Clinical Monitoring and Biomarkers to stratify severity and predict outcomes in children with Cystic Fibrosis: CLIMB-CF

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Declaration of originality

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Abstract

Infection and inflammation, structural damage, and functional changes, is present early in people with Cystic Fibrosis. Periods of increased signs and symptoms (pulmonary exacerbations) can lead to poorer outcomes. Scheduled outpatient appointments allow for snapshots of health within a rigid system that can be cumbersome for families. Also, there is no biomarker which predicts a pulmonary exacerbation. Home monitoring and sample collection may provide an option to identify periods of pulmonary exacerbation earlier, however it is unclear if this is feasible or could have a negative impact on depression, anxiety, or quality of life.

Here I aimed to investigate the feasibility of home monitoring and sample collection for young people with CF and their parents and the impact on mood and quality of life while also exploring the accuracy of home spirometry and novel biomarkers.

With CF patient/ family input, I designed and tested a study specific mobile phone application with integrated Bluetooth equipment and led a multi-site, two country study. 144 participants were recruited and provided data for 6 months and had the option to collect a range of biological samples for biomarker exploration over the last 4 months.

Median requested data completion was 40.1%, significantly lower in adolescence. No negative impact on mood or quality of life was seen. The underread of unsupervised home spirometry compared to supervised clinic spirometry is an important clinical message to be considered by CF teams moving forward. Urinary MMP-9 did not demonstrate utility as a biomarker of pulmonary

exacerbations. Signals from a large panel of urinary biomarkers were highly variable both between and within subjects.

This thesis identifies areas of unmet need in home monitoring, in particular the engagement of adolescents, while showing it does not have an adverse effect on mood or quality of life. I have identified non-invasive samples that are feasible to collect at home but to date, have not identified a suitable urinary biomarker of pulmonary exacerbation.

Acknowledgements

I would like to start by first thanking my supervisors Professor Jane Davies, Professor Andy Bush, and Professor Eric Alton who have taught and guided me through this PhD. I have constantly been amazed by their knowledge and expertise and how willing they are to share that with me, especially when I ask yet another question. I have grown hugely as a researcher under their guidance, and I only hope this thesis is representative of that.

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Writing this PhD while working clinically through the COVID-19 pandemic has been one of the hardest things I have had to do and a special thanks goes to my family and friends who offered constant support, even while it had to be virtual, sent care packages and generally made me smile. Thank you to my Mum, Dad, brother Nick, sister-in-law Jen and Uncle Dave who made me laugh, offered words of wisdom, sent me funny videos of my nephew, and have been my constant cheerleaders through this whole process.

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Publications, Presentations, and prizes arising from the work in this thesis

Peer reviewed publications

- **C Edmondson**, N Westrupp, P Seddon, C Olden, C Wallis, C Dawson, M Brodlie , F Baxter, J McCormick, S MacFarlane , D Rice, A Macleod, R Brooker, M Connon, S Ghayyda, L Blaikie, R Thursfield, L Brown, A Price, E Fleischer, J Itterman, D Hughes, P Barrett, M Surette, C Donnelly, D Mateos-Corral, G Padley, J Wallenburg, K Brownlee, EWFW Alton, A Bush, JC Davies THE FEASIBILITY OF HOME MONITORING OF YOUNG PEOPLE WITH CYSTIC FIBROSIS: RESULTS FROM CLIMB-CF Journal of Cystic fibrosis Online first https://doi.org/10.1016/J.JCF.2021.09.018
- Dixon E, Dick K, Ollosson S, Jones D, Mattock H, Bentley S, Saunders C, Matthews J, Dobra B, King J, **Edmondson C**, Davies JC. Telemedicine and cystic fibrosis: Do we still need face-to-face clinics? Paediatr Respir Rev. 2021 May 19:S1526-0542(21)00054-3. doi: 10.1016/j.prrv.2021.05.002. Epub ahead of print. PMID: 34215541

Oral Presentations

- Invited speaker Fireside chat: Digitalisation in respiratory/child health with Dr Hannah Allen Kings John Price Paediatric Respiratory conference 26th May 2021
- How feasible is it to monitor young people with cystic fibrosis at home? Results of the CLIMB-CF study NIHR Child Health Technology Conference 2 March 2021
- Monitoring Lung Function of young people with CF at home: Is it reliable? Results from the CLIMB-CF study – NACFC Junior investigators best abstract in clinical research award session 20th Oct 2020

- Invited Speaker CLInical Monitoring and Biomarkers to stratify severity and predict outcomes in children with cystic fibrosis (CLIMB-CF) UK Cystic Fibrosis conference 10th Oct 2019
- ePoster oral presentation: ePS5.07 CLInical Monitoring and Biomarkers to stratify severity and predict outcomes in children with cystic fibrosis (CLIMB-CF): results from the feasibility study
- Invited speaker 'CLInical Monitoring and Biomarkers to stratify severity and predict outcomes in children with Cystic Fibrosis (CLIMB-CF) – preliminary results 'CF Canada Broken Arrow Conference 4th April 2019 Toronto Canada.
- Oral Presentation: British Paediatric Respiratory Society Summer Meeting 29th-30th June 2017 'Is paediatric home monitoring in CF feasible? There's an app for that!'
- Invited speaker: European Psychosocial Special Interest Group ECFS pre-conference meeting 'Is Paediatric home monitoring in CF feasible? There's an app for that!' Wednesday 7th June 2017
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Poster presentations

- **Edmondson C**, Westrupp N, Puckey M, Alton E, Bush A, Davies JC 300: Screening for depression and anxiety in parents of children with cystic fibrosis over 6 months November 2021 Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society 20:S144-S145 DOI: 10.1016/S1569-1993(21)01725-2

- Monitoring Lung Function of young people with CF at home: Is it reliable? Results from the CLIMB-CF study **C. Edmondson**, N. Westrupp J. Wallenburg, K. Brownlee, E.W.F.W. Alton, A. Bush, J.C. Davies, The CLIMB-CF Study Team Pediatric pulmonology Volume 55, Issue S2 Supplement: The 34th Annual North American Cystic Fibrosis Conference, October 7–23, 2020 p297
- What is feasible when it comes to monitoring young people with cystic fibrosis at home? The results of the CLIMB-CF study **C. Edmondson**, N. Westrupp J. Wallenburg, K. Brownlee, E.W.F.W. Alton, A. Bush, J.C. Davies, The CLIMB-CF Study Team Pediatric pulmonology Volume 55, Issue S2 Supplement: The 34th Annual North American Cystic Fibrosis Conference, October 7–23, 2020 p290
- Does home monitoring of children with CF affect depression and anxiety levels in their parents? Results from the CLIMB-CF feasibility study **C. Edmondson**, N. Westrupp J. Wallenburg, K. Brownlee, E.W.F.W. Alton, A. Bush, J.C. Davies, The CLIMB-CF Study Team Pediatric Pulmonology Volume 54, Issue S2 p405
- Engagement (or not) of teenagers with CF in health monitoring at home: Results from the CLIMB-CF feasibility study. **C. Edmondson**, N. Westrupp J. Wallenburg, K. Brownlee, E.W.F.W. Alton, A. Bush, J.C. Davies, The CLIMB-CF Study Team Pediatric Pulmonology Volume 54, Issue S2 p430
- P223 Urinary Matrix Metalloproteinase-9 (MMP-9) is not a biomarker of pulmonary exacerbation in cystic fibrosis **C. Edmondson**, N. Westrupp, M. Coates, O. Fletcher, D. Fenn, P. Seddon, C. Olden, C. Wallis, C. Dawson, M. Brodlie, F. Baxter, J. McCormick, M. Connon, L. Blaikie, R. Thursfield, L. Brown, A. Price, J. Itterman, D. Hughes, C. Donnelly, D. Mak, J.

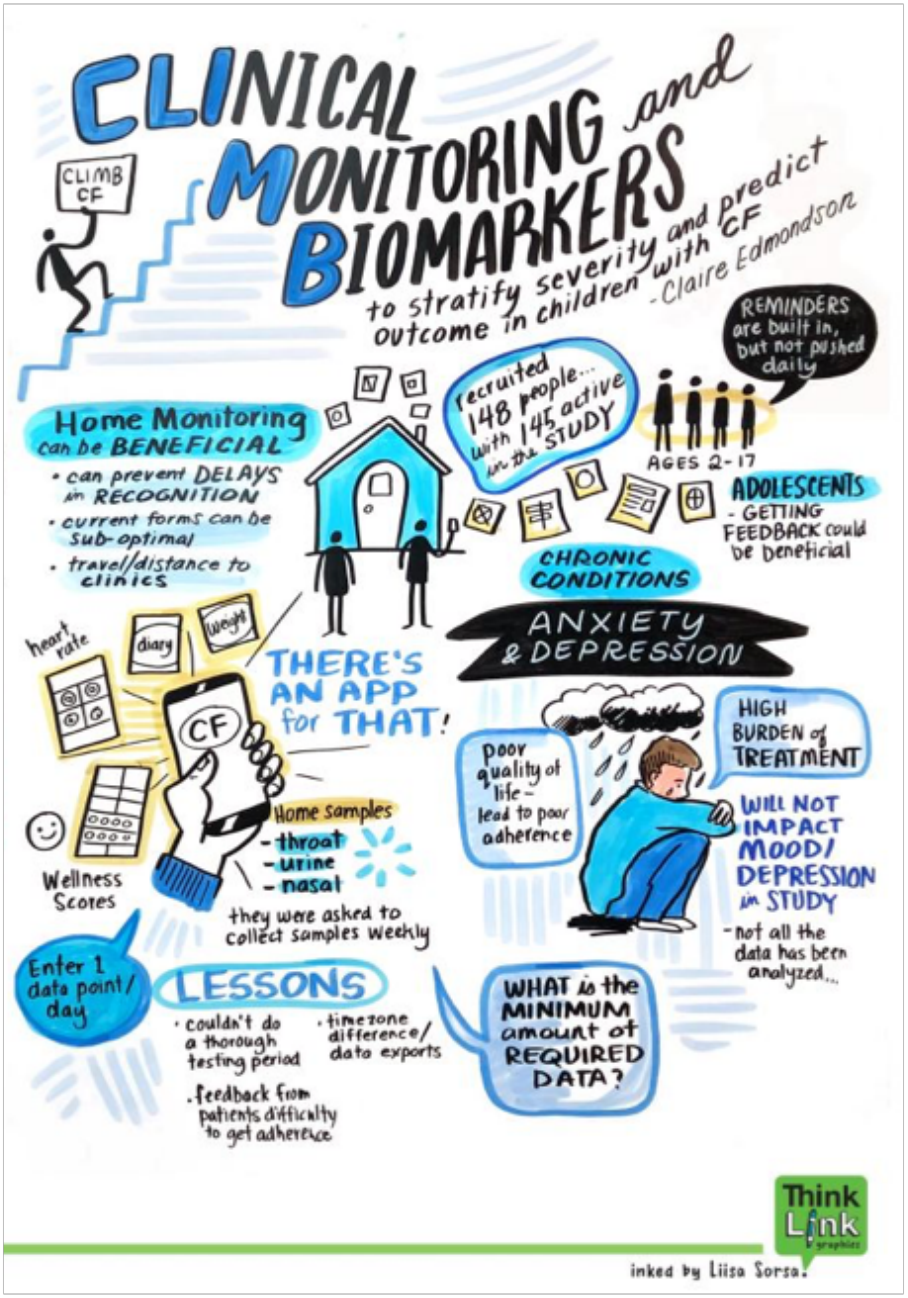
Wallenburg, K. Brownlee, E.W.F.W. Alton, A. Bush, J.C. Davies, The CLIMB-CF Study Team S120 Published in issue: J CYST FIBROS June 2019

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- Best Trainee Oral Presentation Prize at the British Paediatric Respiratory Society Summer Meeting 29th-30th June 2017.
- Highly commended Poster Presentation in the Clinical category at the NHLI post graduate research day 10th July 2018 'Is paediatric home monitoring in CF feasible? There is an app for that'
- Digital Pioneer Fellowship 2018-2019 Digital Health London

Videos resulting from the study

- https://twitter.com/cftrust/status/1177180253049032704?s=11
- https://twitter.com/imperialnhli/status/1142084943146881025?s=11



Supplementary Figure A CLIMB-CF Think Link graphic drawn live during the CF Canada Broken Arrow Conference 2019

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Abbreviations

Abbreviation	Meaning
AI	Artificial Intelligence
AIAT	Alpha-1 antitrypsin
ALD	Alder Hey Children's Hospital
App	Application
ARCI	Acute Respiratory Illness Checklist
ASL	Air Surface Liquid
ATP	Adenosine Triphosphate
BAL	Bronchoalveolar lavage
BMI	Body Mass Index
B2M	Beta-2-microglobulin
BRN	Royal Alexandra Hospital
CC16	Clara cell secretory protein 16
CF	Cystic Fibrosis
CF-START	Cystic fibrosis anti-staphylococcal antibiotic prophylaxis trial
CFQ-R	Cystic Fibrosis Questionnaire - revised
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence interval
COA	Certificate of Analysis
CRP	C-reactive protein
CSV	Comma-Separated-Values
CT	Computed tomography
DBS	Dried Blood spot
DNase	Dornase alpha
EI	Early Intervention
eICE	Early Intervention in Pulmonary Exacerbation

ENaC	Epithelial Sodium Channel
EPIC	Early anti-pseudomonal acquisition trial
ESR	Erythrocyte Sedimentary Rate
FDA	US Food and Drug Administration
FEV	Forced expiratory volume
FEV1	Forced Expiratory Volume in the first second
fMLF	N-formyl-l-methionyl-leucyl-phenylalanine
FVC	Forced vital capacity
GAD	Generalized anxiety disorder
GOSH	Great Ormond Street Hospital
HRQOL	Health related Quality of Life
IL-17	Interleukin 17
IL-6	Interleukin 6
IL-8	Interleukin 8
IQR	Interquartile range
IRT	Immunoreactive trypsinogen
IS	Induced Sputum
IV	Intravenous
IWK	IWK Health
KDM-CF	Knowledge of Disease Management - Cystic Fibrosis
LCI	Lung Clearance Index
LON	London Health Sciences Children's Hospital
LTB4	Leukotriene B4
MBW	Multiple-breathing washout
MCID	Minimal clinically important difference
MDT	Multidisciplinary team
mHEALTH	Mobile Health
MMP-8	Matrix metallopeptidase 8
MMP-9	Matrix metallopeptidase 9

MPO	Myeloperoxidase
MPR	Medication Possession Ratios
MRSA	Methicillin Resistant Staphylococcal aureus
MTP	Multiple Time Points
NE	Neutrophil Elastase
NEW	Great North Children's Hospital
NGAL	Neutrophil gelatinase-associated lipocalin
NICE	National Institute for Health and Care Excellence
P. Aeruginosa	Pseudomonas Aeruginosa
PBS	Phosphate Buffered Saline
PDC	Proportion days covered
PEF	Peak Expiratory Flow
PERT	Pancreatic Enzyme Replacement Therapy
PHQ	Patient Health Questionnaire
PI	Pancreatic insufficiency
PS	Pancreatic sufficiency
PSU	Pseudouridine
RBH	Royal Brompton Hospital
RCPCH	Royal College of Paediatrics and Child Health
RBP4	Retinol binding protein 4
RIA	Radioimmunoassay
RNAse 3	Ribonuclease 3
RSSQ	Respiratory and Systemic Symptoms Questionnaire
RTMM	Real-time medication monitoring
S.aureus	Staphylococcal aureus
SCT	North of Scotland Respiratory Network
SD	Standard deviation
SDQ	Strengths and Difficulties questionnaire
SIV	Site initiation visit

SLPI	Secretory Leukoprotease Inhibitor
STOP-2	Standardized treatment of pulmonary exacerbations -2
TIMP-1	Tissue Inhibitor of Metalloproteinase- 1
TIMP-2	Tissue Inhibitor of Metalloproteinase- 2
TNFα	Tumour Necrosis Factor alpha
UAT	User acceptance testing
UI	User interface
WHO	World Health Organisation
YAG	Youth advisory group

Chapter 1 Introduction

1.1 Origins of CLIMB-CF

There is evidence for structural and functional changes in Cystic Fibrosis (CF) from early in life and that frequent periods of pulmonary exacerbation can worsen outcomes. Currently children and young people with CF are seen routinely in outpatient clinics regardless of their clinical situation which can mean changes in signs and symptoms outside of the scheduled clinic appointments could be missed and/or lead to a delay in the initiation of treatment. It is also apparent that people with CF already have a high treatment burden at home. There is the potential that the addition of CFTR modulator therapies may lead to an improvement in CF health and a change in the current outpatient clinic set up, possibly leading to more individualised treatment and more reluctance to come up to Hospital clinics. Home monitoring has the potential to monitor signs and symptoms in between clinic appointments either allowing for rationalisation of clinic appointments for a stable patient, or identification of a pulmonary exacerbation. There is evidence from large adult studies regarding the feasibility of home monitoring and some evidence that is does not affect mood in the CF patient. However, there is limited evidence for feasibility of home monitoring in paediatrics and only in small cohorts of patients and no previous studies have properly explored the impact on depression and anxiety levels of the caregivers or quality of life for the young people with CF by adding to their treatment burden. Clinical Monitoring and Biomarkers to stratify severity and predict outcomes in children with Cystic Fibrosis (CLIMB-CF) was designed to attempt to answer those questions.

1.2 Cystic fibrosis (CF)

The first description of CF was by Dr Dorothy Anderson in 1938 (1) when she presented post-mortem case series of 49 malnourished children showing fibrosis of the pancreas and coined the term Cystic Fibrosis of the pancreas. A high number of children (44/49) in her case series were also reported to have evidence of respiratory pathology such as bronchiectasis or evidence of pulmonary infection.

In 1948 during the New York heat wave, it was recognised that more than half of the children admitted with dehydration had cystic fibrosis of the pancreas (2). This observation led Di Sant'Agenese and colleagues to explore the composition of sweat in people with this condition. They found that sodium and chloride concentrations were 2 to 4 times higher in patients with cystic fibrosis of the pancreas compared to other conditions (3). They postulated the loss of salt through sweating during the heat wave accounted for the increased hospital admissions with dehydration and that many if not all exocrine glands could be affected by cystic fibrosis of the pancreas. Gibson and Cooke subsequently developed a pilocarpine iontophoresis technique to measure the concentration of sodium and chloride in sweat aiding the diagnosis of CF (4). In 1983 defective chloride transport was identified as the basic defect in CF (5). CF was then identified as a genetic condition, likely inherited in an autosomal pattern in 1945 (6) and subsequently in 1989 the CF gene was identified (7-9).

1.3 Genetics of CF

The CF gene is found on the long arm of chromosome 7 (10). Mutations in this gene cause lack of, or functionally defective, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein (11).

