsuitable studies prior to full-text analysis.

Quantitative and qualitative data of the eligible records were synthesised, extracting common outcome measures and themes identified among the studies. Two researchers selected and reviewed each study to ensure the inclusion of all suitable and relevant research was to be reviewed, while also minimising the risk of bias which can be heightened by individual perspectives, values, and beliefs.

Data items were extracted into a Microsoft Excel spreadsheet, where study characteristics were collated and summarised by the primary researcher. The tabulated data was used to inform the results and discussion and indicated future recommendations for research and clinical practice.

Data Items

Elements of the PICO structure, thematic similarities, and Crowe Critical Appraisal Tool (CCAT) were combined to form the data headings, subjecting the methodology to possible risk of selection and publishing bias. The intentional selection of broad data items was used to encompass varying study designs, interventions, and outcomes, facilitating easier comparison of the studies.

Appraisal of Study Quality and Risk of Bias

Both researchers used the CCAT paired with the CCAT user guide version 1.4, to critically appraise the research and determine the overall quality.[29,30] The framework uses the systematic subheadings: introduction, research design, sampling, data collection, ethical matters, results, and discussion to evaluate the multiple elements which contribute to the overall quality. The CCAT was appropriate for this systematic review due to its applicability across multiple study designs collecting quantitative or qualitative data or combination of both. The tool also consists of a numerical scoring system which allows objective and consistent comparison of

the literature and has been noted as a valid and reliable tool for literature appraisal, assisting in the identification of potential sources of bias.[31]

Potential sources of bias were also identified throughout stages of the methodology including study selection and data extraction and integration. This in combination with the CCAT were considered when interpreting the results and providing clinical recommendations, hence lowering the risk of publication bias. Furthermore, each researcher independently critiqued the records before collaborating on 8 February 2021, to compare their findings and resolve discrepancies in their scoring.

RESULTS

Study Screening and Selection

A preliminary database search identified 15 relevant studies which aligned with the chosen topic and was a sufficient number to systematically review. Data was unable to be pooled due to the heterogenic nature of the patient characteristics and outcome measures within the research, making it unsuitable for a meta-analysis.

Database searching yielded 86 records, while handsearching on Google Scholar located an additional 11 studies. Sixty-three records remained after duplicates were removed. The eligibility criteria were then used to screen titles, abstracts, and keywords, excluding a further 46 records. Seventeen studies underwent full-text screening, with a further three studies excluded (see Figure 1).

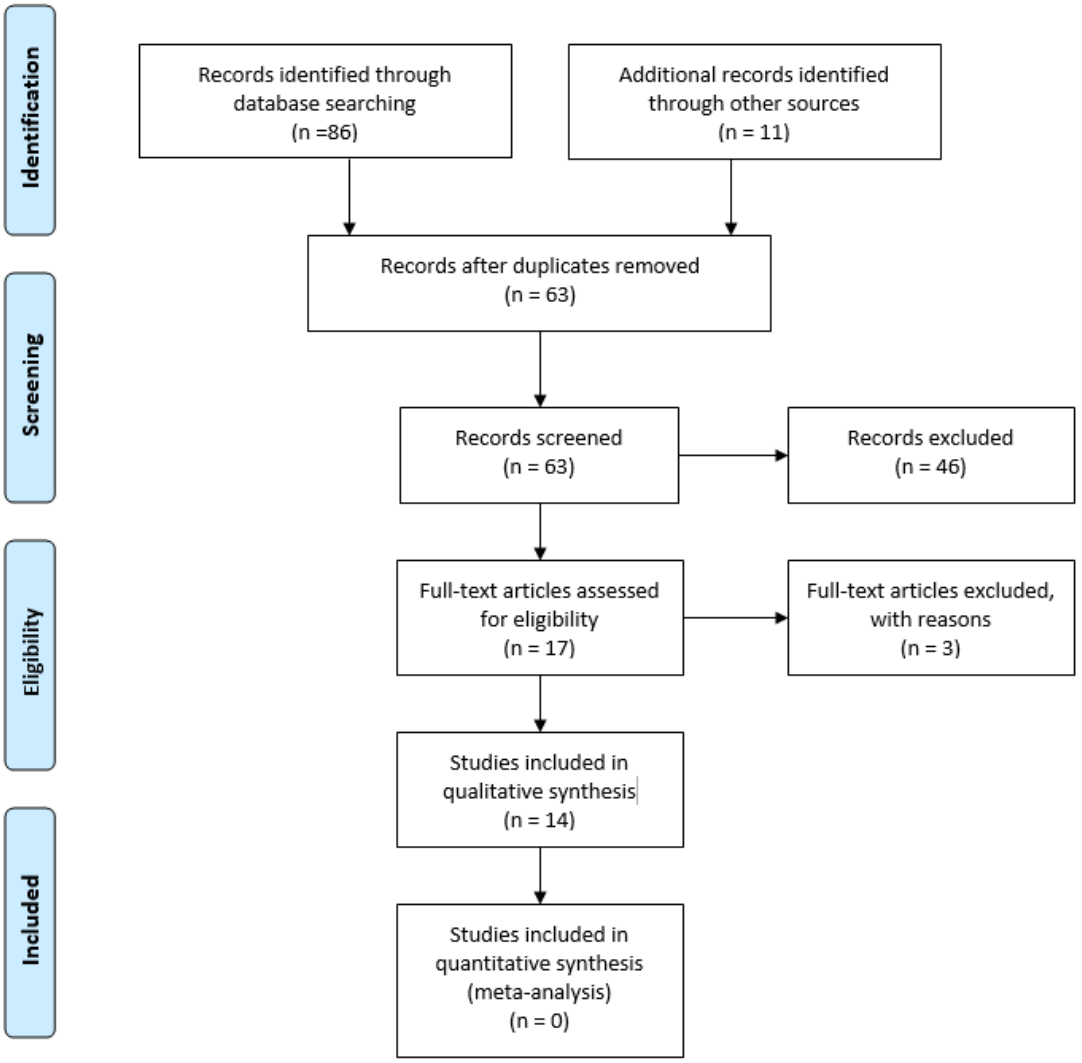

Figure 1. PRISMA Flow Chart[17]

Study Characteristics

Participants

Literature examined paediatric and adult clinically diagnosed CF patients, with ages ranging from 5 to 44 years-old and mean ages lying between 10 to 30 years-old (see Table 2). Telespirometry was undertaken by exclusively children or adolescents in six studies.[5,13,16,22-24] Four studies reviewed adults, or a combination of adults and children aged over 12 years-old.[6,12,15,25] The remaining four studies did not include the participants' ages.[14,26-28] Sample sizes ranged between five and 267 participants.

Characteristically, baseline pulmonary function and clinical stability also varied, as determined by factors such as the number of PExs, significant decreases in mean FEV1 and change in presenting symptoms. Two studies included clinically stable patients, defined as FEV1% predicted values of more than 25%.[15,25] Conversely, three studies included those who recently deteriorated, as indicated by infectious episodes of PExs, significant decreases in FEV1 or worsening of persistent pulmonary symptoms.[5,6,24] Wilkinson et al included patients who were terminally ill and awaiting lung transplantation.[15]

Four studies excluded those deemed as mentally unfit or incapacitated, due to subsequent impaired ability to effectively operate the telespirometer and understand the nature and effect of the study.[6,12,15,24] Other reasons for exclusion included patients with an unavailable land line and who were clinically unstable (e.g. terminally ill, awaiting lung transplantation).[12,24,25] These exclusion criterion reflected those who typically would be unable to perform telespirometry, as the mental and/or physical impairments may alter the validity of the results and therefore limit its use in remote assessment.

Interventions

Six studies included a single telespirometry group (see Table 2).[13,14,16,22,24,27] Nine studies compared a control group - receiving standard care, against a group conducting telespirometry.[5,6,12,15,22,23,25-27] Of the nine studies, three of these ensured both groups were homogenous for baseline characteristics.[5,25,26] Four of these studies also randomised patients between groups.[12,15,25,26] Two studies used the members of the intervention group to act as their own historic controls.[6,23]

Magrabi et al was the only study to conduct telespirometry in a hospital setting, with the remainder being performed in home environments with reference to a CF centre.[13] Access to telephone networks or web servers was ensured for at-home patients as this was required for remote data transmission.[5,6,12,15,16,22-24,27,28] Three studies transmitted data using telephone lines.[5,12,15] Murgia et al utilised acoustic coupling over telephone calls.[14] Six studies uploaded data to or transmitted data via web-based portals such as email for interpretation.[6,16,22-24,27] Three studies failed to describe the means of data transmission.[14,25,26]

The amount of telespirometry training varied. Four studies provided in-person training by a HP.[5,6,22,23] Logie et al assisted patients in real-time over phone or video calls.[16] Two studies supplied written instructions before requiring patients to independently record spirometry data.[13,16] Sarfaraz et al set up a helpline for those patients experiencing technical difficulties.[6]

The frequency of telespirometry tests and data collection ranged from daily to once weekly.[5,6,13,15,22-25] Four studies did not outline the intervention frequency.[14,26-28] Similarly, variation was observed in the nature and frequency of patient follow-up. Five studies followed-up with a mandatory phone call from a HP to review and discuss the results.[5,14,23,27,28] Two studies sent phone or electronic reminders if adherence was poor.[6,24]