Since the discovery of the gene, more than 2000 variants have been described (12) , of which, as of September 2021, 382 are confirmed to be pathogenic on www.cftr2.org. These variants can be divided into separate classes depending on the consequences on the CFTR protein (Figure 0-1), although many have features of more than one class and there is significant overlap between the functional defects caused by each class (Figure 0-2) (13, 14).

Class I mutations

Class I mutations are nonsense mutations causing premature stop codons that result in no functional CFTR protein being made, e.g. Gly542X.

Class II mutations

Class II mutations are the most common *CFTR* gene mutation; they cause protein misfolding, the consequence of which is that the CFTR protein undergoes intracellular destruction and cannot be transported to the cell surface (15). Phe508del is the most common of these; around 90% of people with CF in the UK have at least one copy (16).

Class III mutations

Class III mutations are missense mutations which result in CFTR protein being present on the cell surface but not functioning due to impaired regulation; they are often called gating mutations (17). Gly551Asp is the most common Class III mutation.

Class IV mutations

Class IV, conductance, mutations also result in CFTR protein being successfully trafficked to the cell surface. While CFTR is open however, these mutations lead to reduced chloride current (15).

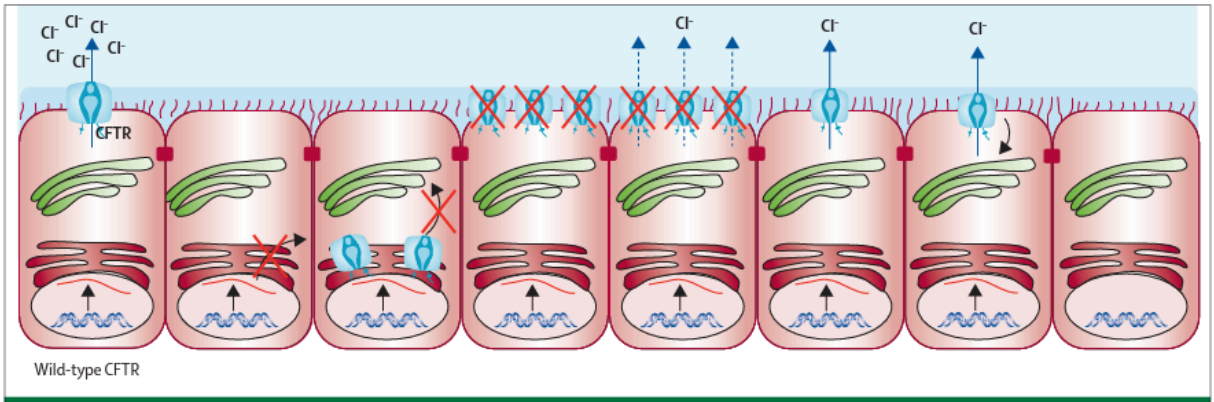
Class V and VI Mutations

Class V and VI mutations result in functioning CFTR protein at the cell surface, though either in lower numbers (V) or with poor membrane stability hence increased turnover (VI) (15, 17).

Class VII Mutations

This class is described as the 'unrescuable' mutation because within this class there is a large deletion of genetic material and are therefore the CFTR protein cannot be rescued pharmacologically (18).

CFTR genotype influences phenotype with class I-III producing the more clinically severe, pancreatic insufficient phenotype compared to classes IV-VI (19, 20).



	Class I	Class II	Class III	Class IV	Class V	Class VI	Class VII
CFTR defect	No protein	No traffic	Impaired gating	Decreased conductance	Less protein	Less stable	No mRNA
Mutation examples	GLy542X, Trp1282X	Phe508del, Asn1303Lys, Ala561Glu	Gly551Asp, Ser549Arg, Gly1349Asp	Arg117His, Arg334Trp, Ala455Glu	Ala455Glu, 3272-26A→G, 3849+10 kg C→T	c. 120del23, rPhe508del	dele2,3(21 kb), 1717-1G→A
Corrective therapy	Rescue synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability	Unrescuable
Drug (approved)	Read-through compounds (no)	Correctors (yes)	Potentiators (yes)	Potentiators (no)	Antisense oligonucleotides, correctors, potentiators? (no)	Stabilisers (no)	Bypass therapies (no)

Figure 0-1 The 6 classes of CFTR mutation. Reproduced from De Boeck and Amaral (18).

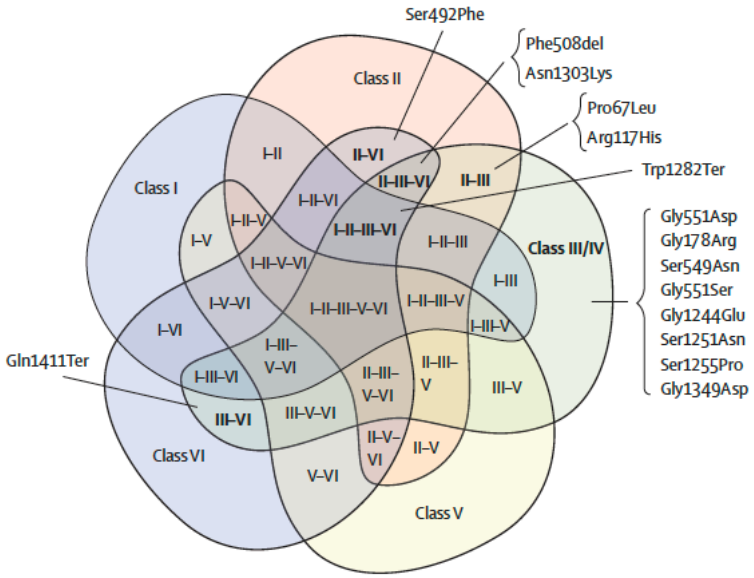


Figure 0-2 The potential overlap between different CFTR classes. Reproduced with permission from Shteinberg et al (14).

1.4 Diagnosis of CF

There are consensus guidelines from the CF Foundation on the diagnosis of CF which were published in 2017 (21). Most high income countries with a high prevalence of CF have instigated newborn screening, allowing for earlier diagnosis and initiation of treatment (22). Newborn screening programmes are developed based on the prevalence of genetic variants within the country as well as the resources available (22). In the UK newborn screening has been universal since 2007 and uses an immunoreactive trypsin (IRT)-DNA-IRT protocol (23). An audit after the first 4 years of universal screening in the UK found 5.5% of confirmed cases with CF had been missed by newborn screening, emphasising that the diagnosis should still be considered in symptomatic children with a negative newborn screen (24). In countries where there is no access to newborn screening, a diagnosis of CF must be considered in patients presenting with signs and symptoms consistent with CF (25). In both the newborn screened population and the nonscreened population sweat chloride testing is advised

as soon as possible (21, 25). There are clear guidelines for carrying out diagnostic sweat chloride testing, including advice on increasing chance of success such as ensuring the patient weighs ≥ 2kg and is ≥36 weeks gestational age (26). A diagnosis of CF requires a sweat chloride level ≥ 60 mmol/l and/or two CF causing *CFTR* mutations (27).

1.5 **Pathophysiology of CF**

The CFTR protein is a cyclic AMP-activated epithelial ion channel enabling efflux of chloride and bicarbonate , as well as inhibiting the activity of the epithelial sodium channel (ENaC) in absorbing sodium (28). CFTR is regulated by both phosphatase and kinase activity in the cell as well as by the cellular levels of Adenosine triphosphate (ATP) which control opening and closing of the channel (29). It is present in the epithelial cells of the respiratory tract, the gastrointestinal tract, the sweat gland, inflammatory cells, the pancreas, and the reproductive system (14, 30, 31). Dysregulation of this channel in CF can have consequences in all these body systems.

1.5.1 **CF lung disease**

CF lung disease is the major determinant of survival, with end stage respiratory disease being the main cause of death (32). CFTR dysfunction and lack of ENaC inhibition in the lung leads to depletion of the airway surface liquid (ASL), and thick, viscous mucus layer (28, 33), leading to impaired mucus clearance and subsequent accumulation (33) and obstruction of the distal airways (34). The low volume hypothesis suggests the mechanism for this is that the cilia on the epithelial side of the cells collapse secondary to the loss of the ASL and can no longer clear the mucus optimally (33). A factor that could be contributing to the increased viscosity of CF mucus in the airway is lower levels of bicarbonate. Bicarbonate has a key role in the expansion of mucins in mucus and therefore the

absence of bicarbonate due to CFTR dysfunction in CF creates thicker mucus in the CF lung (35). Impaired bicarbonate secretion could also influence the airway pH. There is *in vitro* evidence that CF ASL has a lower pH than the ASL of healthy controls (36, 37). Impaired eradication of bacterial pathogens has been shown to be related to the lower pH of the ASL in the lungs of CF pigs (38). In addition, there is evidence that the lower pH could impact viscosity of the mucus (39). The combination of these factors mean bacteria can then become trapped in the thick CF mucus causing infection and inflammation which may become chronic. *In vivo* studies in humans with CF are technically difficult and the results are discrepant (40-42).

Post mortem examination of the airways of children with CF shortly after birth compared to control samples demonstrated some evidence of mucous gland hyperplasia even in non-infected CF airways (43). However, there was no difference between infected CF airway cells and infected controls, although there was evidence of a higher percentage of pulmonary infections in the airways from the CF children (43). Examination of the airway of a CF foetus showed no histological signs of inflammation but did show overexpression of pro-inflammatory proteins regulated by the transcription factor NF-kB prior to any infection (44).

There is evidence of infection and inflammation present from early life in CF. That said, the interplay between abnormal CFTR function and inflammation is incompletely understood (45). The cellular population of the normal airway lumen comprises around 5% neutrophils; however, in the CF airway that number can be as high as 95% (46). There is increasing evidence that CFTR dysfunction leads to changes in innate immunity potentially before exposure to respiratory pathogens (32). An exaggerated inflammatory response appears to be present from an early age and can also be

excessive relative to bacterial burden (45). Increased numbers of neutrophils, free neutrophil elastase (NE) and interleukin 8 (IL-8) have been found in bronchoalveolar lavage (BAL) samples from infants with CF both in the presence of infection and with negative BAL cultures (47-49). IL-8 has also been found to be higher in BAL in children with CF compared to healthy controls. This finding was independent of whether there was a positive bacterial, fungal, or viral culture from the BAL (47, 50). BAL is considered the main method to obtain reliable samples from the airways of young people with CF, however it should be noted that there is a possibility of sampling errors leading to false negative BAL cultures depending on which lobe of the lung is sampled at the time of the bronchoscopy, which may account for the negative BAL cultures in previous studies (51-53). These studies can also not correct for the possibility of a previous respiratory infection with no longer culturable pathogens but a residual inflammatory response. Indeed, there is good evidence of slow resolution of inflammation in CF (54, 55).

Other pro-inflammatory mediators have been found in high concentrations in the CF airway via BAL sampling. Interleukin-17 (IL-17) has been found in excessive amounts, in particular once chronic bacterial infection is established, and promotes an influx of neutrophils which, perpetuates the excessive inflammatory response (45). CF mice have been shown to have higher levels of IL-17 in BAL when compared to wild-type mice and when given an IL-17 inhibitor were shown to have decreased neutrophils in their BAL and better weight gain. Their bacterial burden was also decreased (56). The complexity of the inflammatory state of CF lung disease and possible treatments, however, becomes apparent when exploring inhibition of IL-17 as a possible treatment option as it has also been shown that IL-17 is vital in the defence against both the initial infection and the development of chronic infection with *Pseudomonas aeruginosa (P.aeruginosa)(57)*. Leukotriene B4 (LTB_4) is a

chemoattractant that along with IL-8, plays a significant role in promoting neutrophil chemotaxis and activation. Stimulation of LTB_4 release can occur in the presence of bacteria such as *Pseudomonas aeruginosa* (58). BIIL 284 was an LTB_4 receptor antagonist tested in a double-blind, randomised, placebo-controlled trial exploring safety and efficacy in patients with CF aged ≥ 6 years (58). Primary end points were change in forced expiratory volume in the first second percent predicted (FEV_1 % predicted) and the number of pulmonary exacerbations experienced. The trial was terminated early when the data safety monitoring board noted a disproportionate incidence of worsening respiratory symptoms and pulmonary exacerbations in the group being treated with BIIL 284. There was also evidence of decreased FEV_1 % predicted and increased circulating peripheral neutrophils in the patients receiving BIIL 284 when compared to the placebo group (58). Data on IL-17 and the results from the BIIL 284 trial suggest that some of the inflammatory processes in the CF airway are beneficial and but it is unclear how best to modulate inflammation.

There is evidence for both structural and functional changes in early life. Infant lung function (forced expiratory volume (FEV) in 0.4 seconds and maximum expiratory flow at 25% of forced vital capacity(FVC)) has been shown to be reduced compared to healthy controls, even in the absence of respiratory infection, and evidence of airway dilatation (bronchiectasis, which by definition may be reversible in children (59)) has been seen on CT scans of infants at 3 months of age (60-62). 40% of infants with evidence of bronchiectasis on their CT scan had a positive respiratory culture from their BAL and 38% had increased levels of free NE (62). Early bronchiectasis identified on high-resolution CT scan was also shown to persist in 74% of cases (62). Recent work using CF ferret models also supports the idea that bronchiectasis can develop without the presence of bacterial infection, and possibly secondary to the heightened inflammatory response, as CF ferrets treated with daily broad-

spectrum antibiotics still developed evidence of bronchiectasis. It should be noted that bronchiectasis developed both in CF ferrets who received continuous daily antibiotic treatment and in those only given antibiotic treatment when symptomatic, but those given continuous antibiotics survived longer (63).

The combination of the viscous mucus, bacterial infections and the ongoing inflammatory response contributes to the development of bronchiectasis in CF (22, 64). It is thought the viscous mucus can cause goblet cell hyperplasia, as well as promoting bacterial infection. This leads to an inflammatory response which can cause oedema and subsequent reduction in the size of the small airways (64). This airway obstruction is then worsened by mucus plugging which causes ongoing lung injury, which can become irreversible (22, 64).

1.5.1.1 Infection in the CF lung

Acute and chronic respiratory infection is common in people with CF with the dominant pathogens changing with age. Young children are more likely to be infected with *Staphylococcus aureus (S. aureus)* and *Haemophilus influenza* with *Pseudomonas aeruginosa* becoming the more prevalent pathogen as they get older (Figure 0-3) (16). Specific treatment regimens will be discussed in section 1.7 but are based on eradication, prophylaxis, or suppression of the pathogen.

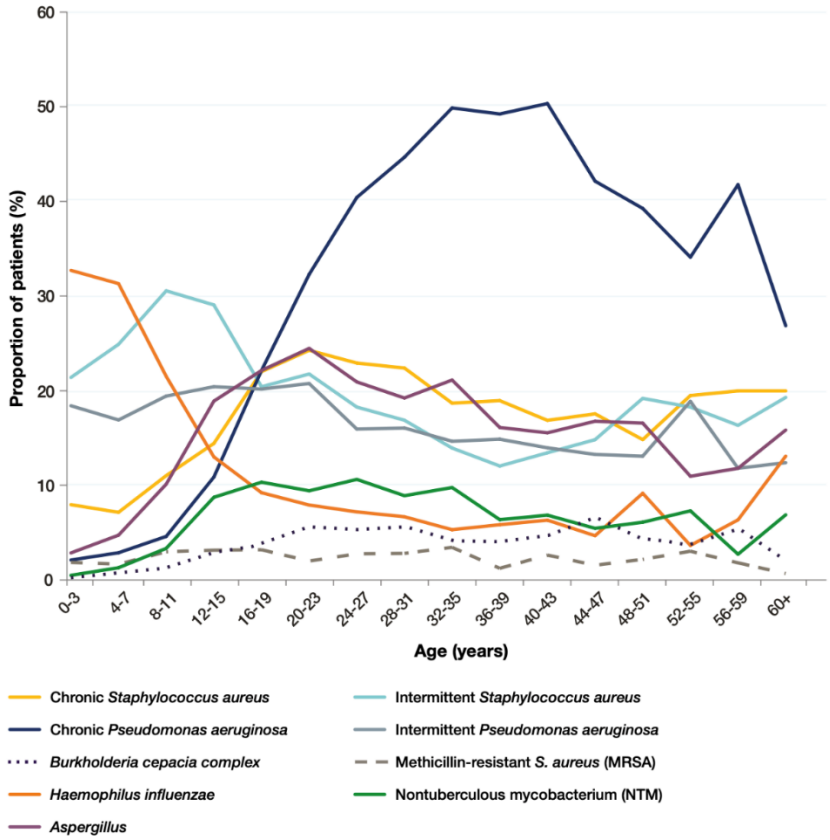


Figure 0-3 The proportion of patients with specific lung infections in 2019 registered on the UK CF registry with corresponding ages of infection. Reproduced with permission from the UK Cystic Fibrosis Registry Annual Data Report 2019 (16)

S. aureus has been found in the anterior nares of 52.4% of children with CF and has also in the anterior nares of members of their families suggesting possible household transmission (65). The presence of *S. aureus* in BAL samples was associated with higher levels of inflammatory markers such as NE, IL-8 and total neutrophil count when compared to culture negative BAL samples (66, 67). Interestingly, higher levels of inflammatory markers were found in BAL samples that cultured *S. aureus* compared to *Haemophilus influenza* (the other prevalent pathogen in childhood) (66). While the presence of *S. aureus* within BAL does not correlate with lung function recorded at the time of the bronchoscopy, it does seem to be associated with worse lung function decline over time (48). Children who culture *S. aureus* within the first 2 years of life also appear to have significantly

decreased lung function at 5 years when compared to children with CF who have been culture negative (68). However, despite this, the effects of early *S. aureus* acquisition on long term survival remain unclear. It has been shown the *S. aureus* infection on its own did not influence survival but co-infection with *S. aureus* and *P. aeruginosa* did reduce 10-year survival (68). Interestingly, the presence of *S. aureus* at the point of transplant consideration has been shown to increase wait list survival but decrease post-transplant survival in children with CF (69). A large Danish study has shown *S. aureus* eradication rates of 74% in sputum using oral antibiotics (70). Despite this, chronic infection can occur. The mechanism of this, in part, is *S. aureus* developing small colony variants that are slow growing and can remain in the lung for longer and which tend to be identified after regular use of antibiotics (71-73). Co-colonisation with *P. aeruginosa* is connected to small colony variant *S. aureus*. 4-hydroxy-2-heptylquinoline-N-oxide is produced by *P. aeruginosa* and while it has been shown to slow down the growth of *S. aureus*, it also appears to provide the *S. aureus* protection from antibacterial activity (74). Levels of Methicillin-Resistant *S. aureus* (MRSA) are low in children with CF in UK and most parts of Europe, however the presence of MRSA is clinically significant (75). Those who are culture positive for MRSA have lower lung function and require more maintenance therapies than those patients culturing Methicillin-Sensitive *S. aureus* (76, 77).