Table 2. Studies Used in this Systematic Review

Study	Participants n, age	Intervention	Outcome measures	Results
Bella et al[5]	IG (n=17): HTS, MA:15.74±5.8 CG (n=28): UC, MA:14.77±5.22	HTS plus standard care Trained by physicians ~2x/week Data sent to CF unit	Spirometry (FEV1) Outpatient rate Hosp rate IV AB rate	Sig diff in AB therapy cycles between IG and CG (p=0.01) Overall average compliance rate 52.4%
De Biase et al[29]	IG (n=44): TS CG (n=110): UC Homogenous for age	HTS using MIR spirotel 2 device	Spirometry (FEV1) BMI Number and type of hosp admissions	No sig diff between groups in 2016-18 for all bacterial colonisations No sig diff in outpatient and day hospital admissions between groups in 2016-18 No sig diff between groups in average changes in respiratory function in 2016-18
Grzincich et al[12]	Adult (≥18 years old) CF patients IG (n=30): HTS CG (n=30): UC	HTS using digital recording device at home Data transmitted via web to CF centres	Spirometry SaO2 Symptoms Q1: pt satisfaction with care pre-study, Q2: inconveniences, Q3: Doctor review	All patients sent data without assistance, learned procedure in <20 mins n=10 found HTS frequency excessive 70% felt safer using HTS and happy self-monitoring >80% intended to continue using HTS All doctors agreed HTS positive for management, no difficulties accessing data
Lechtzin et al[28]	≥14 years old IG (n=135): HTS CG (n=132): UC 14 to >30 years old IG MA: 26.5 CG MA: 12.5	HTS and electronic symptoms recorded 2x/week CF team notified and treated if PEx detected	Spirometry (FEV1) Time to first PEx and subsequent PEx QoL Change in weight	No sig diff in 52-week mean change in FEV1 between groups No sig diff in PExs between groups Frequency of weekly transmissions ↑ from 1-2x/week, adherence ↓ from 50% to 19% IG had sig higher hazard ratio for time to first PEx and ↑ risk for subsequent PExs, IG > CG acute visits (153 vs. 64) IG perceived protocol more burdensome than CG (p<0.001)
Logie et al[16]	25 CF patients 7-17 years old	HTS during home admissions or for home-monitoring via web-based video calls with respiratory scientist Real-time feedback	Spirometry (FEV1, FVC) Distance from home to hospital Family feedback	93% sessions successful Average test time: 22 mins Median distance 238km to hosp HTS provoked immediate hosp admissions in 2 patients and early discharge for home-admitted patients Reports of human error, home interference,

Study	Participants n, age	Intervention	Outcome measures	Results
				equipment failure, delayed internet connections
Magrabi et al[13]	5 CF patients 10-14 years old	Training sessions HTS plus UC ≥1x/day No supervision in CF hospital clinic Data analysed by respiratory physicians and technician, provided to patients Electronic symptom diary	Spirometry (FEV1, FVC) HTS frequency Symptom diary Observation of users with HTS Interview - user feedback Survey – users and clinicians	HTS recorded 9-19 times over 5-9 days totalling to 27-54 transmissions 4 subjects performing more than once/day Patients found instructions clear and system easy to navigate without supervision Feedback: HTS easily integrated into regime, recognised usefulness and convenience. Not all spirometry measures valid due to human measurement errors
Murgia et al[30]	30 CF patients NAD	HTS recording spirometry, SaO2, HR. Phone data transmission Call to discuss results	Spirometry (FEV1)	882 transmissions (1317 spirometry entries) in one year Average adherence (transmission/total days) ~10% 19 hosp admissions
Murgia et al[14]	28 CF patients NAD	HTS and night SaO2 Phone call to collect data and discuss results	Spirometry (FEV1) Monthly average %adherence	1364 transmissions in 515 days Average compliance 10.16% with an increasing trend
Murgia et al[31]	IG (n=16): HTS CG (n=16): UC NAD	HTS recorded spirometry data, SaO2, HR Data emailed to HPs, patients called for result	Spirometry (FEV1)	Total 3,338 transmissions over 5 years Sig ↑ in annual mean FEV1 in IG vs CG (p=0.0021) Sig less ↓ in lung function in IG vs CG (no p-value given) Sig ↑ in adherence to HTS overtime (no p-value given)
Sarfaraz et al[8]	51 CF patients CG (n=19): UC IG served as own control (year before and after) ≥12 years old MA: 26.2	Symptom score and HTS once daily. Analysed by CF team for PEx Phone reminders if did not perform HTS for two successive days	Spirometry (FEV1) Symptom score (cough, sputum, breathlessness, fatigue) PExs Abs (oral, IV)	53 total PExs, 26 required IV ABs No sig diff in PExs from previous or following year. Oral AB courses was greater in study year vs previous year and sig greater in following year (p=0.02) 63.9% average adherence in IG
Shakkottai et al[28]	39 CF patients CG (n=39): UC IG served as own historic controls from previous year 12-21 years old Mean age: 15.89 ± 2.18	Weekly HTS Phoned by researchers to record results and address concerns. Data downloaded during quarterly clinic visits	Spirometry CFQ-R - treatment burden, HRQoL Nutritional status MPR - medication adherence	MPR adherence sig ↑ from previous year (p=0.04) IG mean adherence to weekly monitoring = 59.47 +/- 24.6% Average training time 29.10 mins Good correlation between HTS and clinic FEV1% predicted, high intra-class correlation of 0.8 across all visits No sig change in treatment burden scores

Study	Participants n, age	Intervention	Outcome measures	Results
Shakkottai & Nasr[22]	Survey: 40 adolescents (12-21 years old) with CF HTS: 5 adolescents (10-14 years old) with CF IG (n=3): HTS CG (n=2): UC	Two-part survey: Medication adherence and suggestions to improve adherence HTS: once daily for three months with medication reminders. Phone called weekly for PFT results.	Survey responses Spirometry Treatment adherence (MPRs) BMI percentile PEx frequency CFQ-R for HRQoL	Reported ≥2 barriers to medication adherence (lack of time and forgetfulness most common) HTS: Good correlation between FEV1 measures at-home and in-clinic IG mean adherence: 94.67% IG average training time 30 mins Subjects valued phone call feedback Patient and child CFQ-R treatment burden scores improved sig
van Horck et al[27]	49 paediatric CF patients, 5-19 years old Mean age: 10.3 ± 3.6	HTS 3x/week Presence and severity of symptoms Families transferred data once weekly, reminders if forgotten.	Detection of PEx Spirometry RSS score - cough, sputum, dyspnoea	28 patients had PExs 54% good adherence to HTS Combined mean FEV1% predicted and mean RSS of four to one week before PEx showed good sensitivity and specificity to predict PEx
Wilkinson et al[15]	IG (n=4): HTS CG (n=3): UC 21-38 years old	HTS plus weekly video calls with PT or nurse for clinical assessment, psychological support or general discussion.	Spirometry, SaO2, HR, Temperature MBAS, BADI Sputum CF-QoL questionnaire Hosp or clinic visits GP calls	No sig changes within and between groups in QoL, BADI, hosp admissions, clinic attendances or use of IV Abs Higher FVC associated with a higher positive emotional response for QoL Positive patient response, preference for HTS vs. phone call or clinic visit Subjects used system 71 times to perform weekly PFTs

Abbreviations: Ab – antibiotic, BADI – Beck anxiety and depression inventories, BMI – body mass index, CF – cystic fibrosis, CF-QoL – cystic fibrosis quality of life, CFQ-R – cystic fibrosis questionnaire revised, CG – control group, diff – difference, esp – especially, FEV1 – forced expiratory volume, FVC – forced vital capacity, GP – general practitioner, HP – health professional, HR – heart rate, HRQoL – health-related quality of life, hosp – hospital, HTS – home telespirometry, IG – intervention group, IV – intravenous, MA – mean age, MBAS – modified Borg Anxiety Scale, mins – minutes, MPR – medication possession ratio, NAD – nil age description, PEx – pulmonary exacerbation, PFT – pulmonary function test, QoL – quality of life, Q1 – questionnaire 1 (same applies for 2 and 3), RCT – randomised controlled trial, RSS – respiratory symptom score, SaO2 – oxygen saturation, sig – significant, TS – telespirometry, UC – usual care

RESULTS – MAIN OUTCOMES/THEMES

Feasibility

Patient Adherence

Eight studies compared the total number of transmissions to the total number of study duration days, to calculate the average patient adherence.[5,6,14,22,23-26] Adherence rates sat between 10-11% and 50-65%.[5,6,14,23,25,28] Murgia et al and Murgia et al had study samples of 30 and 28 patients respectively, noting a low average compliance of 10% to biweekly telespirometry tests when compared to the anticipated 40%.[14,28] van Horck et al defined optimal adherence as 70% of the maximum possible number of home transmissions, concluding 54% of children as having "good" adherence.[24] Lechtzin et al recorded a decrease in patient adherence from 50% to 19% as the frequency of weekly transmissions increased from once to twice a week.[25] Shakkottai et al identified a slightly higher adherence (60%) with once-weekly spirometry, implying compliance to still be problematic even with decreased testing frequency.[23] Sarfaraz et al was an outlier, reporting average compliance to daily telespirometry to be 64%.[6] Despite this, patient adherence in this study was still considered to be low considering researchers and technicians were contactable as needed. Shakkottai and Nasr recorded the highest mean adherence (95%) to weekly telespirometry testing, however the intervention group consisted of three subjects, therefore limiting the power of the study.[22]

The total number of telespirometry transmissions was also used by three studies to measure patient adherence.[13,15,27] Magrabi et al recorded 27-54 data transmissions among its five participants, who were the only patients across the literature to not perceive the frequency as a limitation and expressed their willingness to conduct daily spirometric tests.[13] Logie et al was the only study to measure the portion of successful telespirometry readings, that being 93%.[16]

In spite of adherence being objectively poor, subjects and clinicians provided positive qualitative feedback regarding telespirometry's usefulness and convenience.[12,13,15,16] Grzincich et al found that 70% of users were happy to self-evaluate their respiratory health and felt safer with the monitoring and increased health knowledge.[12] Meanwhile, all doctors had no difficulties accessing the telespirometry data and raised no concerns surrounding the feasibility of the intervention.[12]

Duration for Learning and Conducting Telespirometry

Time taken to learn the telespirometry protocol or to physically conduct the assessment was recorded by four studies.[12,16,22,23] Three studies concluded 30 minutes or less to be sufficient to learn the procedure.[12,22,23] From interviews, time taken to perform telespirometry tests was not perceived as barrier, with all patients disagreeing with telespirometry being described as "time consuming".[13]

Level of Assistance Required

Four studies recorded the amount of assistance provided to perform telespirometry.[12,13,15,16] Grzincich et al found 90% of patients required no domiciliary assistance and 100% were able to send data with no assistance at all.[12] Questionnaire responses further supported these results, with over 80% agreeing to future telespirometry use. Magrabi et al observed patients as requiring only a single demonstration and requiring no assistance after the initial training period.[13] Subjects also preferred the convenience of the telehealth platform over in-person visits.[15,16] Technical difficulties however were encountered in two studies, due to incompatible operating systems or computer models, as well as intermittent internet connections with delays in audio and visual.[16,25] These barriers were significant as they may have reduced data transmissions and delayed the detection of pulmonary deterioration.