P. aeruginosa acquisition in early life is associated with increased morbidity in children with CF (68, 78). There is conflicting evidence regarding the correlation between acquisition of *P. aeruginosa* and lung function decline (79, 80), however acquisition and failed eradication has been shown to increase the frequency of pulmonary exacerbations (80). The Australasian Cystic Fibrosis Bronchoalevolar Lavage randomised controlled trial attempted to determine whether targeting antibiotics to positive cultures from bronchoscopy compared to oropharyngeal cultures in the first 5 years of life improved

outcomes (81). All participants had CF diagnosed on newborn screen and of the 168 participants, 53% acquired *P. aeruginosa* during the first 5 years of life. 44% of those participants reacquired *P. aeruginosa* after eradication during the study period, although only one participant was classified as chronically infected (82). The study failed to meet its primary endpoint, with therapy directed at bronchoalveolar lavage cultures not reducing structural abnormalities seen on computed tomography (CT) scan or *P. aeruginosa* infection rates at 5 years of age (81). Early detection and eradication in the first year of life may have longer term benefits: no difference was seen in CT scans, lung function or body mass index (BMI) at 6 years of age when comparing those children with *P. aeruginosa* positive cultures and successful eradication in their first year of life with those who were culture negative (83). Heltshe *et al* followed children diagnosed with CF before the age of 2 years for 5.5 years to explore the emergence of chronic *P. aeruginosa* after initial acquisition (84). Two thirds of the children followed had a culture positive for *P. aeruginosa* within the study period, with 13% being classified as chronically infected (3 positive cultures for *P. aeruginosa* samples in the preceding year). They noted that those children with Class I-III mutations were more likely to acquire *P. aeruginosa* earlier and more likely to develop chronic *P. aeruginosa* infection. The most commonly used definition of chronic infection is the Leeds criteria which defines chronic infection as >50% positive cultures over 12 months, intermittent infection as ≤ 50% positive cultures and infection free as no positive cultures in 12 months (85). This definition is based on the collection of monthly microbiological samples which is not standard practice in many CF centres (86). Early eradication is suggested as a way to prevent chronic *P. aeruginosa* infection, and acceptance that this may need to be repeated is important (87).

1.6 Monitoring of CF lung disease

Most CF centres arrange their CF outpatient clinic appointments based on the age of the person with CF and their clinical need. There are guidelines advising centres on the optimal number of clinic appointments a person with CF should be offered. In the UK the National Institute for Health and Care Excellence (NICE) guidance is that routine reviews should be offered weekly for people with CF in their first month of life, then every 4 weeks between 1 month and 12 months, every 6 to 8 weeks until they are 5 years old, every 8 to 12 weeks when they are over 5 years of age and every 3 to 6 months as adults (88). This ensures all patients get seen regularly but potentially means a lack of flexibility if a patient needs to be seen outside of their regularly scheduled appointments due to limited clinic space.

1.6.1 Pulse oximetry

In the UK it is recommended that all people with CF have pulse oximetry carried out during routine clinic appointments (88). In the USA as there is limited evidence in the utility in the under 5-year-olds they do not recommend for or against its use in the younger age group (89). In older children however, lower day time oximetry is associated with lower nocturnal oxygen saturations (90) and lower nocturnal oxygen saturations are associated with poorer lung function (91).

1.6.2 Microbiology

It is recommended that respiratory cultures are taken quarterly as a minimum (88, 92). In practice, however, respiratory cultures tend to be taken more frequently and when people with CF are symptomatic. Respiratory sampling in children with CF can be more challenging as they tend to be unable to expectorate sputum. Bronchoalveolar lavage (BAL) is the gold standard in terms of

sampling the lower airway, however the need for a general anaesthetic in children, the potential preoperative anxiety, the documented side effects, and increased healthcare costs does mean it has some limitations (81, 93-95). Oropharyngeal swabs provide a non-invasive way of sampling the airway of children with CF, but concern remains regarding the reliability of upper airway sampling to predict the pathogens in the lower airway (96, 97). Induced sputum (IS) has the potential to bridge the gap between oropharyngeal swabs and BAL. IS has been shown to be safe and acceptable in children (98) and the CF-Sputum Induction Trial showed it to be superior to oropharyngeal swabs and a credible surrogate for BAL (51). There is concern that IS is too time consuming to be carried out in clinic (89), an alternative may be that people collect a sample at home. Home sputum induction was shown to be 96% successful if participants had undergone at least one hospital IS and were given clear instructions (99).

Consideration should also be given to sending virology samples in young patients with CF. In 2019 it was shown that in infants with CF prescribed antibiotics for respiratory symptoms, 52% of patients had viruses identified (100). They also showed that post viral infection these infants had higher BAL neutrophil counts and elevated bacterial isolates (100). Viral upper airway infections are present in similar number in children with CF compared with healthy controls (101), however children with CF are more likely to have symptoms that are present for longer, develop lower respiratory tract infections as a consequence of the viral infection and have been shown to have a deterioration in their lung function (101-103).

1.6.3 **Spirometry**

Spirometry is one of the most used clinical markers of lung health in CF patients. Children as young as 3 years of age can attempt the procedure whilst supervised in clinic (89). There are clear standards and guidelines to ensure the procedure is correctly carried out (104). Spirometry is a forced manoeuvre which measures the maximal volume of air expelled with maximal effort. The most quoted spirometry results are Forced expiratory volume in the first second of the manoeuvre (FEV_1) and Forced Vital Capacity (FVC) which is the total volume expired in full expiration (104). An individual's spirometry result can then be used to calculate their FEV_1 percent predicted (FEV_1 % predicted) based on predicted reference ranges based on their age, sex, height, and ethnicity (105).

As mentioned earlier declining lung health is the biggest cause of morbidity and mortality in CF. There have been several risk factors associated with worsening FEV_1, these include female sex, poor nutritional state, and *Pseudomonas aeruginosa* infection (106, 107). Decline in lung function is also associated with worsening quality of life (108). Adolescence also seems to be a key time for lung function decline and interestingly those adolescents with a higher starting base line lung function appear to be at higher risk of substantial decline (109, 110).

Despite spirometry being the gold standard for lung function testing (104) the minimal clinically important difference (MCID) remains unknown (111). Spirometry also does not appear to correlate to other measures of lung disease such as structural lung damage, inflammatory markers, or positive microbiology (112-114).

1.6.4 **Emerging models of assessment**

Multiple breath washout (MBW) is a tidal breathing technique which is being utilised in clinical trials and shows feasibility through infancy into adulthood (115). MBW produces measures of ventilation distribution, the most reported measure being lung clearance index (LCI) (116). It has been shown that LCI at pre-school age does predict subsequent lung function (117) and that LCI in children appears to correlate with structural damage seen on CT scan (118) As with spirometry, to date there is no validated MCID and work is ongoing to determine variation during periods of stability (119, 120). In preschool children studied longitudinally over a year the inter-test variability in healthy children has been shown to be $\pm$ 15%, in stable children with CF the inter-test variability was $\pm$ 25% (121). The authors concluded that as it remains difficult to differentiate biological variability from changes in disease state changes therefore an LCI of > 15% could be considered physiologically relevant while carrying out further investigation. In a smaller yearlong study of older children with CF (aged 5-18 years) between session variability was shown to be up to 25% (122). A recent 2-year prospective study using LCI as an outcome measure showed a detrimental change in LCI of 10% was associated with pulmonary exacerbations and that as a group LCI did improve after treatment but did not return to baseline (123). There remain challenges to MBW becoming established in routine clinical care including but not limited to the cost of the equipment and the time taken to complete the test (111, 124).

1.7 **Pulmonary exacerbations**

CF pulmonary exacerbations are poorly understood periods of increased respiratory signs and symptoms; there is no agreed definition. The exact cellular/physiological mechanisms of pulmonary exacerbations remain unclear although changes in inflammatory markers, viral pathogen acquisition and changes in microbiology of the CF airway has been reported (125). Infections with Respiratory

Syncytial Virus and Influenza have been associated with the development of pulmonary exacerbation symptoms (102, 126). Interestingly while pulmonary exacerbations may be associated with the acquisition of a new bacterial pathogen, they may also be associated with the overgrowth of an already present pathogen as a reduction in the amount of *P. aeruginosa* present in the airway after treatment for a pulmonary exacerbation is associated with an improvement in lung function (127, 128).

To date there are no clear diagnostic criteria for a pulmonary exacerbation (129). Currently in clinical practice the decision to treat a possible pulmonary exacerbation is clinician dependent and the decision to treat or not treat may ultimately affect long term outcomes (130). For example, it has been shown that the number of exacerbations requiring hospitalization in children aged 5 years and younger predicts morbidity and mortality (131). People with CF who have more pulmonary exacerbations tend to have more rapid lung function decline (132, 133). While the mechanism remains poorly understood, 25% of people with CF who experience a pulmonary exacerbation fail to regain their baseline lung function (134, 135). Exacerbations are also associated with decreased quality of life (136) and are known to adversely affect sleep and subsequently tests of neurobehavioural performance (137).

Some studies have reported increases in inflammatory markers, such as IL-8 and NE, in the sputum at the start of a pulmonary exacerbation which have then been noted to decrease after antibiotic treatment (112, 138, 139), although these results have not been consistently replicated, particularly in paediatrics. Karpati *et al* found higher levels of Tumour Necrosis Factor Alpha (TNFα) and IL-8 in 10 exacerbating adult patients (mean age 29.5 years) at the start of their treatment course compared

to the end (140). Both cytokines were inversely related to lung function measures and IL-8 was positively correlated with C-reactive protein (CRP). When TNFα and IL-8 were explored in paediatric patients over the age of 4.5 years using ELISA no significant difference was seen in either during stability or exacerbation (141). 31 of 78 participants approached were unable to produce sputum (141). There was also no significant change in IL-8 and NE elastase levels in sputum in young people with CF (n=17, mean age 12) whose pulmonary exacerbations were treated with three weeks of oral antibiotics (142). These results were similar to a cohort of children treated with IV antibiotics (n=14, median age 14 years); IL-8 demonstrated a nonsignificant reduction at the end of treatment and no consistent correlation with NE levels were noted (143).

Matrix metalloprotease -9 (MMP-9) is a marker of neutrophil activation which can be inhibited by tissue inhibitor of metalloproteinase-1 (TIMP-1). MMP-9 has been shown to be higher in sputum in stable adult patients with CF and significantly higher in CF patients hospitalised for an exacerbation (n=33), however no significant change was seen in values obtained at the start of treatment and the end of treatment and there was no correlation with lung function (144). Sputum NE levels were also found to be raised in this study and were strongly correlated with levels of MMP-9. The authors postulated that NE impacted activation of MMP-9, partly due to its ability to degrade TIMP-1. High levels of MMP-9 have also been shown in 10 exacerbating children with CF, with MMP-9 levels decreasing significantly at the end of an IV antibiotic course. The authors also noted imbalance between MMP-9 and TIMP-1 (145).

Rates of pulmonary exacerbations requiring antibiotics increase with age, as shown in Table 0-1 taken from the UK CF Trust registry report 2019 showing the percentage of patients per age group who required at least one course of IV antibiotics in the previous year as reported on the registry (16).

Table 0-1 The UK CF Trust Registry Annual data report 2019 showing the number of patients per age group who required at least 1 course of IV antibiotics in the previous year as reported to the registry. Reproduced with permission from the CF Trust (16).

		Home		Hospital		Total	
Age	**N**	**Patients n (%)**	**Median days (IQR)**	**Patients n (%)**	**Median days (IQR)**	**Patients n (%)**	**Median days (IQR)**
0-3	803	25 (3.1)	7 (5-12)	183 (22.8)	14 (5-12)	184 (22.9)	14 (9-17)
4-7	1075	86 (8.0)	14 (8-24)	263 (24.5)	14 (8-24)	276 (25.7)	14 (13-28)
8-11	1105	123 (11.1)	18 (11-28)	302 (27.3)	14 (11-28)	323 (29.2)	25 (14-41)
12-15	983	179 (18.2)	16 (11-33)	401 (40.8)	15 (11-33)	436 (44.4)	26 (14-43)
16-19	812	181 (22.3)	14 (10-28)	360 (44.3)	16 (10-28)	389 (47.9)	26 (14-42)
20-23	996	317 (31.8)	15 (11-31)	489 (49.1)	16 (11-31)	567 (56.9)	28 (14-49)
24-27	902	298 (33.0)	21 (13-39)	432 (47.9)	16 (13-39)	528 (58.5)	28 (14-49)

Pulmonary exacerbations tend to be treated with an escalation in treatment, which might include oral, IV or nebulised antibiotics. As there is no clear definition of a pulmonary exacerbation, both diagnosis and treatment course are dictated by the clinician responsible for the patient and their care (129). Treatment choice is important; for example, there is observational evidence from the USA that adults with lung function in the highest quartile have received more courses of IV antibiotics than patients in the lowest quartile, potentially suggesting that more aggressive treatment of potential pulmonary exacerbations could be protective (130). However, more aggressive treatment with IV antibiotics can lead to further complications such as antimicrobial resistance (146). Antibiotic side effects must also be considered including acute kidney injury, ototoxicity, and antibiotic allergy (147). There is a lack of evidence in pulmonary exacerbation guidelines not only on treatment type but also

optimal treatment duration. VanDevanter and colleagues analysed data from a CF exacerbation management study and found a range of antibiotic durations from 4 to 27 days; with the highest observed FEV_1 % predicted value recorded at 8.7 days (148). It may be that no consensus is available because the decision is patient specific. The Standardised Treatment for Pulmonary Exacerbations 2 (STOP-2) trial explored the clinical efficacy and safety of different durations of IV antibiotic treatment. The study used changes in spirometry and symptoms scores at day 7-10 of treatment to allocate participants to early responder or non-early responder groups. Participants in the early responder group were then randomised to receive either 10 or 14 days of IV antibiotics and those in the non-early responder group randomised to receive either 14 or 21 days. The hypothesis was that 10 days would not be inferior to 14 days for early responders and 21 days would be superior to 14 days in non-early responders (149). The results have just been published and have shown that 10 days are not inferior to 14 days but that 21 days were not superior to 14 days (150). A pilot study in paediatrics (STOP-PEDS) is currently enrolling participants aged 6-18 years of age, comparing immediate antibiotics and increased airway clearance with tailored therapy (increased airway clearance alone plus the addition of oral antibiotics for worsening symptoms or failure to improve) (NCT04608019).

Children with CF are more likely than adults to present with 'milder' symptoms of a pulmonary exacerbation and therefore more likely to receive a course of oral, rather than IV, antibiotics (151). Data exploring the use of oral antibiotics for 'milder' pulmonary exacerbations are limited. In 2016 it was shown that while courses of oral antibiotics to treat clinician diagnosed pulmonary exacerbations in children tended to be in those who had a less than 10% drop in their lung function, in 20% of these events lung function did not return to pre-exacerbation levels (152). Pulmonary exacerbations treated with oral antibiotics are associated with loss of lung function compared to baseline and are

associated with a cumulative effect on lung function over time, which is more significant the greater the number of oral antibiotic courses received (152, 153). While this is also true for exacerbations treated with IV antibiotics (134, 154), the concern is how to recognise those children who are having frequent courses of oral antibiotics for 'mild' pulmonary exacerbations and, how to treat them and when they warrant more intensive treatment to prevent long term consequences (152). (135). A recent study exploring the use of LCI in children with CF around acute respiratory events found that while the change in LCI was less in events clinicians had decided not to treat as they presented with milder symptoms when compared to those events that received treatment, in a quarter of the untreated participants LCI did not return to baseline on follow up leading the authors to suggest these untreated events could be more clinically meaningful than perceived by the patient or the clinician (123).

Attempts have been made to define a pulmonary exacerbation for clinical trials (128, 155), however these tools have not been formally validated and have not translated to clinical care (129). One of the most used in trials is the Fuchs criteria which labels a respiratory event with the presence of 4 or more of the 12 signs and symptoms shown in Table 0-2 diagnosing a pulmonary exacerbation (155).

Table 0-2 Fuchs sign and symptoms criteria. A collection of 4 or more of the listed signs and symptoms corresponds to a diagnosis of a pulmonary exacerbation. Reproduced from VanDevanter et al 2021 (156).

Fuchs sign and symptom criteria
• Increased cough
• Change in sputum
• New or increased hemoptysis
• Increased dyspnea
• Malaise, fatigue, or lethargy
• Temperature above 38 °C
• Anorexia or weight loss
• Sinus pain or tenderness
• Change in sinus discharge
• Change in physical examination of the chest
• Decrease in pulmonary function by 10% percent or more from a previously recorded value
• Radiographic changes indicative of pulmonary infection

VanDevanter *et al* analysed data collected in a clinical trial of ataluren to explore differences between criteria-based exacerbations and investigator assessed exacerbations (156). Within the study there were 254 defined pulmonary exacerbations with ≥ 4 Fuchs criteria but 27% of those were not assessed as pulmonary exacerbations by the clinical investigators. This was because just over half of those events were felt to be upper respiratory tract infections and the others were considered to be normal variation of their baseline symptoms. There were also an additional 166 respiratory events that did not meet the Fuchs criteria of a pulmonary exacerbation but were deemed to be exacerbations by the investigators. The authors postulate that an objective measure, such as Fuchs, does not consider the insights of patients who may experience frequent respiratory events in their lifetime which are not all pulmonary exacerbations, as well as the relationship the patient may have with their clinician and the subsequent dialogue that may follow regarding treatment (156).

The group also explored the completeness of Fuchs criteria collection and found that 90% of the respiratory events recorded were in fact missing at least one datum point within and around a third were missing data for four of the criteria. These missing data values tended to be related to data that

would be collected in a face-to-face visit such as spirometry, temperature, or radiological investigations. The authors went on to acknowledge that these missing data may lead to falsely low exacerbation rates as events may not be meeting the relevant criteria (156).

Further work has explored diagnostic criteria that do not rely on radiological or pathological specimen collection, finding that changes in reported symptoms (especially increased cough and decreased appetite) and clinical signs (weight loss and crackles on chest auscultation) can identify pulmonary exacerbations. These criteria can be strengthened with the addition of decrease in FEV_1 (157, 158). There is the risk that waiting for an arbitrary spirometry cut off, such as a drop in FEV_1 % predicted of ≥ 10%, may delay treatment of pulmonary exacerbations. One study showed that of 208 clinician diagnosed pulmonary exacerbations in which spirometry was available, only 44 showed a drop in FEV_1 % predicted of ≥10% (156). The counter argument may also be true, and clinicians may actually over diagnose pulmonary exacerbations, over-treating patients and subjecting them to long hospital stays. Schechter argued that given the current diagnostic quandary the consequences of missing a pulmonary exacerbation are more severe than over treating and that if a clinician had the benefit of guaranteed close follow up they may decide it would be safe to observe and not start treatment, however if this was not guaranteed they may be more inclined to treat (159). Spirometry is also not available for all patients, most notably for most children with CF who are <6 years of age meaning, therefore, that different clinical characteristics may lead a clinician to a diagnosis of a pulmonary exacerbation. The Epidemiologic Study of Cystic Fibrosis identified 4 signs and symptoms closely associated with a diagnosis of a pulmonary exacerbation for age-based sub-groups of 9 or 10 subjects. In the 3 paediatric age groups (<6, 6-12 and 13-17 years of age) increased cough and new crackles on auscultation were characteristics in all groups. In children <6 years decline in weight and increased

sputum were the other two characteristics. A decline in FEV_1 % predicted of ≥ 15% was the third characteristic in both the 6-12 and 13-17 age groups. The final characteristic in the 6-12 age group was new acquisition of *P. aeruginosa* and in the 13-17 age group was haemoptysis. The authors stated that having 3 or more of these characteristics was predictive of a pulmonary exacerbation (158). While most criteria use a collection of signs and/or symptoms, some are divided into major criteria and minor criteria, with the presence of one major criterion establishing a diagnosis of a pulmonary exacerbation. One such criterion was utilised in the Early anti-pseudomonal acquisition trial (EPIC). The major criteria were either a decrease in FEV_1 % predicted from baseline of ≥10% or oxygen saturations <90% in room air or ≥5% decline from previous baseline or changes on chest x-ray or haemoptysis on more than one occasion in the previous week (160). Rosenfeld and colleagues compiled physician completed questionnaire data from a randomised control trial of tobramycin and developed models based on the reported characteristics put forward to standardise diagnosis of pulmonary exacerbations in future clinical trials, however this has not been uniformly adopted (157). In an attempt to summarise the criteria being used in clinical trials to identify a pulmonary exacerbation Goss and Burns compared Fuchs criteria with three other criteria used in clinical trials; the criteria used by Ramsey and colleagues, the Acute Respiratory Illness Checklist (ARIC) and the Respiratory and Systemic Symptoms Questionnaire (RSSQ) (129). Table 0-3 is adapted from Goss and Burns (129) with the addition of the criteria in other studies discussed in this section.

Table 0-3 Criteria used to define a pulmonary exacerbation in CF. Adapted from Goss and Burns(129). Criteria that require a hospital attendance are highlighted in red. Abbreviations WBC-white blood cells. ESR- Erythrocyte sedimentary rate (157, 158, 160-162).

	Fuchs	Ramsey	ARIC	RSSQ	ESCF (Rabin)	Project Breathe	Dakin	Rosenfeld	EPIC
Signs and symptoms (new or increased)									
Pulmonary									
Cough	X	X		X	X	X	X	X	X
Change in sputum	X				X	X	X	X	X
New or increased Haemoptysis	X		X	X	X		X		X
Increased dyspnoea	X			X				X	
Decreased exercise tolerance				X			X	X	X
Increased work of breathing			X				X		
Difficulty breathing						X			
Chest tightness						X			
Day cough			X						
Night cough			X						
Wet or congested cough			X						
Chest congestion				X					
Frequency of cough				X					
Wheezing			X		X	X		X	
Increased sputum volume		X	X	X					
Change in sputum appearance		X		X				X	
Change in sputum colour			X	X					
Change in sputum consistency			X	X					
Increased respiratory rate		X					X	X	X
Decreased lung function	X	X			X		X	X	X
O2 saturations <90% or ≥5% decline from baseline									X
Change in oxygen saturations							X	X	
Radiographic changes indicative of pulmonary infection	X						X		X
Change in physical exam of the chest	X				X		X	X	X
Presence of *P. aeruginosa* in respiratory cultures					X				
Sputum microbiology							X		
Upper respiratory tract symptoms									
Sinus pain/tenderness	X			X	X				
Change in sinus discharge	X			X				X	
Sore throat/runny nose		X	X						
Constitutional signs and symptoms									
Malaise/fatigue/lethargy	X			X		X		X	
Feverish						X	X	X	
Chills/Sweats						X			
Temperature above 38^{o}C	X	X		X					
Change in resting heart rate							X		
Difficulty sleeping						X		X	
Decreased appetite/anorexia	X	X		X			X		
Weight loss		X		X			X	X	X
Reduction in activity levels						X			
Increased worry						X	X		
Feeling cranky						X			
Feeling sad/depressed						X			

Feeling frustrated						X			
Work/school absenteeism		X		X		X		X	
Other									
Blood ESR/CRP/WBC							X		
Increase in neutrophil count		X							

Dakin *et al* used questionnaire responses from clinicians to identify signs and symptoms that they found helpful or very helpful in diagnosing a pulmonary exacerbation in children with CF (162). Interestingly 58% of clinicians reported they found chest x-ray changes helpful or very helpful in diagnosing a pulmonary exacerbation. These criteria, along with the criteria from 2 other paediatric studies were combined and showed good concordance (Table 0-4) (163). All three studies included the change of chest sounds within their criteria, but only one included change in chest x-rays in their criteria. When looking at pulmonary exacerbations in people with CF over the age of 6 years 33% (152/460) were noted to have changes on clinical exam and of the 83 who had chest x-rays 60% had changes noted during a pulmonary exacerbation. This is compared to 68% (508/751) who had an increased cough and 45% (337/751) who had changes in sputum production (156). However, it should be noted in this study that while children over 6 years could be included the mean (SD) age was 23.6 (13.5) years and there is no attempt to separate paediatric patients from adult patients in the analysis. A recent prospective study using lung function to track acute respiratory events in children with CF (mean age 9.6 years) reported of 124 pulmonary exacerbation events only 1.5% had chest x-ray changes compared to 98.5% who presented with increased cough, although it is not clear if chest x-rays were carried out at each pulmonary exacerbation event (123).

Table 0-4 Comparison of signs and symptoms associated with a pulmonary exacerbation in 3 paediatric studies. Reproduced with permission from Ferkol et al (163).

Table. Signs and symptoms associated with a pulmonary exacerbation

Clinical or laboratory characteristic	Rosenfeld et al[26] (OR)*	Dakin et al[30] (%)†			Rabin et al[27] (OR)‡			
		Age <5	Well child	Advanced disease§	<6 yrs	6–12 yrs	13–17 yrs	≥18 yrs
Increased cough	24.5	100	98	93	3.9	4.4	2.3	2.8
Exercise intolerance	22.4	NA	91	98	–	–	–	–
Change in sputum production	11.4	–	91	88	2.2	1.5	3.0	1.8
Change in activity	15.2‖	91	86	98	–	–	–	–
Hemoptysis	–	–	79	91	3.2	2.0	2.3	2.4
Change in appetite or weight	15.2 (appetite) 2.1 (weight)¶	91	93	91	2.2#	1.4#	2.0#	1.7#
School or work absenteeism	5.6	–	–	–	–	–	–	–
Retractions or use of accessory muscles	12.9	–	–	–	–	–	–	–
Change in chest sounds	4.3	74	70	56	7.8**	2.8**	2.7**	2.5**
Change in respiratory rate	14.1	74	62	65	–	–	–	–
Fever	5.9	40	35	49				
Change in spirometry	2.7††	–	95	93	–	4.1	3.7	3.8
Oxygen saturation	–	37	30	53	–	–	–	–
CXR changes	–	58	58	49	–	–	–	–

*Odds ratios for association of characteristics with the presence of a pulmonary exacerbation from univariate logistic models,
†Percentage of questionnaire respondents managing children and adolescents rating item helpful or very helpful (among 43 respondents),
‡Odds ratios for the presence (vs absence) of a pulmonary exacerbation with mutual adjustment for all variables,
§Scenario involved a patient with established bronchiectasis and chronic sputum production,
‖Increased fatigue,
¶Weight loss ≥1 kg over past month
#Relative decline in weight-for-age percentile,
**New crackles,
††Decline in FEV_1 ≥ 10% during the past month.

The lack of clear criteria to diagnose a pulmonary exacerbation alongside delay in recognition and varying treatment courses may impact the long-term lung health of people with CF (125). Early identification, prior to substantial drops in FEV_1 % predicted, using more regular monitoring i.e., remote monitoring or alternative biomarkers may be key to improving outcomes. While some of the above investigations (e.g., chest x-ray) require a hospital, visit, the addition of remote monitoring may allow for spirometry and measurement of vital signs. Electronic stethoscopes have been shown to be reliable in identifying crackles in CF and remote use has been shown to be feasible, however they currently have to be used in real time with the health care team (164-166). Attempts in 2021 to create a mobile phone application (app) that could be used to store lung sounds offline and then

upload them to a clinician shows some promise but further work is needed to ensure it agrees with traditional auscultation as adventitious sounds were only present in 14% of recordings from 134 participants (167).

The advent of new CFTR modulators (discussed in further detail in section 1.7.5) have reduced the number of pulmonary exacerbations in people with CF who have access to them, despite this pulmonary exacerbations remain a clinically important event. Therefore, the emphasis on early detection and correct treatment remains vital. There is the potential that the addition of extra home monitoring would allow for more frequent monitoring of symptoms and observations, therefore earlier detection and earlier treatment of pulmonary exacerbations and potentially improved outcomes for people with CF.

1.8 **CF respiratory treatments**

Until recently CF respiratory treatments have been reactive, focused on treating the consequences of the CFTR protein dysfunction, with emphasis on treating CF mucus accumulation, respiratory infection, and inflammation. However, over the last few years pro-active therapies that target the basic defect, known as CFTR modulators, have become available. These treatments will be considered in more detail below.

1.8.1 **Airway clearance**

Airway clearance can be divided into physiotherapy (including exercise) and medication strategies. Physiotherapy has been one of the mainstays of respiratory therapy in CF. Commonly used airway clearance techniques include autogenic drainage, active cycle breathing techniques or positive

expiratory pressure therapy but the optimum strategy is still not clear (168, 169). Results from an international study exploring the impact of a partially supervised exercise programme on lung function are awaited (170) and the use of high frequency chest wall oscillating devices remains controversial with some evidence of increased pulmonary exacerbations associated with their use (171).

The most frequently used medication for airway clearance is hypertonic saline. Hypertonic saline increases hydration at the airway surface and therefore aids mucociliary clearance. Initial studies in adults exploring the effect of hypertonic saline found that while it did not change the rate of decline of lung function, it did reduce the number of pulmonary exacerbations (172). These findings were not replicated in children under the age of 6 (173). Hypertonic saline has recently been shown to improve LCI in children aged 3-6 years, possibly therefore an early intervention in CF (174).

1.8.2 **Mucolytic agents**

The most commonly used mucolytic agent in CF is Dornase alfa (DNase). DNase is a recombinant human deoxyribonuclease which is delivered in nebulised form. It has been shown to cleave the extracellular DNA that has accumulated in CF sputum secondary to neutrophil necrosis and this cleavage allows for better airway clearance (175). The use of DNase in children has been shown to significantly improve LCI (a measure of lung homogeneity) in children aged ≥ 6 years (176) and to result in increased body mass index (BMI) in children started on DNase at less than 2 years of age (175). In people with CF aged ≥ 5 (mean age 11.8 years) DNase has been shown to positively impact airway inflammation by stabilising levels of neutrophils, NE and IL-8 in BAL samples when compared

to untreated CF control samples (177). Treatment with DNase has also been shown to reduce the number of pulmonary exacerbations experienced (178).

1.8.3 **Antimicrobial agents**

Antimicrobials can be used in various ways in CF depending on the context. They have a use in prophylaxis, treatment of early microbial infection, suppression of chronic infection or to treat an increase in respiratory symptoms.

There are differing guidelines in terms of prophylaxis in childhood in Europe and the USA (27, 179). When prophylaxis is used it is anti-staphylococcal because Staphylococcal aureus (*S.aureus)* tends to infect younger children with CF. However, improvements in clinical outcomes have not been shown (179) and there have been concerns regarding increased rates of *P.aeruginosa* acquisition (180). The CF anti-staphylococcal antibiotic prophylaxis trial (CF START) is an ongoing trial trying to address these issues (ISRCTN 18130649). Newly diagnosed infants (before 70 days of age) will be randomised to either "prevent and treat" (receiving prophylactic flucloxacillin) or "detect and treat" (targeted antibiotic therapy based on microbiology results) and will be observed until 48 months of age. The primary outcome is time to *first P. aeruginosa* acquisition. The study is expected to run until 2028.

Treatment of early infection is aimed at eradication to prevent the development of chronic infection. Again, there are differences between treatment regimens between Europe and the USA (27, 181). If eradication fails and the infection becomes chronic, treatment changes to suppressive in nature (27). The most common pathogen in CF to require chronic suppressive therapy is *Pseudomonas aeruginosa* (Figure 0-3). Chronic suppressive therapies tend to be nebulised antibiotic therapies using either

colomycin or tobramycin or more recently aztreonam, and in adults, levofloxacin (182). Nebulised antibiotics are delivered directly to the site of the infection which limits systemic side effects (183). One of the issues with regular nebulised antibiotics to suppress chronic infection is adherence. CF treatments are burdensome (184) and while exact adherence is difficult to measure, adherence to nebulised antibiotics is reported to be between 33-48% using a combination of medication possession ratios and data from intelligent nebulisers (185-187).

1.8.4 **Anti-inflammatory agents**

As inflammation plays a significant role in the pathology of CF lung disease there has been interest in the role of anti-inflammatories as a treatment option. Results have been mixed. Systemic steroids have some benefit but significant associated side effects (188). Inhaled steroids, while potentially reducing the side effect profile due to the mode of delivery, have been shown to be of limited benefit (189).

Azithromycin is a macrolide antibiotic shown to reduce inflammation in cell and animal studies although the mechanism is not fully understood (45). While it has been shown to have benefits in patients both with and without *Pseudomonas aeruginosa* infection (190), there have also been concerns regarding the effect azithromycin may have on concomitant tobramycin treatment, with a study showing significantly earlier antibiotic requirement and a lack of improvement in lung function in participants using both therapies when compared to those on tobramycin alone (191) and also potential emergence of non-tuberculosis mycobacteria in patients on azithromycin (192, 193). It is the most commonly prescribed anti-inflammatory agent in CF (45).

Ibuprofen, a nonsteroidal anti-inflammatory, has been shown to have benefit in high doses (194, 195); concern remains over the potential side effects and therefore it is not generally routinely used (195).

1.8.5 **CFTR modulators**

Currently available CFTR modulators are divided into two categories. Correctors address processing, misfolding and trafficking errors, allowing misfolded CFTR protein to get to the cell surface whilst potentiators act on the CFTR protein at the cell surface and increase channel opening ability (18). The potentiator, ivacaftor, is used as a single agent for patients with gating and some conductance defects. It is also part of all combination therapies alongside corrector(s) (Figure 0-4). Four CFTR modulators are currently available clinically with more being explored in clinical trials (https://www.cff.org/Trials/Pipeline).

Modulator therapy and classes of CF variants

Trade name	Generic name	Variant class	Common variants
Kalydeco	Ivacaftor	Class III–V	G551D, S549N, G1349D, R117H, 3849+10kbC→T
Orkambi	Lumacaftor-ivacaftor	Class II	Phe508del homozygous
Symkevi/Symdeko	Tezacaftor-ivacaftor	Class II–V	Phe508del homozygous, Phe508del and a residual function variant—L206W, 3272-26A→G, P67L, heterozygous for one of 154 responsive variants
Kaftrio (UK)/Trikafta (USA)	Elexacaftor-tezacaftor-ivacaftor	Class II–V	Phe508del homozygous, Phe508del and any other variant, heterozygous for one of 177 responsive variants

Figure 0-4 *Currently available CFTR modulator therapy with the classes of CFTR mutations that respond to each treatment. Reproduced from Edmondson et al (196)*

Ivacaftor was the first agent clinically available following impressive results in clinical trials of people with CF with at least one Gly551Asp (gating) *CFTR* mutation. Data from clinical trials showed improvement in lung function, reduction in pulmonary exacerbations by 55%, and improvement in nutritional parameters and quality of life (197-199) and these results have been replicated in real life studies (200, 201). In participants aged 12 and older, FEV_1 % predicted increased by 10.4% by the 24 week point in the 48 week double-blind, placebo-controlled trial and this treatment effect remained until the end of the 48 weeks (197). In a subsequent study of 6-11 year olds the difference in FEV_1 % predicted was 12.5% at 24 weeks (198). The effect previously seen on pulmonary exacerbations was not replicated in this cohort. However, this was likely to be due to the fact the overall occurrence of pulmonary exacerbations during the study period was low with only 4 documented pulmonary exacerbations occurring in the ivacaftor group compared to 3 in the placebo group (198). Sweat chloride was used as a measure of CFTR function and decreased by 48.1 mmol/l in those patients aged 12 and over in the ivacaftor group (197). In children aged 6-11 years a larger decrease was seen (53.4 mmol/l) (198). In younger children who were unable to perform reliable spirometry (those aged 5 and younger), sweat chloride was used as a marker of CFTR function and reductions were seen in those aged 2-5 (44mmol/l), 12- 24 months (73.5mmol/l) and 4 to 12 months (55.7 mmol/l) (199, 202, 203). Change in faecal elastase, a marker of pancreatic function, was used as a secondary outcome in younger children. In the three main studies in children aged 5 and younger a number had an increase in faecal elastase levels moving them from the pancreatic insufficient category into the pancreatic sufficient category (199, 202, 203), perhaps suggesting that starting CFTR modulators in early life may help restore exocrine pancreatic function. Real life data from 18 children who started ivacaftor at a mean age 5.8 years and have been on treatment for a mean of 4.5 years have shown

that 11 patients became pancreatic sufficient and stopping pancreatic enzyme replacement therapy and three others having detectable levels after ivacaftor treatment (204).

A combination of correctors and potentiators is required to treat patients with the most common *CFTR* variant, Phe508del. The first combination therapy available, lumacaftor/ivacaftor (Orkambi), only showed a moderate improvement in FEV_1 % predicted (2.8%) in participants aged ≥ 12 years (205) and only a 10 mmol/l decrease in sweat chloride (205, 206). A combined analysis of the TRAFFIC and TRANSPORT trials showed that pulmonary exacerbation rates were 30 to 39% lower in the lumacaftor/ivacaftor participants when compared to those receiving placebo (205). As children and young people with CF may have normal spirometry (207), during an open-label phase III trial of lumacaftor/ivacaftor study of participants aged 6-11 years another measure of ventilation inhomogeneity (lung clearance index [$LCI_{2.5}$]) was included as an exploratory end point in a subgroup of patients (208). The results of this study showed no significant change in FEV_1 % predicted, however there was a clinically significant improvement in $LCI_{2.5}$ by week 24 of treatment, with a mean reduction in $LCI_{2.5}$ of -0.88 units. Subsequently $LCI_{2.5}$ was used as a primary end point in a phase III randomised, double-blind placebo-controlled trial of lumacaftor/ivacaftor in participants aged 6-11 years. In this larger study a significant improvement in $LCI_{2.5}$ was seen by week 24 (mean decrease of 1.09 units). There were significant reductions in sweat chloride (mean decrease of -20.8 mmol/l) and significant increases in BMI; FEV_1 % predicted stayed stable in the treatment group and decreased in the placebo group (209). The next combination therapy tested in clinical trials was tezacaftor/ivacaftor (Symkevi), this combination therapy had similar efficacy to lumacaftor/ivacaftor but was generally better tolerated (210-212).