Efficacy

Pulmonary Exacerbations

The definitions and criteria used to classify a PEx varied greatly among the literature. A reduction of more than 10% in FEV1 from previous stable baseline measures was used on its own or in combination with other factors [6,14,24,25,27,28] Four studies examined the total or average number of PExs which were reflective of deterioration.[6,22,24,25] Sarfaraz et al recorded 53 total PExs, ranging from zero to seven PExs per patient.[6] van Horck et al recorded 28 patients who had PExs.[24] Two studies recorded no significant differences in the number of PExs between the control and experimental groups.[22,25]

The time to the first and/or subsequent PEx was analysed by two studies.[24,25] Lechtzin et al observed a significantly higher hazard ratio of 1.45 (p=0.01) for the time to first PEx and increased risk of subsequent PExs in the telespirometry group compared to the control.[25] Despite the groups having no statistically significant differences in the number of PExs detected, the intervention did provoke faster diagnosis of PExs The trends of home monitored FEV1% predicted scores and respiratory symptom scores (RSS) were analysed by van Horck et al to determine the efficacy of telespirometry in predicting PExs before physically occurring.[24] The combined FEV1% predicted scores produced by telespirometry in conjunction with the RSS was able to predict PExs one to four weeks before symptoms presented, having a sensitivity and specificity of 92.9% and 88.9% respectively. This was higher than the control group which used the RSS alone, only showing significant increases two weeks preceding a PEx. The RSS however was not a validated outcome measure for symptom recording, which was accounted for when interpreting the results.

Medical Intervention – Antibiotics and Hospitalisations

As antibiotics are commonly used to treat PExs, antibiotic delivery was also used to determine the efficacy of telespirometry in detecting pulmonary decline.[5,6] Bella et al identified no significant changes in antibiotic delivery rates from pre-intervention to follow-up.[5] Sarfaraz et al on the other hand found a significant increase in the intervention group (p=0.02) in the number of oral antibiotics courses administered in the study period, when compared to the parallel six months of the previous and following years.[6]

Five studies analysed hospitalisation rates, as an outcome of respiratory deterioration.[5,16,25,26,28] According to three studies, there were no significant effects of telespirometry on inpatient hospitalisation rates between groups.[5,25,26] Lechtzin et al also recorded more than twice as many acute visits in the intervention group compared to the control (153 vs. 64), translating to increased likelihood of acute visits in the telespirometry group (57% vs. 29%).[25] Nineteen hospital admissions based on telespirometry data were recorded by Murgia et al.[28] Meanwhile Logie et al included no statistical indicators for hospitalisation rates.[16]

Validity and Reliability of Telespirometer devices

Two studies identified good correlation between FEV1% predicted values measured at-home compared to those in-clinic.[22,23] Shakkottai et al reported a high intra-class correlation (0.8) across all visits.[23] The positive results obtained by the Spiro PD device however were confounded by significant inconsistencies in FEF25-75% predicted values of those obtained at home versus in the clinic.[23]

The telespirometers' validity was unclear due to dependency of patient effort. This was highlighted by a respiratory laboratory technician, who indicated that human error (such as poor technique) in unsupervised tests led to variation in the measurements' validity.[13] Logie et al recorded two failed spirometry readings from a patient due to 'inexplicable equipment failure', however on further investigation and calibration testing it was suggested that human error or environmental interference was at fault.[16]

Quality of life

Both participants and health clinicians responded positively to the intervention's usefulness in three studies.[12-14] Clinician questionnaires deemed home spirometry as a valuable tool for monitoring patient deterioration and relieving the workload of staff at CF centres.[12] Wilkinson et al recorded all five participants to have perceived telespirometry as a convenient and comforting way of maintaining contact with HPs, preferring it over telephone calls or additional clinic visits.[15]

Risk of Bias Across Studies

Overall, the CCAT indicated study quality was generally poor, with common weaknesses which led to potential sources of bias. These included selection bias, random allocation, lack of blinding and attrition bias from incomplete data and loss to follow-up, which were considered when interpreting the results.

As gauged by the CCAT, overall study quality ranged from 23-85%, averaging an overall score of 55%. Shakkottai et al was rated the highest quality study (85% score), with the lowest scoring (23%) study being Murgia et al.[23,27] Within the CCAT, the preliminaries, introduction and results sections scored strongly with average scores or 3.14, 3.78 and 3 out of 5 respectively. Four studies scored two or below for the preliminaries.[14,22,27,28]

The CCAT indicated sampling and ethical matters as the poorest scoring areas, averaging to 1.2 and 1.5/5. With the exception of Shakkottai et al, literature received scores of two or less for sampling, 11 of which failed to outline their sampling methods.[6,12-14,22,23-28] The remaining three studies utilised purposive sampling.[15,16,23] Five studies did not include their sample size.[6,22,23,24,27]

Eleven studies scored two or below for ethical matters.[5,12-14,16,22,25-28] Six of which scored zero raising concerns regarding patient safety.[5,14,28-31] Half the literature documented obtaining consent from participants.[6,12,13,15,23,24] While only five studies recorded gaining ethical approval and mention of funding sources.[6,15,22-24]