While the above combination therapies only showed moderate improvement in lung function compared to the ivacaftor results (205, 206, 210, 211), the addition of another corrector (elexacaftor) to create triple therapy elexacaftor/tezacaftor/ivacaftor (Kaftrio) had striking results in phase III trials in patients 12 years and older, with $\geq$1 Phe508del. There were improvements in lung function, decreased pulmonary exacerbations and nutritional improvement. Absolute increase in FEV_1 % predicted was 10% in patients homozygous for Phe508del, treated with elexacaftor/tezacaftor/ivacaftor when compared to tezacaftor/ivacaftor, which was the primary end point (213). Reductions in sweat chloride (mean -45.1 mmol/l) were also seen as well as improvements in CFQ-R respiratory domain scores (213). In heterozygote patients FEV_1 % predicted increased by a mean of 14.3% by 24 weeks compared to placebo (214). There were decreases in sweat chloride concentration and pulmonary exacerbation rates (by 63%) and improvement in CFQ-R respiratory domain scores (214). In children aged 6-11 there was an improvement in $LCI_{2.5}$ (mean decrease of 1.71 units), a mean increase in FEV_1 % predicted of 10.2% and a decrease of 60.9mmol/l in sweat chloride after 24 weeks of treatment (215). An increase in BMI and CFQ-R respiratory domain scores were also seen (215). Kaftrio is currently available clinically to those aged 12 years and above in Europe (216). Phase III trials in children aged 2 to 5 years have recently started (NCT04537793).

All the above CFTR modulators are safe and generally well tolerated. The most common adverse event was derangement of hepatic enzymes (197, 198, 202, 208-211, 213, 214). This has led to interruptions in treatment but only rarely to discontinuation of the CFTR modulator. Clear guidelines have been developed on monitoring of liver function tests (217). It should be noted that the long term effects of CFTR modulators on liver histology or function are not yet known (218). Specific to paediatrics is a concern regarding cataract development. In preclinical laboratory studies young rats

exposed to ivacaftor (dose of over 10mg/kg, 3 times the recommended human dose) were noted to develop cataracts (219), and subsequently there have been reports of non-congenital cataracts in children taking ivacaftor (220). There are clinical guidelines on ocular examinations in children on ivacaftor and results are awaited from a study exploring the ocular safety of ivacaftor treated patients aged 11 years and younger (NCT01863238) (217).

As CFTR modulators have become clinically available, results from longer open label studies and real-world evidence of effects are becoming available. Ivacaftor may have resulted in reduced *P. aeruginosa* infections (201, 221). This has also been shown after treatment with lumacaftor/ivacaftor (205). *In vitro* studies of the interaction between lumacaftor/ivacaftor and *P. aeruginosa* in Phe508del expressing cells show some conflicting results; lumacaftor/ivacaftor reduced the pro-inflammatory response stimulated by *P. aeruginosa*, however, *P. aeruginosa* has been shown to decrease the CFTR activity stimulated by lumacaftor/ivacaftor (222, 223). In a 6-year UK registry study as well as lower levels of *P. aeruginosa,* a reduction in levels of *Aspergillus species* were also seen. There was no significant change in levels of *Burkholderia cepacia* (224). This has also been replicated in another study, however since levels of *Burkholderia cepacia* are low in the CF population the studies may be underpowered (201, 225).

Registry data of ivacaftor treated patients from both the USA (after 3 years of treatment) and UK (2 years of treatment) were interrogated and compared with untreated propensity-matched controls. No additional safety concerns were identified and improvements in respiratory health and nutritional status were maintained (226). There were significant improvements in the number of pulmonary exacerbations and hospitalisations in the ivacaftor treated group, as well as lower numbers of lung

transplants and death (226). There was a significant decline in the lung function of the untreated group over the period of the study which was not seen in the ivacaftor treated group (226). A subgroup of ivacaftor treated patients and untreated matched controls were followed up for 5 years in total and the same results in lung function, pulmonary exacerbations and nutritional status were seen (227). A recent systematic review found 7 studies showing a reduction in pulmonary exacerbations in patients on ivacaftor when compared to either pre-initiation of ivacaftor data or untreated comparator cohorts (228). While the introduction of CFTR modulator therapies does decrease the number of pulmonary exacerbations, they do not seem to impact lung function recovery after an exacerbation. Interestingly, despite the potential benefits of ivacaftor treatment, adherence levels to the medication vary and decrease over time (229, 230).

Long term outcomes in 40 adolescents treated with lumacaftor/ivacaftor have been explored by comparing the 2 years prior to treatment with data from 2 years after treatment. While improvement in lung function, nutritional status and sweat chloride levels were noted, no improvement in exacerbation rates or antibiotic usage were seen (231). In a larger post-approval lumacaftor/ivacaftor study of homozygous Phe508del patients aged 6 years and over, significant improvements in sweat chloride and nutritional status have been documented, but no significant improvement in lung function, exacerbation and hospitalisation rates, or infection with *P. aeruginosa* were seen (232). Prediction modelling of elexacaftor/tezacaftor/ivacaftor in patients with CF aged ≥ 12 years (using available data from clinical trials) estimates a reduction of between 16.1-43.6% in intravenous (IV) antibiotic use over a 1-year period (233).

The effects of CFTR modulators on CF comorbidities such as CF-related diabetes (CFRD) have also been investigated. Ivacaftor was shown to improve insulin secretion in two small studies (234, 235) and the two USA and UK registry studies showed reduced reported prevalence of CFRD in the ivacaftor treated group (226, 227). The results for lumacaftor/ivacaftor treatment are mixed and based on smaller and shorter studies. Improved glucose tolerance was seen in 40 adults who had evidence of impaired glucose tolerance or CFRD and who had been receiving lumacaftor/ivacaftor for a year (236) however similar results were not seen in 9 children treated for a mean of 26 weeks (237). The impact of early CFTR modulators on the risk of developing CFRD or glucose intolerance is currently unknown (225).

The safety of CFTR modulators in pregnancy has not been fully established, however small case studies in pregnant females with CF have reported no significant consequence to the foetus even when CFTR modulators were used through all three trimesters (238). The effects on CF positive human foetuses are also unknown, although the consequences in ivacaftor on CF ferrets has been explored. CFTRG551D knock in ferrets treated in utero with ivacaftor showed a reduced incidence of meconium ileus, protection of the male reproductive tract and partial preservation of pancreatic exocrine function (239). A recent case report highlighted a baby born to a mother who was taking elexacaftor/tezacaftor/ivacaftor during pregnancy, who was negative on newborn screening, had a normal faecal elastase and had relatively low sweat chloride at 60 mmol/l and who was homozygous for Phe508del (240).

While people with CF who already have established disease may continue to require a similar amount of medical intervention despite the addition of CFTR modulators, there is the potential that the

landscape of CF care may change significantly if CFTR modulators are instigated early in childhood, thus preventing, or greatly delaying end stage CF disease. Currently there are two randomised non-inferiority trials recruiting in the UK and USA exploring the effect on FEV_1 of stopping either hypertonic saline or DNase while being on elexacaftor/tezacaftor/ivacaftor (241) (NIHR award 131889). As people with CF on CFTR modulators see improvements in their health, they may not want as much contact with their CF team. This potential must be considered when planning the provision of CF care in the future, potentially by developing a more individualised service (196).

1.9 Extrapulmonary manifestations of CF

CF affects multiple organs in the body. Figure 0-5 provides an overview of some of the organs affected and the consequences.

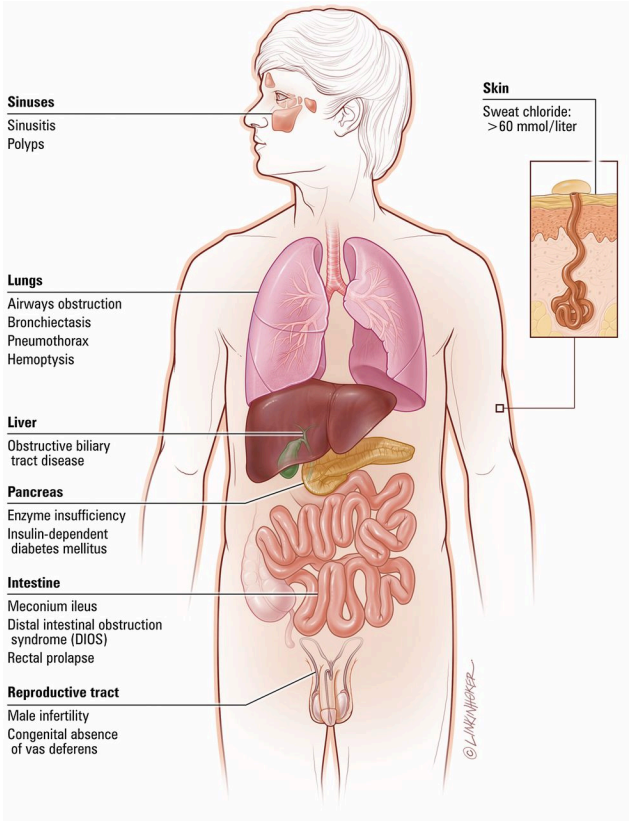


Figure 0-5 *Some of the body systems affected in CF and the consequences. Reproduced from Paranjape and Mogayzel (242)*

CF upper airway disease

A significant proportion of people with CF have signs and symptoms of chronic rhinosinusitis and nasal polyps (243, 244). These conditions have been shown to adversely affect quality of life in these patients (245). Treatment options are both medical (topical nasal corticosteroids) and surgical although outcomes are variable (244).

CF gastroenterological disease

CF affects multiple levels of the gastroenterological system. CFTR is highly expressed in the pancreas and mediates chloride and bicarbonate secretion, alkalising the pancreatic ductal fluid, allowing for optimum pH for food digestion (14). The effects of a defect in the CFTR protein start in utero with impaired bicarbonate and chloride secretion leading to increased thick secretions with high protein concentrations that obstruct the pancreatic ducts, and the process continues after birth (246). Gastroenterological signs and symptoms can be the first presenting feature of CF, with young children (if unscreened or a missed screening diagnosis) presenting with failure to thrive and symptoms of malabsorption (247). It is important these symptoms are identified and acted on as optimal nutritional status has been associated with improved outcomes and survival (248). These symptoms are normally associated with pancreatic exocrine insufficiency (PI) secondary to pancreatic duct obstruction and are typically seen in Class I-III and VI *CFTR* mutations (14). Faecal elastase is used as a marker for pancreatic function and defining PI or pancreatic sufficiency (PS) (14). Up to 90% of people with CF are pancreatic insufficient and require pancreatic enzyme replacement therapy (PERT) (249). Those children identified by newborn screening and started on PERT early have better long-term nutritional parameters than those who have been diagnosed based on the presence of

clinical symptoms (250). The importance of nutrition carries on into adult life where it has been shown that body wasting is an independent predictor of survival, regardless of lung function (251).

Idiopathic acute pancreatitis is seen in people with CF at higher rates than the general population, although it remains a rare CF complication (246). Higher levels acute pancreatitis are seen in patients who are PS with a milder phenotype (252). It is thought this is because acinar tissue needs to be present in the pancreas to develop pancreatitis and, in patients with PI, complete loss of acinar tissue occurs (252, 253).

Up to 10% of people with CF can develop CF related liver disease, the exact pathophysiology of which is unknown (254). It tends to present within the first decade of life and onset after puberty is rare. Both PI and CF related liver disease increase the risk of fat soluble vitamin deficiency, therefore most CF patients are started on vitamin replacement therapy (249).

CFRD differs from type I and type II diabetes mellitus and is associated with PI and *CFTR* mutations in Class I-III. It is associated with worsening lung function (255). CFRD has a 3.5-fold greater mortality rate when compared to people with CF who do not have diabetes and this rate has remained static over recent years (256) . Annual screening is recommended from 10 years of age. Treatment involves modifications to diet and subcutaneous insulin (255).

Around 20% of patients with CF can present with meconium ileus and it can often be the first sign of CF (257). Thick meconium blocks the terminal ileum and the small intestine proximal to the blockage becomes dilated (258), meconium ileus can become further complicated by a volvulus, intestinal

perforation or ischemic necrosis (257). The pathophysiology of meconium ileus is thought to be connected to abnormal bicarbonate secretion in the small intestine (259). Normally bicarbonate chelates calcium within the gut wall which loosens the mucin matrix. In CF patients there is abnormal bicarbonate secretion in the gut and therefore the mucin matrix is not disrupted creating thick mucus. Distal intestinal obstruction syndrome (DIOS) occurs when thick sticky faecal matter in the terminal ileum or ascending colon cause a partial or complete obstruction (244, 260). The exact pathophysiology is unknown but is thought to result from one or more of the following: inadequate pancreatic enzyme replacement therapy, dehydration, and intestinal dysmotility (244). Treatment involves rehydration, laxatives and can require surgical intervention (244).

Effects of CF on the reproductive tract

CF has effects on both male and female reproduction. Women with CF have normal reproductive anatomy but can have evidence of subfertility secondary to both oligomenorrhea and abnormal thick cervical mucus (261). Pregnancy in CF does not seem to have an immediate impact on health, although pregnant women do have more intense monitoring, but has been shown to have longer term impacts such as more courses of IV antibiotics and lower quality of life scores (262, 263). Over 98% of males with CF are infertile secondary to congenital bilateral absence of the vas deferens (244) however, techniques such as intracytoplasmic sperm injection after testicular sperm aspiration are providing males with CF the option of becoming fathers (264).

1.10 **Depression, anxiety, and quality of life in CF**

Rates of depression have been shown to be higher in patients with a chronic illness compared to the general population (265-267). High rates of depression and anxiety in adult and paediatric patients and parents/caregivers have been shown to impact management of chronic health conditions, including CF, by affecting adherence, risk taking behaviour and quality of life (268-272).

One of the largest studies in CF exploring this was carried out across 9 countries and explored levels of depression and anxiety in people aged ≥ 12 years with CF and parents/caregivers. Within this large cohort they noted that 10% of adolescents showed elevated symptoms of depression and 22% of adolescents reported symptoms of anxiety. When they explored depression and anxiety levels in parents, they found higher levels of both in mothers compared to fathers (37% vs 31% respectively for depression and 48% vs 36% for anxiety) (273). The impact of CFTR modulators on levels of depression also should be considered moving forward. There are registry data that suggests the addition of ivacaftor has reduced levels of depression in treated people with CF (226), conversely the initiation of lumacaftor/ivacaftor has been associated with increased reports of depression and suicidal ideation. Data are currently not available for the newer CFTR modulator therapies (274).

European standards of care recommend yearly screening for anxiety and depression (275) and UK standards of care recommend a clinical psychologist forms part of the multi- disciplinary team (MDT) (88). While there remains some discussion about the untested nature of these measures in CF (276), currently the International Committee on Mental Health in CF recommends that the measure used to assess parents/caregivers for depression is the Patient Health Questionnaire -8/9 (PHQ-8/9)

(dependent on if a question on suicidal ideation is included) and then the Generalised Anxiety Disorder Assessment-7 (GAD-7) for anxiety (277).

Health related quality of life (HRQOL) measures can be used for several reasons including "to describe the impact of a disease on a patient's daily functioning" and "to aid clinical decision making" (278). One of the first attempts at a CF specific quality of life measure that could be applied to both children aged 6 and over and adults with CF as well as parental care givers was developed in France in the 1990s – the Cystic Fibrosis questionnaire (279). In 2000 this measure was translated into English (280) and then in 2003 was shown to be reliable in children (281). The Cystic Fibrosis Questionnaire – Revised (CFQ-R) is now one of the most commonly used HRQOL measures used (282) and has a MCID (change in score of ± 4) recognised for the CFQ-R respiratory scale (283). In the paediatric population lower CFQ-R scores have been shown in inpatients when compared to outpatients (284) and improvement in CFQ-R respiratory scores were seen after IV antibiotic treatment for a pulmonary exacerbation (285). Van Horck and colleagues have shown than in young people with CF observed over a year, those patients aged >12 showed worsening CFQ-R scores by the end of the year. This was not seen in participants aged <12 (286). Although it did not meet statistical significance, there did seem to be an association with the number of pulmonary exacerbations (286).

There is currently no validated CF patient reported outcome measure for children under the age of 6 years. The strengths and difficulties questionnaire (SDQ) is a brief behavioural screening questionnaire which can be used for children aged 2 years and above (www.sdqinfo.org). The SDQ provides a total difficulties score, changes in which can be used to assess the impact of an

intervention (287). It has been shown previously that children with CF have higher total difficulties scores than a control population (288).

1.11 **Adherence in medicine**

Paediatric and adolescent adherence to medical treatments can be a significant issue in chronic medical conditions, including but not limited to CF, diabetes and asthma (289). Adherence has been defined as "The extent to which a person's behaviour (in terms of taking medications, following diets or executing lifestyle changes) coincides with medical or health advice" however one of the difficulties currently is there is no accurate way to measure adherence levels to the prescribed advice (290). Adherence rates have routinely been reported to be below 50% (290, 291). The more complex the intervention prescribed, the higher the chance of non-adherence, which is particularly relevant in CF with the prescribing of nebulised treatments (292-294). The level of family cohesiveness has been correlated to adherence, with higher levels of adherence being found in cohesive families (294). Caregivers do report concerns regarding conflicts that develop over resistance to treatment by the child and the impact this may have on daily family life (295). The consequences of nonadherence can be significant, including the development of drug resistance, increased dosages of medication, withdrawing of medication felt to not be effective, or escalation to more toxic medication (296-298). A 2002 metanalysis of patient adherence and medical treatment outcomes reported that paediatric nonadherence to prescribed treatments compromised health outcomes by 33% (296). Generally, adherence can be measured by self-report questionnaires, patient interviews, daily diaries, or electronic monitoring (299). None of these measures are fool-proof, however there is evidence that written daily diaries are poorly completed and tend to be completed just prior to the hospital or clinic appointment (300). In a study of 65 asthmatic children requested to record peak flows twice daily

over a 3-week period, half were randomised to receive a normal peak flow meter and half received a peak flow meter with an electronic "covert" recording meter (301). By the third week the percentage of documented missing days had increased from 1.4% to 10.6% in those who had received a normal peak flow meter. Of those participants who received a peak flow meter with a "covert" recording meter, by week 3 there was 15% of days missing from their paper diaries compared to 52% of missing data from their peak flow meter. This was despite 76% of participants saying the monitor was easy to use. More recently real-time medication monitoring (RTMM), with a text message being sent if the device was not used, was trialled in children with asthma aged 4 to 11 years (302). Mean adherence was higher in the group using the RTMM compared to the control group (69.3% compared to 57.3%) however this did not equate to improvements in quality of life, or a reduction in the number of exacerbations experienced during the study period. The cost of the intervention group was also higher than the control group, although not significantly so.