All studies underwent non-randomised recruitment methods due to the nature of the study designs and intervention. Six of which intentionally selected patients with reference to certain criteria.[13,14,24,26-28] Two studies also recruited participants by invitation only.[6,23]

Randomisation of participants between intervention and control groups occurred in five studies, minimising the effect of allocation bias.[12,15,22,25,26] Being case series, three studies did not involve allocation to intervention and control groups.[6,23,27] Two of these used the same group of participants in the intervention group to serve as their own historic and future controls.[6,23] Two studies matched control groups to those undertaking the intervention based on demographic characteristics such as age, sex, respiratory function and complications.[5,27] Overall sequence generation was inadequately described, with three studies failing to outline their randomisation methods.[12,26,29] Lechtzin et al reported conducting a 1:1 randomisation of CF patients to the control or intervention group.[25] Only one study performed allocation concealment, involving the preparation of sealed envelopes by a third party.[15]

Blinding was unable to occur due to the nature of telespirometry, which increased the risk of bias among the literature. Within those studies comparing an intervention and control group, patients performing telespirometry may have been exposed to more frequent clinical monitoring and received more medical attention.[5,6,12,15,23,25-27] This may have unintentionally altered patient effort and responses to the study protocols, impacting patient compliance and increasing the risk of performance bias. All studies failed to document any measures taken to blind outcome assessors when analysing the data.

Only two out of the nine studies with two patient groups provided detail regarding incomplete data or loss to follow-up.[23,25] Lechtzin et al reported five telespirometry patients and six usual care patients who were lost to follow-up and mentioned other reasons for withdrawal which included "subject decision" or "other", subjecting the study to risk of attrition bias.[25] Overall the intervention group had more withdrawals than the control (24% vs. 16%).[25]

Table 3. CCAT Results

Study	Study design	Prelim	Intro	Design	Sam	Data	Ethical	Results	Disc	Total	%
Bella et al[5]	Non-randomised controlled trial	4	4	3	1	3	0	4	4	23	58
De Biase et al[29]	Case-control	3	4	1	0	1	0	1	2	12	30
Grzincich et al[12]	Multi-centre RCT	4	5	2	2	3	1	3	2	22	55
Lechtzin et al[28]	Non-randomised controlled trial	3	5	2	2	1	0	5	5	23	58
Logie et al[16]	Exp single-system	3	4	3	2	3	1	3	2	21	53
Magrabi et al[13]	Case study	4	5	3	0	1	2	4	5	24	60
Murgia et al[30]	Case series	1	2	1	1	3	0	3	2	11	28
Murgia et al[14]	Case series	2	4	2	0	1	0	2	3	14	35
Murgia et al[31]	Case series	1	1	1	0	2	0	2	2	9	23
Sarfaraz et al[6]	Case series	4	5	4	2	5	4	3	4	31	78
Shakkottai et al[26]	Case series	4	5	4	3	4	5	4	5	34	85
Shakkottai & Nasr[22]	Mixed methods	2	5	4	1	3	2	4	4	25	63
van Horck et al[27]	Obs cohort	5	5	4	1	4	4	4	5	32	80
Wilkinson et al[15]	RCT	4	3	3	2	4	2	4	3	25	63

Abbreviations: Disc – discussion, exp – experimental, intro – introduction, obs – observational, prelim – preliminary, RCT – randomised controlled trial, sam – sampling

DISCUSSION

Telespirometry is a useful clinical tool for remote lung function monitoring of paediatric and adult CF patients, allowing for accurate anticipation and detection of pulmonary deterioration. Its ease of usage and short testing duration reflects its potential to replace in-person testing, in turn being effective in prompting early medical intervention and improving quality of life.[12,13,15,16,22,23] The translation of telespirometry into clinical practice however is not yet appropriate for all CF populations. It is limited by poor patient adherence and lack of consistency among testing devices and thresholds/definitions for PExs, suggesting that further research is required to increase the success of its uptake and recording accuracy. [5,6,14,23-25,27,28] Currently it is suitable for those CF sufferers who are highly motivated and willing to abide by the telespirometry guidelines, as well as rurally and remotely located patients whereby access to CF centres is limited.

The diversity amongst the literature's study designs, patient demographics, methods, outcomes, and quality, was consistent with previous systematic reviews examining telehealth usage for CF and other chronic respiratory conditions.[4,11,32] The majority of studies in this review were small, observational trials which were subject to high risk of biases and had limited external validity, restricting their generalisability to the broader CF population. With respect to age, studies commonly included younger participants up to 44 years old, reflecting the average CF population with a prognosis of 46.[33]

The differences in disease severity and baseline lung function raised uncertainties when evaluating and comparing studies' internal validity. Depending on their baseline, patients may have been more susceptible to PExs and thus increasing the sensitivity of the telespirometry to detecting deterioration. Inconsistency in the study protocols and outcome measures also limited the comparability of the results and the confidence of clinical recommendations made. Other systematic reviews also assessing the use of telehealth for chronic disease management were met with similar barriers within their methodologies.[32]