1.11.1 **Adherence in CF**

The James Lind Alliance Priority Setting Partnership in CF developed the top 10 clinical research questions, one of the questions in the top 10 was "What are effective ways of simplifying the treatment burden of people with CF" (303) . A recent survey of people with CF showed that people with CF have a median (IQR) of 10 (6-15) treatments to complete a day and the median (IQR) time to complete those treatments was 2 (2-3) hours (304). 70% of respondents admitted to missing treatments when they were tired or busy, and the most commonly reported missed treatment was their nebulisers and/or airway clearance. These two treatments were also noted to be the most time consuming. Adherence in CF is reported to be similar to other chronic health conditions at around 50%, and this can worsen in adolescence (292, 305, 306). The development of technologies that allow

for electronic monitoring of nebuliser usage allows for the comparison between self-reported adherence and adherence levels documented electronically by the device. A study of 81 adults found that while self-reported adherence to nebulisers over the previous 3 months was 80%, data downloaded from the nebulisers showed a median adherence of only 36% (187). The same study also showed that clinicians overestimate patients' adherence, with adherence levels of their patients thought to be 50-60%. Electronic nebuliser monitoring, as well as a daily phone diary and the prescribed treatment plan questionnaire, has also been utilised in a study exploring the effects of age and parental supervision on adherence in adolescents (307). The mean age (SD) of the 103 participants was 13.4 (1.8) years. They found that adherence reduced with age in the cohort until the age of 15 years, this age was also associated with the least amount of parental supervision, with 15-year-olds being left to complete 90% of their treatments alone, leading to poorer adherence. Interestingly parents appeared to become reengaged with participants aged 16-17 years and overall adherence increased. It should be noted that data from this study are cross sectional and longitudinal studies are needed to identify if the described uplift in adherence seen in the 16-17 year olds is actually due to parental reengagement over time. Electronic monitoring of nebuliser usage over a year in 24 adolescents (mean age 13.9 years) showed a mean (SD) adherence rate of 65% (28%) with a significant difference seen between adherence levels on a weekday (mean [SD] 67% [28%]) and adherence levels on a weekend (mean [SD] 60% [29%]) (p=<0.001) (308). Term time adherence was also significantly better than adherence during holidays (66% compared to 51%, p=<0.001). The adherence to pancreatic replacement enzymes in children, using a medication event monitoring system which records each time the pill bottle is opened, showed an average adherence of 49% (309). Only 5% of the participants routinely met the recommendations from their medical teams. Significantly lower levels of adherence (35%) were seen in parents presenting with symptoms of

depression (assessed using the Epidemiologic Studies Depression Scale). A recent study explored adherence to ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor using the national specialty pharmacy database in the USA to calculate the proportion days covered (PDC) using refill data for 2,548 patients over a year period (310). The maximum PDC obtainable is 1. They found that the PDC was highest for tezacaftor/ivacaftor (0.92) and in subgroup analysis children and adolescents had a significantly higher PDC for both lumacaftor/ivacaftor compared to adults. There was no significant difference between the groups for ivacaftor. It should be noted though that while PDC is a valid measure to assess adherence it does not guarantee the medication has been taken. The use of regular text messages to improve adherence in children with CF has been assessed (311). Electronic monitoring nebuliser data from the 6 months prior to recruitment in the study were compared with data obtained during the 6-month study in 28 patients with CF (mean age 12 years). Only 13 participants completed the study with no difference in adherence seen between the two time periods (adherence in the pre study 6 months was 81% compared to 80% adherence during the study 6 months). Six of the 13 participants returned their end of study questionnaires and 83% of those said they did not mind receiving daily reminder text messages. The authors do postulate if the prospective nature of their study led to the most adherent patients being recruited. The factors that lead to adherence or non-adherence are complex and multifactorial and moving forward more reliable and valid measures of adherence are needed (312).

1.12 **Digital health technology in medicine**

The sections 1.10 and 1.11 explore digital health technology in Medicine before the COVID-19 pandemic. After completion of data collection on CLIMB-CF the use of digital health technology

changed due to the emerging COVD-19 global pandemic. This post COVID-19 landscape will be discussed in the final chapter (chapter 8).

The use of digital health in medicine has expanded rapidly over recent years but despite this there is no clear all-encompassing definition for the term. One of the most accepted definitions is from Paul Sonnier who defined digital health as “Digital health is the convergence of digital and genomic revolutions with health, healthcare, living and society” (313). By comparison the U.S Food and Drug Administration (FDA) define it as “The broad scope of digital health includes categories such as mobile health (mHealth), health information technology, wearable devices, telehealth and telemedicine, and personalized medicine” (314). The World Health Organisation (WHO) bases their definition on the ability of everyone being able to access health care; “The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of diseases and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities” (315).

Due to the multiple definitions the terms digital health, home monitoring, remote monitoring and mHealth tend to be used interchangeably in publications.

Digital health tools include; health system disease management apps, patient facing mobile phone apps, wearables, connected biometric sensors, smartphone cameras, clinical trial patient information collection tools, In-home connected virtual assistants, telemedicine and virtual physician visits,

personal health records, web-based interactive programmes, and text messaging or emailing (316) (Figure 0-6).

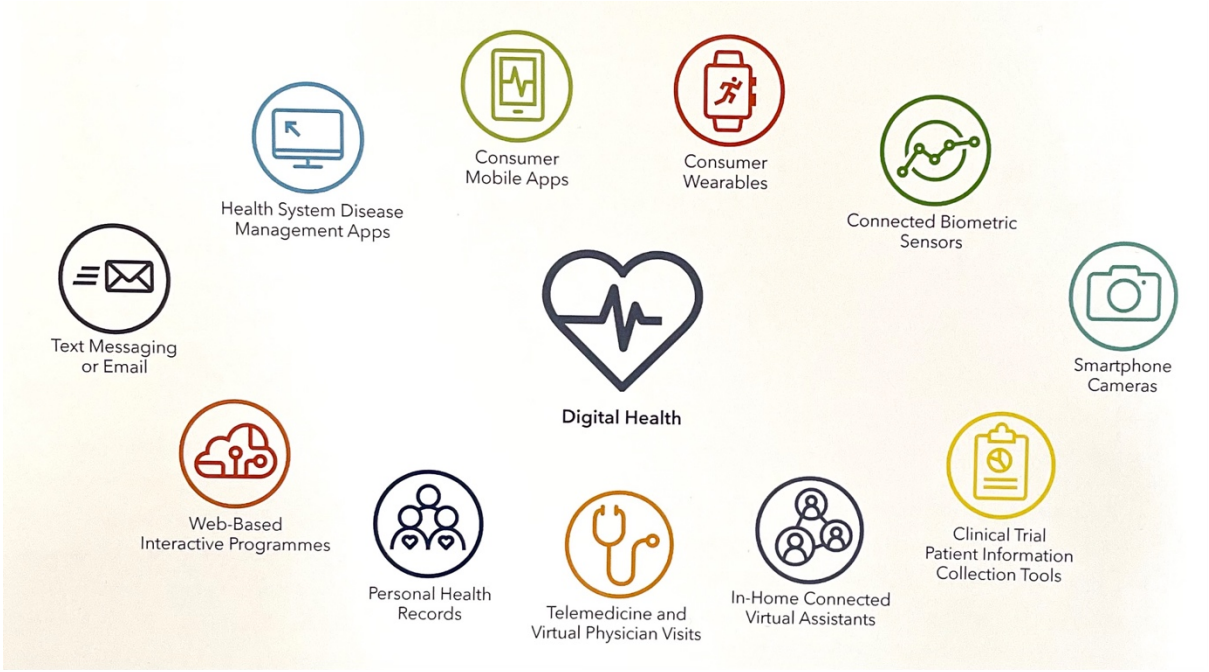


Figure 0-6 Digital health tools. Reproduced from the IQVIA institute 2017 report (316)

The concept of asynchronous or synchronous remote monitoring is also in the literature. This concept revolves around whether the patient is connected in real time to the health care provider (synchronous) or whether data from a patient can be uploaded remotely without the requirement of the health care provider being online at the same time (asynchronous) (317, 318). The figure below from Davies and colleagues provides examples and differences of asynchronous and synchronous remote monitoring in Asthma, Figure 0-7 (318).

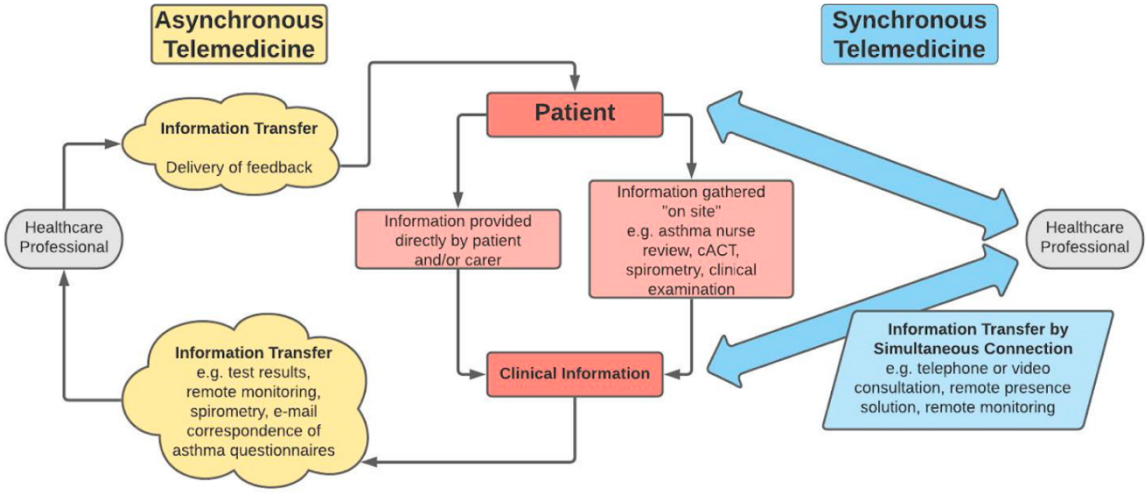


Figure 0-7 Schematic illustrating the key differences in asynchronous and synchronous remote monitoring. Reproduced from Davies et al 2021 (318)

While there has been a significant increase in interest in digital health recently, the concept of remote monitoring in patients' homes is not new. It started in the 1960s with the adaption of home haemodialysis and the need to develop a way to monitor these patients at home. Patients were taught how to set up and monitor their haemodialysis circuits and how to record their blood pressure (319). The first evidence in paediatric home monitoring comes from the 1970s when techniques to monitor infant heart rate at home were developed (320). Then in 1976 the first paediatric respiratory home monitoring study was presented. Tager and Speizer compared home surveillance telephone calls, parent-completed diaries and monitoring for school absences to try to identify the best surveillance technique for respiratory illness and concluded that no one method could provide accurate estimates of respiratory illness (321).

Remote monitoring in paediatrics has been around since the 1970s. However, the paediatric age group can have additional challenges to remote monitoring when compared to adults, especially those children with chronic health conditions. It does provide the potential to either improve patient

care or patient safety but thought needs to be given to the challenges it can pose (322). Lack of access to internet compatible equipment, a strong internet connection or even access to landlines has been identified as a risk factor for paediatric home monitoring by the WHO and has been noted in previous feasibility studies of children with cardiac disease (315, 323). Paediatric patients and/or their parents must also have adequate health literacy to understand the tasks requested of them and the manual dexterity to use the equipment provided (324). Consideration is also required when the language the remote monitoring is being delivered in is not the first language of the family using the monitoring device (325).

Privacy and data protection remains an issue that must be considered with any form of remote monitoring, especially when transferring paediatric data (322).

One objection raised to remote monitoring is that patients like to see their clinicians face to face and may be worried about the level of care delivered remotely (325). To counteract this the General Medical Council developed remote consultation guidelines which specify that clinicians should apply principles of "Good Medical Practice" to all remote consultations (326). There is also evidence that remote monitoring can reduce the burden on families with chronic illness as they do not need to miss school or work to attend appointments and potentially are saved the expense of travelling to a face-to-face clinic (327-329).

Adolescence can be a challenging time for people with chronic illnesses. They have been shown to achieve fewer milestones or achieve them later than their peers (330), as well as decreased

adherence and self-management skills (331). These issues may transfer to adherence to, and hence the utility of, home monitoring.

Concerns regarding abnormal readings increasing anxiety, dwelling on their illness, or even receiving reminders that they are not 'behaving' have been reasons given by adult patients for nonengagement in remote monitoring (325). While not all these themes have been explored in paediatric patients and their parents it would be reasonable to assume these issues may be relevant to this population as well.

There are concerns that the addition of remote monitoring may cause increased stress and anxiety of both paediatric patients and their parents. A study in the 1980s, exploring the impact of home monitoring for apnoea, in children at risk of sudden infant death syndrome or known to have sleep apnoea reported parental, in particular maternal, depression which in some cases required medical treatment. The apnoea monitors in the study were rented by the family and all families reported a significant financial burden because of this (332). One limitation the authors note is that this group of patients have a higher risk of dying than most paediatric patients with chronic disease (332). More recently it has been shown that continuous glucose monitoring of children with Type 1 Diabetes Mellitus can have the effect of both increasing and decreasing anxiety in both the children and their parents (333, 334). In one study it was noted that monitoring might initially increase anxiety but then decrease it as the family get used to the devices and outcomes (333). In asthma there is some evidence that remote monitoring improves quality of life (335). There is also evidence that asthmatic children receiving increasing exacerbation triggers or alerts may have worsened quality of life (336).

A recent systematic review exploring randomised controlled trials in telemedicine in paediatrics found eleven articles in 8 specialties (including asthma and CFRD). They concluded that telemedicine is comparable and may be beneficial when compared to in-person visits and recommended further research should look to eliminate barriers of telemedicine and improving access to care. They also recommended further work on cost effectiveness (337).

1.13 **Remote monitoring and digital health in CF**

The first study in remote monitoring in CF was in 1986. The investigators provided people with CF paper diaries with the intention of detecting adverse trends in health earlier than just using routine clinic visits. Patients were randomised a control group (receiving their normal standard of care) and a home monitoring group (provided with a scale, an inspirometer (a portable device able to measure vital capacity) and paper diaries with stamped addressed envelopes). Participants were studied for 5 years. They were requested to collect data daily. 196 participants were randomised to the home monitoring group with 173 providing data (23 moved or were lost to follow up) (338). In a subgroup analysis using the Taussig clinical severity score (339) there was no significant difference between clinical outcomes over a 2-year period between the two groups (338). The same group retrospectively looked at data from a subgroup of 50 patients from their study (25 from the control group and 25 from the home monitoring group) and found no significant difference in lung function, growth or psychological status between the two groups, leading them to postulate that there was no negative impact to home monitoring (340).

More recently there has been increased interest in remote monitoring in both the adult and paediatric CF communities. A lot of that interest has focused on the potential for earlier detection of a pulmonary exacerbation and how that might impact clinical outcomes.

The largest of the remote monitoring studies in CF was the Early Intervention in Pulmonary Exacerbation (eICE) study (341). This study explored whether early detection of pulmonary exacerbations using home spirometry and symptom monitoring would slow the rate of lung function decline at a year compared to a control group. They randomised 267 adolescents (≥14 years) and adults with CF prior to the interim analysis, from a target of 320, to either the early intervention (EI) arm or the control arm and used the criteria of a drop in FEV_1 in litres of 10% or a specified change in symptom score to identify a pulmonary exacerbation. The Data Monitoring Committee advised stopping recruitment after the interim as they projected the study would not be able to detect a difference between the two arms. The study detected more exacerbations in the EI arm, and they received more course of oral antibiotics, but this did not result in a slower decline in lung function. It was noted that changes in spirometry triggered pulmonary exacerbation alarms to clinicians more than did changes in symptom scores (341). When they carried out a subgroup analysis, they found no difference in decline in FEV_1 between those participants who were highly adherent to home monitoring (>80% completion) and those participants who returned < 80% of the requested data (341). The authors postulated that one of the reasons they may not have met the primary outcome was due to suboptimal treatment of pulmonary exacerbations in the EI arm. While criteria were given to the study teams about identifying a pulmonary exacerbation based on home monitoring results, no guidance was given regarding treatments (either oral or IV antibiotics) and more pulmonary

exacerbations were treated with IV antibiotics in the control arm which may have influenced the primary outcome (341, 342).

In 2020 Wood *et al* published a small, randomised control trial exploring the effects of remote monitoring using a symptom monitoring app compared to standard care. The primary end point was the number of exacerbations requiring IV. The patients in the intervention arm (n=29) used a study specific app to complete symptom scores at home, with a CF nurse practitioner contacting participants to discuss the need for treatment if their symptom scores worsened. They found that while the use of their home monitoring app did reduce the time to identification of an exacerbation, it did not affect the number of courses of IV antibiotics required. They also found no clear effect on their secondary outcomes including spirometry, weight, or nutritional status. In a small subgroup analysis (n=15), those participants in the intervention arm who completed >80% of the requested measures had an increased number of oral antibiotic courses and subsequently a reduced number of IV antibiotic courses (343).

Recently the results from the UK SmartcareCF study have been published (344). The investigators used machine learning to interrogate data collected from 147 adults to try to identify pulmonary exacerbations. Participants provided data daily for 6 months including spirometry, pulse oximetry and self-reported symptom scores and they retrospectively analysed the remote monitoring data with known dates of treatments for pulmonary exacerbations. They identified three distinct profiles of classes of pulmonary exacerbation based on their machine learning algorithm; Class 1 exacerbations were more common if chronically infected with *P. aeruginosa*, Class 2 exacerbations had a lower CRP at the start of IV antibiotics and Class 3 identified participants who had a second

exacerbation within 4 weeks of the initial exacerbation. The algorithm could potentially predict an exacerbation ten days before a course of antibiotics had been started (344).

There are several small studies in children and adolescents with CF. Bella and colleagues monitored spirometry readings and overnight saturations in a subgroup of adolescent and young adult patients (with matched controls) in an attempt to detect pulmonary exacerbations earlier and therefore improve lung function over time. They analysed data from 17 patients (Mean [SD] age 15.74 [± 5.8] years) allocated to the remote monitoring arm and found no statistically significant difference in decrease in FEV_1 when compared to controls at the end of the follow up period 29.3 ±13.3 months) (345). While it is not clear regarding the exact numbers of oral antibiotics or IV antibiotics the remote monitoring group received, they did receive more therapy cycles than the control group.

Van Horck et al explored whether early detection of pulmonary exacerbations using home monitoring was possible in children. Participants aged 5 to 19 were recruited and followed for a year and asked to provide spirometry and answer three symptom questions three times a week. Forty-nine participants were recruited, with 37 participants providing data for analysis. When comparing those participants in their study who had an exacerbation during the year with those who did not, they concluded that home monitoring of spirometry and symptoms can probably be used for early detection of pulmonary exacerbations. Interestingly though symptom scores were worse in the exacerbation group four weeks before the diagnosis of an exacerbation was made and dropped further in the next two weeks whereas a similar drop was not seen in FEV_1 % predicted (346).

In parallel to this, studies have explored if remote monitoring may improve adherence. CFFONE^{TM} is a web-based platform developed to improve adherence in adolescents aged 11-17 (347), the results from a randomised controlled trial over 6 separate sites are pending (NCT01183286). A study in adolescents and young adults examined whether the addition of home spirometry could improve medication adherence, explored using medication possession ratios (MPR) for inhaled hypertonic saline, PERT, DNase, and fat-soluble vitamins. They found that the MPR for all 4 medications increased during the yearlong study, however this did not equate to a change in the rate of decline of FEV_1 over the year (348).

CFHealthHub was a multicentre UK randomised 12-month self-management intervention study in adults with CF, with pulmonary exacerbation rates being the primary outcome (349). When randomised to the CFHealthHub intervention arm, participants and their care team would be able to see real time adherence data from nebulisers and be provided with behavioural change tools and tailored interventions. There was no significant difference seen in the number of pulmonary exacerbations in the intervention arm when compared to the conventional treatment arm at the end of the 12-months. No significant difference in FEV_1 was seen between the groups. No difference in depression or anxiety scores were seen between the two groups at the end of the 12-month period either (349). MyCyFAPP is aiming to provide people with CF the ability to self-manage their PERT therapy (350) and the Swedish 'Genia' application which allows for young people with CF to share data with their clinical team and is currently being tested in an ongoing clinical trial (351) (NCT03910881).

Physiotherapy and exercise are also areas benefiting from remote monitoring (352) , either via the use of online video calling to encourage exercise training (353), comparing online interfaces with standard clinical care and even the addition of gamification into the physiotherapy routine (354).

1.13.1 **Feasibility of remote monitoring in CF**

In the 1980s Finkelstein *et al* divided the participants in their home monitoring study into consistent, inconsistent, and non-responders. A consistent responder was categorised as returning over 50% of the requested diaries (these were daily symptom questions with return of the diaries being requested weekly). Non- responders returned four or fewer diaries over the first 2 years of the study. They recruited 173 participants to the home intervention arm. 62 subjects were excluded as met the criteria as a non- responder. 79% of the remaining 111 participants maintained a consistent response pattern returning between 65-80% of the requested diaries at various time points in the study (338). They also noted that those participants living further away from their CF centre (>100 miles) appeared to be more consistent responders (338). When they retrospectively analysed a subgroup of participants from both the home monitoring arm and the control arm of the study, they found no difference in participants who had required referrals for psychological support between arms (340).

The largest of the remote monitoring studies in CF was the eICE study. People randomised to the early intervention arm completed symptom diaries and home spirometry. 50% of participants used their spirometer once a week for 80% of the study period. However, spirometry was requested twice weekly and only 19% of the EI cohort provided twice weekly data for ≥80% of the study period. There was a withdrawal rate of 24% in the EI arm (341).

In 2010 a smaller study exploring the feasibility of an electronic home monitoring system to detect pulmonary exacerbations in adults with CF found that of 51 patients enrolled in the study, only 19 patients recorded sufficient data to be analysed in the 6-month study (355). When the results from this study were compared with a parallel study involving patients with chronic obstructive pulmonary disease (COPD), they found the patients with CF had a significantly higher non-adherence rate than those with COPD (63% vs 5%). It was not clear the reasons for this discrepancy, however one theory was the age difference between the 2 groups. The patients with COPD were older so potentially had more free time to carry out home monitoring (356).

In 2020 Wood et al published data showing an adherence rate to weekly data entry (answering 14 questions via a mobile phone app) of mean (range) 77% (25-100%) in the 29 CF patients allocated to the intervention arm over their year-long randomised control trial (343). Participants were contacted by text message if they failed to answer the questions for a week. 48% of the participants used the app <80% of the study period. Participants rated the app highly on usability scales at both 6 months and 1 year into the study and using the Hospital Anxiety and Depression scale showed no difference between the intervention arm and the control arm.

A small study in terminally ill adults with CF showed that being randomised to remote monitoring or standard care had no significant impact on anxiety or depression or quality of life (357). However, those participants who were in the remote monitoring arm did have a significant improvement in their perception of body image. Participants reported they found remote monitoring helpful, but 2 participants reported technical issues with the remote monitoring equipment.

An Italian pilot study in CF of home spirometry, a symptom diary and pulse oximetry reported a 50% failure rate. Failures were identified as: if the patient refused, the patient failed to carry out 4 home spirometry readings in the first week, if the patient sent no acceptable oximetry data in the first week or if after the first week the participant failed to upload an acceptable spirometry and oximetry reading every week (358). At the end of the study 80% of the remote monitoring participants wanted to continue, however 7/30 requested less frequent data transfer (requested daily for first week and twice weekly for final 3 weeks of the study) and 8/30 requested improvements in the equipment. Four medical professionals reported no difficulties in using the equipment and thought remote monitoring was feasible and could be useful to identify clinical changes. One doctor thought remote monitoring may reduce the CF centre's workload.

In a study including adolescents and young adults with CF, while 30 patients were originally recruited, a dropout rate of 43% was noted (n=13) (345). Of the 13 patients excluded from the final analysis 11 were excluded due to their transmission of remote monitoring data being too short (< 6 months). When the remaining 17 participants daily upload compliance was explored, it was found to be 52.4%.

SmartCareCF recruited 147 participants to provide remote data to test machine learning pulmonary exacerbation prediction algorithms, however they had to exclude 29% of participants from their final analysis as they had not provided enough data. When asked at the end of the study 92% had found the remote monitoring equipment easy to use and 76% reported that it was either 'very helpful' or 'helpful' to track their health (344).

In van Horck et al study exploring whether early detection of pulmonary exacerbations using home monitoring was possible in children, of the 37 participants who provided enough data for analysis, 54% of them demonstrated good adherence (arbitrarily set by the authors as 70% adherence to requested measures) (346). Adherence to requested measures was median (IQR) 77% (44-88%) for the 37 participants. It should be noted that from the 49 participants initially recruited, 4 were excluded from the analysis because of no home monitor use and 4 were excluded for not providing home monitoring data in the 4 weeks prior to an exacerbation and are not included in the quoted adherence percentage.

Shakkottai et al explored the feasibility of weekly home spirometry in 5 children for three months and found a mean percentage adherence rate of 94.7% (359). The same study group later explored the impact of home monitoring on medication adherence in 39 adolescents with CF, they found a mean adherence rate of 59.5% ± 24.6% to the weekly requested spirometry readings over the yearlong study. Based on the results of these two studies the authors concluded that monitoring spirometry at home was feasible (360). It should be noted that 9 of the 39 subjects (23%) did not complete the yearlong study and within that subgroup the mean adherence to weekly spirometry was 36.58 ± 21.47% (348).

1.14 **Hypotheses, Aims and Objectives**

1.14.1 **Hypothesis**

- Home monitoring and sample collection will prove feasible and acceptable for patients and families whilst not adversely impacting on mood or quality of life.

- Home monitoring and non-invasive sample collection could be used to predict pulmonary exacerbations earlier than clinically detectable.

1.14.2 **Aims**

To test these hypotheses, I:

- Assessed the feasibility of home monitoring in children with CF, including the amount of requested data submitted as well as the quality of data received where possible, and the impact on quality of life and well-being both for them and their carers.
- Assessed variability during clinical stability of the monitored parameters and changes around periods of pulmonary exacerbations (defined as leading to a change in treatment by an independent clinician) within the home-monitored group.
- Assessed the types of requested non-invasive home samples received.
- Explored the utility of non-invasive biomarkers.

1.14.3 **Objectives**

My objectives within CLIMB-CF were:

- To design and lead an international, multicentre study of the feasibility of home monitoring, training, and coordinating of teams at partner sites and to recruit up to 20 RBH patients and 160 patients internationally. This included documenting the proportions of patients who completed each monitoring task, requested sample collection and acceptability of these interventions, and impacts on quality of life, with questionnaires at scheduled points during the 6 months to track change.

- To use data received to describe the variability in clinical measures during periods of stability and the variability in clinical measures around a period of pulmonary exacerbation.
- To measure levels of selected biomarkers in the non-invasive samples received from home.

Chapter 2 – CLIMB CF study rationale, set up, app design and recruitment

1.15 Introduction

''Mobiles are now part of the fabric — every day in everybody's life. So, if you're not looking at mobile solutions, then you're not really looking at all solutions."

Mal Postings Global CTO — IT Advisory Ernst & Young(361)

Approximately 85% of adults in America and the UK report owning a smart phone (361, 362). However, of potentially more concern is the use of smartphones in children. In America three quarters of adolescents own a smartphone (363) and 50% of them admitted to 'feeling addicted to' their smartphones (364). Studies have also found that children aged 5 years and younger can be exposed to 1 to 5 hours of screen time a day, including from smartphone devices (365). In 1999 the American Association of Paediatrics recommended no screen time for children less than 2 years of age and that screen time of ≥ 1 hour a day in children is considered excessive (366). The scientific evidence behind these recommendations is weak, and as a consequence the Royal College of Paediatrics and Child Health (RCPCH) has not put a finite time on recent screen time recommendations for parents but has produced a guide for parents and clinicians about controlling screen time (367). These factors need to be taken into account when designing future health technology.

When adolescents were asked their perspectives on apps they could use to improve their health and ways to communicate with their health care provider (368), three key desires emerged:

- To be able to have questions answered outside of their routine clinic visits.

- To have greater access to their health care provider in order to build a relationship.
- To share health data between visits.

The most recent Iqvia Institute for Human Data Science report (November 2017) stated there were over 318,000 health-related apps worldwide with approximately 200 new apps being added each day (316). When this is further categorized to medical apps (defined as apps not connected to general wellness, health promotion and fitness), there were around 50,000 individual apps available on both the Apple and Google Play app stores at the end of 2020 (369, 370). There is an increasing body of peer-reviewed evidence for the use of digital health apps (316). However, many apps lack proven validity. Although they may have disclosures in their terms and conditions about clinical use, the expansion of this field has resulted in the development of independent guidelines for medical apps (371-373). Of the 50,000 health apps available only 91 have been adopted by the NHS apps library (374). Of these, only 11 fall under the categories of child health or respiratory, with two of them being targeted at either children and adults with asthma. In order to be included in the NHS apps library the app needs to have been reviewed by the NHS and deemed clinically safe (374). NHS England and the National Institute for Health and Care Excellence (NICE) have developed an evidence standards framework for digital health technologies (375).

The disconnect between health care providers, patients and app developers may be a cause of some of the delay in the integration of more health apps into accepted clinical practice. This could be due to a number of discrete issues, financial, regulatory and time (376). Rudin and colleagues suggested that multidisciplinary teams including developers, health care providers and patients are required but that there is also a need for an awareness that health care providers and patients have different

needs and expectations from their technology, and that technology has to be provided with a platform where it can be tested quickly, with the expectation that some of it will fail, be redeveloped and tested again (376).

One of the key methodologies in app development is the agile method. It is based around several core principles which match the suggestions of Rudin and colleagues for health app development. The core principles are: focus on the user needs, deliver iteratively, fail fast, learn quickly and keep planning (377).

This chapter will describe the project design considerations, the process of the CLIMB-CF app and website development, study set up and recruitment, as well as discuss some of the issues with equipment that arose during the CLIMB-CF study.

1.16 Methods

1.16.1 Project design considerations

Remote monitoring is not standard CF care and an area that warrants further research therefore CLIMB-CF was designed as a multi-centre, two country study exploring the feasibility of remote monitoring in children and young people with CF, exploring the amount of requested data collected as well as the quality of the data received. Acceptability for families was also examined. The impact of remote monitoring on quality of life for the participants and their parents was explored. It was also important to establish that the addition of home monitoring did not negatively impact depression and anxiety in parents/caregivers.

Clinical trial criteria for pulmonary exacerbation signs and symptoms are different and widespread (155, 160) and the characteristics that appear to identify pulmonary exacerbations most in children can vary by age group (158). In view of this we combined multiple signs and symptoms and created 7 subjective wellness questions, one sleep disturbance question and 7 objective measures to be collected via a study specific CLIMB-CF mobile phone app (documented in section 2.2.5.2.1). These included spirometry, weight, temperature, oxygen saturations and questions on cough, sputum, breathlessness, and tiredness as included in Fuchs *et al* and Treggiari *et al* pulmonary exacerbation criteria (155, 160). There is mixed evidence for the role of oxygen saturations in pulmonary exacerbations in young people with CF which warranted further investigation (378, 379). Activity monitors were included as previous research has shown an association in adults between activity levels and the number of pulmonary exacerbations experienced (380). Questions on sleep and tiredness were also included based on evidence in adults that pulmonary exacerbations have a negative impact on sleep quality (137). These are explored in more detail below. Due to the nature of remote monitoring and the limits of the technologies available there are items that are included in some pulmonary exacerbation criteria that could not be incorporated. The most significant of these being the ability to auscultate the chest and the fact there are no ways to perform a chest x-ray. At the point of designing this study remote stethoscopes were not available that could be used without direct clinical supervision and only recently has this technology started to be explored. There are minimal data regarding how often a chest x-ray is abnormal at the point of diagnosis of a pulmonary exacerbation, or even if it is routinely done in the paediatric cohort but a recent study reported only 1.5% of all documented pulmonary exacerbations in children had chest x-ray changes, suggesting that alternative signs and symptoms may be better predictors (123).

Prior to the CLIMB-CF study a selection of adult and paediatric patients at the Royal Brompton Hospital (RBH) were asked by their CF clinical team which samples they would be willing to collect in principle at home. Of the 56 participants asked; 80% said they would collect throat swabs, 86% nasal mucus samples, 71% would collect urine samples, 61% would collect expectorated sputum and 49% stated they would be willing to collect dried blood spots (DBS) (unpublished data). While 61% would be willing to collect expectorated sputum, it is known in the paediatric population that many children are unable to expectorate, therefore it might be prudent to consider other sample types that could potentially be easier to collect and provide the ability to carry out exploratory work looking for objective biomarkers to diagnose a pulmonary exacerbation. To our knowledge prior to CLIMB-CF no paediatric study has explored which sample types are easy for patients to collect at home or collected multiple longitudinal samples with the aim of tracking potential biomarkers which is a strength of the study design. Prior to deciding which biomarkers to explore I wanted to see the number and quality of different sample types that could be collected and stored at home. Depending on the feasibility of both home monitoring and home sample collection attempts would then be made to use the data to try and identify variability of measures in both stability and during a pulmonary exacerbation to try and identify periods of pulmonary exacerbation earlier.

1.16.2 **CLIMB-CF Study design**

Participants aged up to 17 years of age were recruited for the thesis. CLIMB-CF included three recruitment arms:

- Arm 1 – Smart app and home monitoring: Arm1 was a multi-centre international study which aimed to recruit 120 children across six UK sites and 40 children in two Canadian sites, aged 2 to 17 years, to assess feasibility of home monitoring.
- Arm 2 – Web based symptom diary and biomarkers: Arm 2 aimed to recruit up to 50 patients at the Royal Brompton Hospital (RBH) aged 0-17 years in order to assess a web-based interface; our assumption was that levels of engagement with this interface would be lower than with the more convenient app.

Figure 0-1 below shows the two arms that participants at RBH had the option of joining and the requirements during the study. Participants at RBH were approached about the study and were informed that they might choose to participate to a greater or lesser extent depending on which arm they wished to join.

Other CLIMB-CF participants were mainly approached at routine clinic appointments at their CF centre and were provided with information on the study. However, some participants were contacted via email or phone prior to their clinic appointments if they were noted to have upcoming clinic appointments. Recruitment occurred on an *ad hoc* basis based upon previously scheduled clinic appointments.

As this was a feasibility study inclusion was largely based on family/participant willingness, but attempts were made to include children across the age range at each site.

The results from Arm 1 and Arm 2 are presented in this thesis.

1.16.3 **Sample size**

As CLIMB-CF was a feasibility study no formal sample size calculation was carried out. The recruitment target as documented above was decided pragmatically based on available funding for the mobile phones and Bluetooth devices.

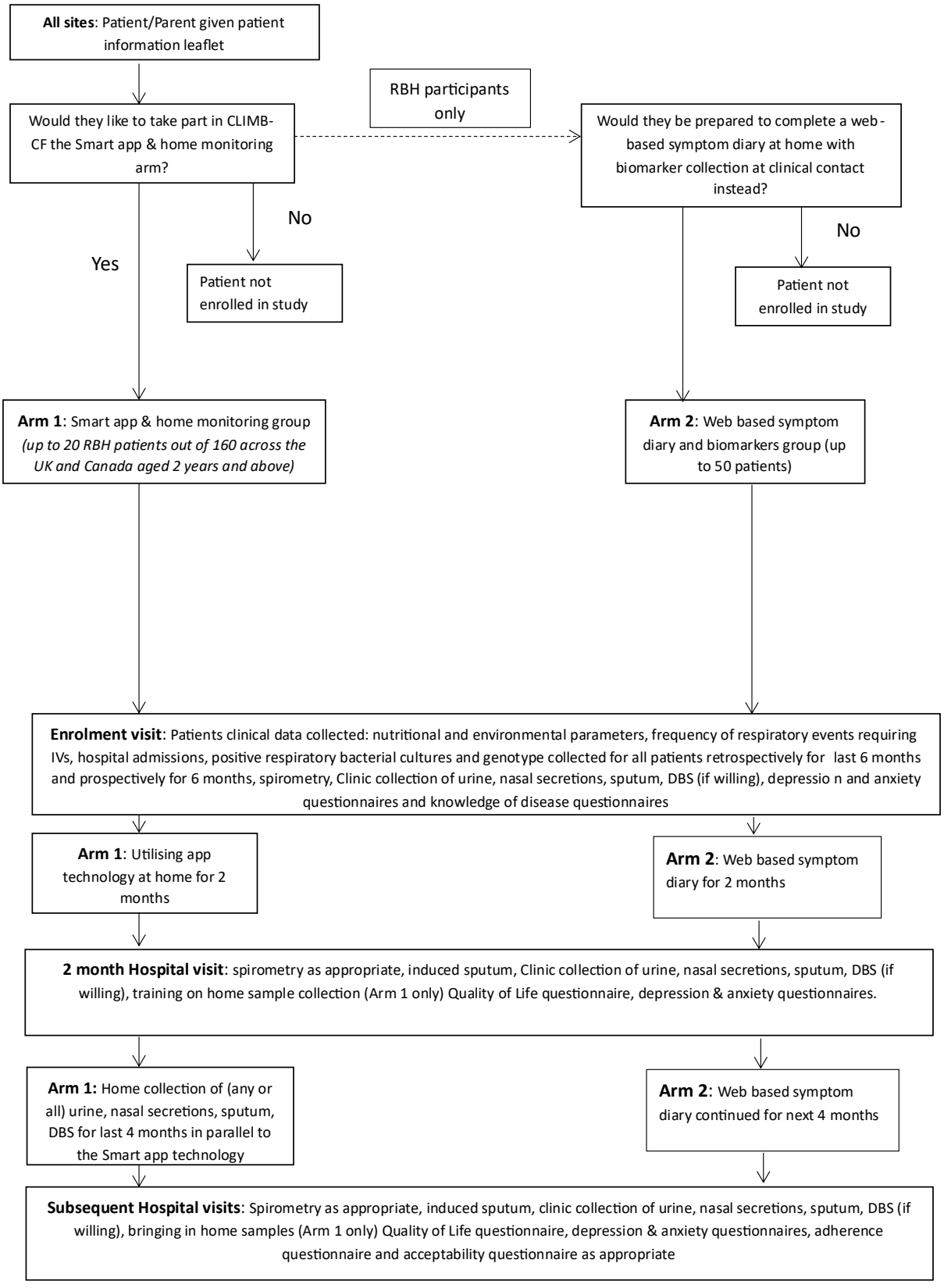


Figure 0-1 Reference diagram of the 2 arms participants had the option of joining in CLIMB-CF .