The key findings revealed that despite telespirometry being theoretically feasible and effective, further investigation is required to have widespread clinical use. Ongoing research focusing on strategies to improve patient adherence and detection of pulmonary decline are imperative prior to the substitution of in-hospital assessments with at-home telespirometry. Current feedback is promising and is in keeping with previous studies which have noted positive patient and family responses to telehealth use.[34] CF patients and their families typically burdened with extensive regimes, were able to acknowledge the usefulness and convenience of telespirometry.[12,13,15,16] As highlighted by Logie et al, particularly those with difficulty accessing their major CF centres frequently, valued the reduction of expenses associated with transport, accommodation and lost income, not dissimilar to previous studies which utilised telehealth in regional, rural and remote settings.[16,35]

Despite these perceived advantages paired with successful data transmissions, patient adherence across all ages was poor. This potentially indicated that the addition of telespirometry to their regime needs to be modified to prevent patients from being

overwhelmed.[5,6,14,23-26,28] This was observed even in studies whereby minimal time was needed to effectively operate the systems and support was offered, which was reinforced by patients reporting the telespirometry process as too burdensome or extreme.[6,12,25] This trend was similarly observed in previous literature which noted decreased patient adherence with higher frequency of transmissions or increased monitoring.[11] The literature therefore implies that although being feasible, telespirometry may still be too complex or frequent for CF patients, compared to their usual regime and hence not yet practical for full implementation.

To increase patient compliance, more realistic approaches to telespirometry include adjusting the frequency of data transmissions. Decreasing the regularity of telespirometry tests, is likely to be perceived as less onerous and hence have better uptake. For paediatric CF patients, incentivised telespirometry tests may also improve adherence, through use of a game-type interface or increased visual aids.[13] This would provide simpler testing targets for patients, improving their technique and strengthening the accuracy and validity of the readings. Further qualitative data would also be valuable to highlight barriers to its successful implementation and obtain patients' recommendations on how to improve the intervention.

This review used several outcomes to determine the efficacy of telespirometry, however it was found that those directly related to the PExs themselves were most useful. These included the number of PExs detected and how early these were identified before symptoms presented. These outcomes were of particular importance as they provided the basis for instigating ongoing interventions such as antibiotic administering and hospitalisation and therefore should be used consistently in future research to evaluate telespirometry testing. Within this systematic review establishing efficacy was unfortunately complicated by inconsistencies in what constituted a PEx, with criteria being based on patients' symptoms, telespirometry readings or both.[6,27,28,30,31] The limited comparability between studies therefore weakened the evidence and systematic review and should be addressed in ongoing research to ensure more definite conclusions can be drawn.

Lack of standardisation in the set-up, calibration and utilisation of the telespirometry interventions also diminished comparison of studies and obstructed evaluation of the tool's efficacy. Validation of the telespirometer devices and reporting of the accuracy and reliability of the readings relative to in-clinic results was poor among the studies. Validity of the obtained results was also questionable, due to their variance depending on human effort.[13,16] The high rates of non-compliance in combination with small sample sizes also blurred the determination of overall efficacy due to lack of sufficient data for analysis.

Limitations

Research as indicated by the CCAT was generally poor and highlighted common weaknesses in sampling methods and ethics. Study samples tended to be small and carefully selected, potentially reducing their ability to detect a true effect and increasing the possibility of detecting false negatives. Moreover, the specificity of the samples also undermined the external validity of the results.

Patients were also at risk of performance bias as they were unable to be blinded, suggesting that results may have been skewed by behavioural influences and not directly a product of the intervention alone. This unavoidable consciousness of their assigned treatment may have also affected patients' perceptions and responses to the treatment and as a result impacted patient compliance which was largely poor. The poor compliance, as seen by the less than expected total transmissions, resulted in insufficient amounts of data to be analysed, posing further challenges to establishing the efficacy of telespirometry.

The inconsistency in defining a PEx, stemming from the absence of universal CF-specific PEx criteria, was an additionally identified limitation. Varying combinations of signs, symptoms, patient scores and/or spirometry results were used to classify PExs, creating inequalities as to which patients required further medical intervention. A potential classification of a PEx could be based on those criteria for chronic obstructive pulmonary disease (COPD), which categorises PExs by type and includes a minimum number of presenting symptoms such as sputum volume and purulence, dyspnoea, cough severity and frequency.[36]

Additionally, telespirometer device models across the literature differed, therefore varying in calibration and validation protocols which decreased studies' comparability and the reliability and efficacy of the tool. Procedures also varied in the amount and nature of instruction given. Together these inconsistencies and absence of a universal protocol for telespirometry made it difficult to establish the efficacy of telespirometry, diminishing the certainty in recommending its broader use for CF management.

Implications for Future Research and Clinical Practice

This systematic review has shown the potential for telespirometry to monitor CF patients remotely. The majority of participants have described it as easy to setup and conduct with or without the assistance of HPs and identified it as a convenient and feasible alternative for lung function monitoring. In spite of these positive results, the literature highlighted inconsistencies among research methods which may have decreased adherence and clinical efficacy. Telespirometry for CF patients would therefore benefit from more extensive research to ensure successful implementation in a clinical context.

To be more robust, future research should aim to be multi-centred, have larger samples and occur over longer durations to reflect the chronicity of CF and allow better generalisability of results. Studies would also benefit from broader inclusion criteria to accommodate for a wider range of CF patients who vary in age and disease severity. Furthermore, as current studies are largely observational, completion of more experimental trials would strengthen these findings. Studies should also consider using and clearly documenting randomised allocation methods to reduce the risk of selection bias.

To improve the studies' validity, telespirometers should be calibrated against certified recommendations, such as those outlined by the American Thoracic Society.[18] This standardisation would also increase the accuracy of the readings to better detect PExs, while allowing better comparison of the literature, as outcomes would have less variation with consistent interventions.

Unlike other chronic conditions such as COPD, CF lacks uniform signs and symptoms which classify a PEx. In turn, studies varied in their sensitivity to detecting pulmonary decline, making it hard to determine the efficacy of telespirometry. With standardised criteria, more consistent and potentially earlier detection of PExs would occur, prompting therapeutic intervention and preventing unnecessary hospitalisations.

Although telespirometry has been recognised as being feasible for CF monitoring, it may be more suited to highly motivated patients willing to incorporate this testing into their current regime or who have frequent access to supports to ensure good compliance. It is also a more convenient and feasible option for those patients unable to attend regular clinic consults such as individuals and families living rurally/remotely. A positive shift in the uptake of and attitude towards telehealth for CF management has also been observed following the recent COVID-19 pandemic.[38] Remote monitoring typically seen as an additional service is now being utilised as a replacement for face-to-face interactions. Its widespread use showcases a promising new mode of chronic health care which reduces risk of infection, particularly for vulnerable populations, and extends well beyond this pandemic period.[38]

CONCLUSION

This systematic review aimed to summarise and evaluate the feasibility and efficacy of telespirometry assessments to monitor pulmonary function for CF patients. With the inclusion of quantitative and qualitative data, strengths and gaps in the current evidence base were identified, warranting the need for further research to enhance its incorporation into regular clinical practice.

Overall, the literature has revealed telespirometry as a promising tool, which was well received by patients and their families. CF users were able to appreciate its convenience and navigate the systems and devices with ease. With evidence showing no clear clinical efficacy, compounded with the complexity of CF and inconsistencies in defining a PEx, future research with standardised telespirometry protocols and criteria for deterioration is warranted before it can be regularly incorporated to replace in-person assessments. These modifications are essential to improving the validity of the readings and to clarify its ability to prompt earlier therapeutic intervention and prevent hospitalisation. As patient compliance was poor throughout, studies should also aim to adjust elements of the assessment regime such as transmission frequency or electronic reminders to increase patient uptake.

This systematic review suggests that telespirometry is feasible for use by specific CF patient groups, to supplement in-person spirometry testing. Those most suited to use the technology include those who do not reside in metropolitan areas and subsequently infrequently access specialist care, in addition to motivated individuals willing to independently adhere to the regime. With more definite research, telespirometry can be utilised effectively to increase continuity of care and in turn improve patient outcomes and QoL.

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APPENDIX
Appendix 1: Search Syntax

CINAHL search one

"cystic fibrosis"
AND
"mobile health" OR telehealth OR telemedicine OR telemonitoring OR ehealth OR mhealth
AND
spirometry OR spirometer OR pulmonary function test OR lung function test OR respiratory function test OR lung volume measurements

CINAHL modified search

"cystic fibrosis"
AND
"mobile health" OR telehealth OR telemedicine OR telemonitoring OR ehealth OR mhealth
AND
Spirometry OR respiratory function test+

Emcare (Ovid) search

"cystic fibrosis"
AND
"mobile health" OR telehealth OR telemedicine OR telemonitoring OR ehealth OR mhealth
AND
spirometry (subject heading, search as keyword) OR spirometer (search as keyword) OR lung function test* (search as keyword)

*the scope function was used to confirm that lung function test was inclusive of:

- function test, lung
- function test, pulmonary
- pulmonary function test
- respiratory function test
- respiratory function tests
- respiratory test
- ventilation test

Medline (Ovid) search

"cystic fibrosis"
AND
"mobile health" OR telehealth OR telemedicine OR telemonitoring OR ehealth OR mhealth
AND
Spirometry (no subject headings chosen) OR spirometer (include all subheadings) OR pulmonary function test OR lung function test OR respiratory function test OR lung volume measurements

PEDRo search phrases

The search terms were combined to form a singular Boolean phrase however no results were found. The following two phrases were used instead:

- "cystic fibrosis" spiromet* (yielded 29 records, none were of relevance)
- "cystic fibrosis" "telehealth" (yielded 0 records)

Scopus search

(TITLE-ABS-KEY ("cystic fibrosis") AND TITLE-ABS-KEY (spiromet* OR "pulmonary function test" OR "lung function test" OR "respiratory function test" OR "lung volume measurement") AND TITLE-ABS-KEY ("mobile health" OR telehealth OR telemedicine OR telemonitoring OR ehealth OR mhealth))

Appendix 2: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			Page no.
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3-4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3, 15
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3-4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3-4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2-3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	n/a
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3-4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	n/a
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	3-4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n/a
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4-5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4
Study characteristics	17	Cite each included study and present its characteristics.	4-8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9-10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	n/a
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-11
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	3
Competing interests	26	Declare any competing interests of review authors.	n/a
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	n/a

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71