1.16.4 **Inclusion and exclusion criteria**

Inclusion criteria

1. Cystic fibrosis confirmed by standard diagnostic criteria (27).
2. Males and females aged 0-17 years (only those aged 2-17 years of age eligible for Smart app home monitoring arm).
3. Written informed consent obtained from parent or young person (aged 16 years or over); age-specific assent sought as appropriate from the child.
4. Permission to inform GP (and shared care CF team, where applicable) of participation in study.

Exclusion criteria

1. Clinical instability at screening defined by:
    a. Any new prescription of antibiotics (i.e., excluding routine, long-term treatments) within the previous 2 weeks.
    b. An increase in symptoms, such as change in sputum production/colour, increased wheeze or breathlessness over the previous 2 weeks irrespective of whether they led to an antibiotic prescription.
    c. A change in regular respiratory treatments over the previous 4 weeks.
        - If any of these applied, entry into the study was deferred.
        - These exclusions only applied to study entry and did not affect the status of individuals already enrolled.
2. Repeated non-attendance at scheduled clinic visits (or, once the study commenced, at study related visits or booked phone calls). Non-attendance was defined as not attending/not being brought to more than 50% of their scheduled clinic visits.

3. Active participation in an interventional clinical trial at the point of enrolment.
4. Participation in any trial of a CFTR-modulating drug within the previous 60 days.
5. Inability, after training by study team, to operate the smart technology or devices (Smart app home monitoring arm only).
6. Pregnant or breastfeeding.

1.16.5 CLIMB-CF application development and testing process

As a result of the adult SmartCareCF study funded by the CF Trust (381) there was a skeleton android mobile phone app with no-touch Bluetooth-enabled equipment integrated within it. Due to the cost and extra development time that would otherwise have been required, the decision was made to develop an app that would only be available on an android platform and to provide participants with an android phone with the app pre downloaded. As part of the paediatric project, working closely with the CF Trust, I created a system requirements document (Appendix 1) involving the addition of a thermometer, changes to the incorporated wellness questions and collection of the data via a study specific web page. The development of the app and the back-end website was carried out by an app development company called Fatfractal.

The adult app had been linked to a set of digital weighing scales, a thermometer (which was not Bluetooth-enabled), a pulse oximeter, a spirometer, and an activity monitor. In addition, participants, were asked 2 wellness questions concerning general wellness and cough. These were recorded on a scale of 1 to 10 (1 equating to worst ever and 10 to best ever). They were also asked to rate their sleep on an unvalidated 5-point scale. Within the adult app, participants were only shown the numbers not the wording associated with the scale, allowing for potential misinterpretation of the

scale. During the development of the paediatric CLIMB-CF app I reviewed the subjective questions and tested 2 new pieces of equipment that we considered needed to be integrated. We also explored whether there were any further measures we would like to try to gather.

The paediatric study required the incorporation of both a new set of weighing scales (as the scales used in the adult study were no longer commercially available) and a Bluetooth enabled thermometer, to allow for no touch entry of data i.e., the data would not need to be manually entered by the participant but would automatically be uploaded from the thermometer to the app. Both pieces of equipment were tested for accuracy by me prior to incorporation into the app.

1.16.5.1 Testing of the weighing scales and thermometer

Weighing Scales

I tested the Pyle Health Digital Scales (PHLSCBT2BK, Pyle Health, New York USA) at 2 weights, one to simulate a younger child and one using an adult weight. I weighed a 9.1 kg package 91 times and weighed myself 26 times. Both weights were consistent with minimal variation as shown by the coefficient of variation, suggesting we would be able to identify a change in a child's weight of ± 1% (Table 0-1). The scales were subsequently approved for inclusion within the study.

Table 0-1 Mean and standard deviation of two weight trials of Pyle Health Digital Scales with coefficient of variation as a percentage

	Mean weight (kg)	Standard deviation	Coefficient of variation %
9.1 kg weight	9.08	0.06	0.65%
72 kg weight	72.02	0.05	0.07%

Thermometer

I tested the Pyle Health thermometer (PHTM20BT, Pyle Health, New York USA) and compared readings taken using the forehead mode versus the ear mode built into the thermometer. After completing 33 dual readings on healthy afebrile adults, the coefficient of variation for the forehead mode was found to be higher than the ear mode on the thermometer (Table 0-2). Due to these inaccuracies, and the fact that the use of the ear to measure temperature is only recommended in the over 2 year olds, it was decided that for the study we would only use the ear recording function to measure temperature and only allow recruitment of the over 2 year olds (382). Using the ear mode within the thermometer we would be able to detect a change in temperature of $\pm$ 0.2^{o}C.

Table 0-2 Mean and standard deviation of ear versus forehead temperature readings with coefficient of variation as a percentage

	Mean temperature (^{o}C)	Standard deviation	Coefficient of variation %
Ear	36.5	0.07	0.19%
Forehead	36.7	0.79	2.20%

1.16.5.2 System requirements and CLIMB-CF app development

Prior to the app development a system requirements document was developed. The document covered the front-end website, back-end database, the app, the webpage interface, the electronic proforma and the subsequent data export. This dictated all adaptions we required in the final application, and whether components had to be completed prior to the first release or could be

developed for the second or final release. The document underwent 3 revisions over a 2-month period prior to our final document. It covered functional, technical, and non-functional requirements. Every requirement was allocated a priority i.e., MUST or SHOULD. Each requirement was allocated acceptance criteria, which allowed the team to confirm completion. The document also dictated the number of readings that could be stored for the day, and the fact that data could not be retrospectively entered by a participant. This document was finalised by me, with the CF Trust (the funders) and Professor Davies also providing approval (Appendix 1).

1.16.5.2.1 Wellness scores

Studies in COPD patients suggest that symptom scores, including dyspnoea, sputum production and cough, deteriorate earlier prior to an exacerbation than does lung function (383). Attempts have also been made in CF to create patient symptom reporting outcome measures including respiratory symptoms, tiredness, and appetite by interviewing adults and adolescents with CF and parents of children aged 5-11 years with CF (161). In view of this I reviewed and broadened the range of wellness questions to incorporate in the app. It was also important that the scale and wording incorporated within the app were easy to interpret by young people. Therefore, I simplified the unvalidated scale to be out of 5 rather than 10 and adapted the wording throughout the development period, based on responses from testers as described below, to ease understanding.

The final questions developed were:

Please rate on the following scales:

- Wellness: Much better than usual, slightly better than usual, same as usual, slightly worse than usual and much worse than usual.

- Sleep activity: Much better than usual, slightly better than usual, same as usual, slightly worse than usual and much worse than usual.
- Appetite: Much better than usual, slightly better than usual, same as usual, slightly worse than usual and much worse than usual.
- Tiredness: Much better than usual, slightly better than usual, same as usual, slightly worse than usual and much worse than usual.
- Cough: No cough, slight cough, moderate cough, bad cough, and very bad cough.
- Breathlessness: Not breathless, slightly breathless, moderately breathless, badly breathless, and extremely breathless.
- Sputum volume: No sputum, a little bit of sputum, some sputum, quite a bit of sputum, lots and lots of sputum.

If a participant indicated that they were producing sputum, a submenu was designed to pop up asking for the colour (clear/white, yellow, green, or brown with corresponding-coloured tiles). This submenu would only appear if a participant was productive, ensuring participants did not have to complete sections that were not relevant to them. Parents of non-expectorating participants were advised to select “No sputum” if they were unable to visualise sputum but to measure change in cough on the cough scale.

1.16.5.2.2 Respiratory rate and number of sleep disturbances

In addition to data on oxygen saturation and heart rate gathered by the pulse oximeter it was decided we could train parents to count respiratory rate, which could be manually entered into the app. Also,

in an attempt to quantify sleep, we asked parents or participants to enter the number of times they or their child knowingly woke up during the night.

1.16.5.2.3 Sprints

The development was split into Paediatric Sprints based on the agile software development principles (https://agilemanifesto.org/). A sprint is a term used by app developers to define a period within which certain work needs to be completed. Each of our sprints was based around an agile development cycle (Figure 0-2). Our app development was split into 8 fortnightly sprints (Appendix 2). Fortnightly, after the completion of a sprint, there was a teleconference and a subsequent testing period. Depending on the aspect of the app that was completed at the end of the sprint, testing was either carried out by myself and a business analyst at the CF Trust, or by both of us and a small testing group. The testing would only look at the specific component completed in that sprint and test the functionality of that component. This mainly involved using test patient accounts and carrying out multiple trials of the aspect being tested, i.e., repeated monitoring of heart rate and oxygen saturations over several days and recording any issues or discrepancies between the readings. Between sprints, issues that were identified or required interim testing were released on to a study-specific GitHub account to which all parties had access. Table 0-3 is a summary table of the sprints throughout the CLIMB-CF app development; further details on acceptance testing and the user interface development are included later in this chapter.

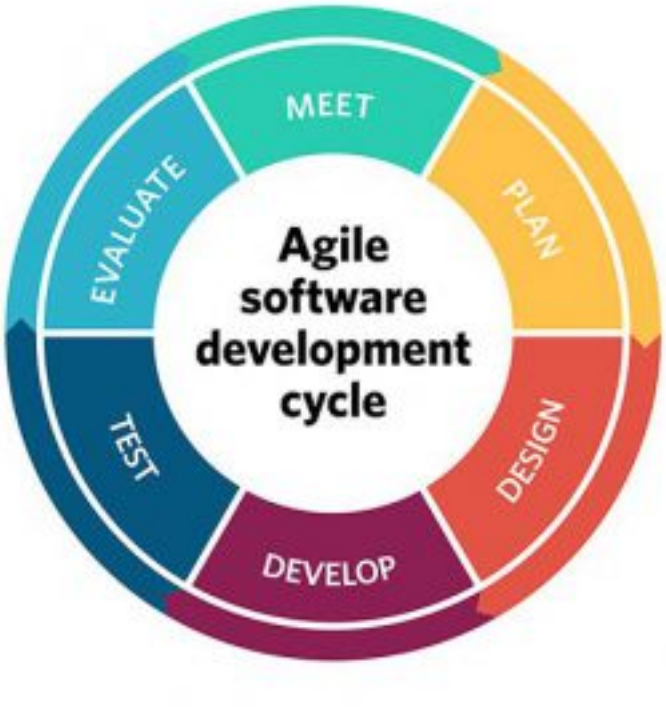


Figure 0-2 Agile development cycle diagram from https://project-management.com/10-key-principles-of-agile-software-development/ accessed 24th March 2020

Table 0-3 The 8 sprints included in the development of the CLIMB-CF app, the allocated tasks and the problems encountered in the sprint

Sprints	Allocated task for sprint	Tasks for sprint and problems encountered
1	Refactor Metadata	Conversion of adult app to paediatric app for CLIMB-CF study. Develop of metadata within the CLIMB-CF app
2	Packaging Pulse-ox device Lung device Activity device Weight device Temperature device	Integrate listed devices into CLIMB-CF app. Problems – pulse oximeter not registering requiring extra testing Once registered noted that if you clicked 'retry' it would disconnect and turn off. In view of this an alert was added to the app to give clear instructions on how to repeat the measure

3	Symptom entry Sleep entry Respiratory entry Indicate samples Supp. info Study data (web) Data export (web)	Addition of the wellness questions, sleep disturbances and respiratory rate and supplementary data. Development of the web page and export During the sprint it was noted the wellness score was out of ten and the appetite question was missing
4	Acceptance testing	Testing of app and devices in real time over the 2-week sprint Wording noted to still be from adult study and needed changing. In respiratory rate the format was stretched across the screen so read 'breaths/min' across 2 lines Entries in the diary were noted to not be visible on the patient summary graph
5	Create user accounts	Work done on the back end to incorporate the user accounts needed for the study
6	Select devices (web) Clinical measures (web) Patient user Acceptance testing	Work on back-end website, front facing study website and user journey through website
7	Reminders Clinical data (web) Export testing User interface implementation	Addition of reminders to the app and changing the visual look of the app to meet criteria During the 2-week sprint, noted not all sections had been updated in first update, corrected by next update
8	User interface testing Acceptance testing	Final testing sprint Minor changes to wording and 'doodles' attached to each 'tile' on the app

After sprint 4 there was a period of user acceptance testing (UAT). The UAT period was used to assess the basic functioning of the app itself to ensure that it recorded inputted data correctly and consistently connected to the Bluetooth equipment that had been integrated into the app. The app

design had not been developed by this point. This testing was carried out by myself, the business analyst at the CF Trust as well as two families connected to the CF Trust. These families were approached as they were aware of the project, happy to help and provide objective feedback. At the end of the testing period families were asked to give feedback about how the app functioned (Table 0-4, Table 0-5). One family had a 9-year-old, the other family had a 7-year-old and a 3-year-old. Data had been entered by a combination of parents and their children who were testing the app.

Table 0-4 Feedback from UAT questionnaire after testing period by families from the CF Trust

Question (out of 5)	Tester 1	Testers 2 + 3
Is the app content (visuals, language) appropriate for the target audience?	5 - Designed specifically for the target audience, no issues found	4 - Designed for the target audience, with minor issues
How accurately/fast do the app features (functions) and components (buttons/menus) work?	4 - Mostly functional with minor/negligible problems	3 - App works overall. Some technical problems need fixing, or is slow at times
How easy is it to learn how to use the app; how clear are the menu labels, icons and instructions?	4 - Easy to learn (or has clear instructions)	4 - Easy to learn (or has clear instructions)
Does moving between screens make sense; does app have all the necessary links between screens?	4 - Easy to understand/navigate	5 - Perfectly logical, easy, clear and intuitive screen flow throughout, and/or has shortcuts
Are arrangement and size of buttons, icons, menus and content on the screen appropriate?	4 - Mostly clear, able to select/locate/see/read items	5 - Professional, simple, clear, orderly, logically organised
Would you recommend this app to people who might benefit from it?	5 - Definitely	4 - There are many people I would recommend this app to
What is your overall rating of the app?	4 Stars	4 Stars

Table 0-5 Free text comments after UAT testing period from families from the CF Trust

	Free text comments
Tester 1	The app worked fine. It was hard to set up. When the email came through the link didn't let you download the app. It seemed fiddly with having to set up an email address and a password for that and then another one for the app. It took a while to set up and wouldn't have been managed by a child. Sometimes it was a little slow to find the different devices, but it was intuitive and there were no issues in saving the information and A did not need help from me to record anything and he could use all the devices once I had shown him once.
Tester 2 + 3	We were quite happy with using this app. It was often slow for the phone to find the device, but it got there after cancelling and trying again once or twice. B our 7-year-old was able do some of the recording himself with me confirming he had the right bit or was doing it correctly. I think if he had to do this every day for a long period, he would have no trouble doing it all himself once he had learnt how it worked. I would just need to help if he had any glitches. Neither of my children were able to use the lung monitor but neither have ever done or seen a lung function test. Easy for a parent to understand but a child had to have some things explained e.g., enter manually which had to be explained. Both children liked wearing the activity monitor, I think they saw it as a bit of a challenge to be active. In practical terms my kids didn't really like wearing the watch strap and preferred the clothes clasp. This meant we had to take it off at bath/bedtime and remember to put it on again in the morning. I think if I was doing it seriously, I'd have to build it into our routine as we often forgot it. On lazy days where the kids didn't get dressed early then we missed some of the morning's activity. The clothes clasp also has to be removed before clothes go into the linen basket, this is something we forgot sometimes! The only other comments I have are around the options there are for some recordings. For example, Cough. C who has CF normally has no cough at all. It is only when he gets ill that he starts to cough. The options of much better than usual, slightly better than usual, same as usual, slightly worse, or much worse, wouldn't apply to him as it implies your normal is to have a cough. The same would apply for breathlessness and possibly tiredness. Could it go from No breathlessness to Extremely breathless? Thanks for letting us get involved with this project. I think it is really great and will be very useful to people.

After the feedback from the testing was received, wording for some of the wellness questions was reviewed and changed. The decision was made to download the final app onto all phones ahead of time to simplify the setup process. Fatfractal also reviewed the Bluetooth connectivity of all pieces of equipment.

The user interface (UI) was designed with the assistance of Andrew Thirsk (www.thirskywork.com) who created example home screens -first screen seen on opening the app. These home screens were then used in an app design working group at the CF Trust, which included the CF Trust's Youth Empowerment Officer and Design Content Producer, the CLIMB-CF CF Trust project team and myself. The meeting took place on the 13th of September 2016. We discussed the fact that the language had to be neutral throughout the app as it was being used by both parents and participants. We also designed the app around the CF Trust's branding and colours while trying to ensure it remained engaging for young people.

Once the possible designs were finalised (Figure 0-3), they were shown to the UAT testing group, other parents, and children approached within the CF Trust and the CF Trust Youth Advisory Group (YAG) who voted on their favourite design. The YAG are a group of young people with CF aged between 14 and 25 years of age. The group was developed to allow young people to influence the CF Trust and ensure the voices of young people are heard. Due to the infection control issues around focus groups for young people with CF, the YAG communicate over What's app rather than face to face. The CF Trust's Youth Empowerment Officer sent the images to the YAG What's app group and collated the responses. Five of the YAG responded to the images with ages ranging between 14 and 22. Responses were received in October 2016 and feedback and votes for the two home screens were collected from both groups and collated (Table 0-6, Table 0-7).

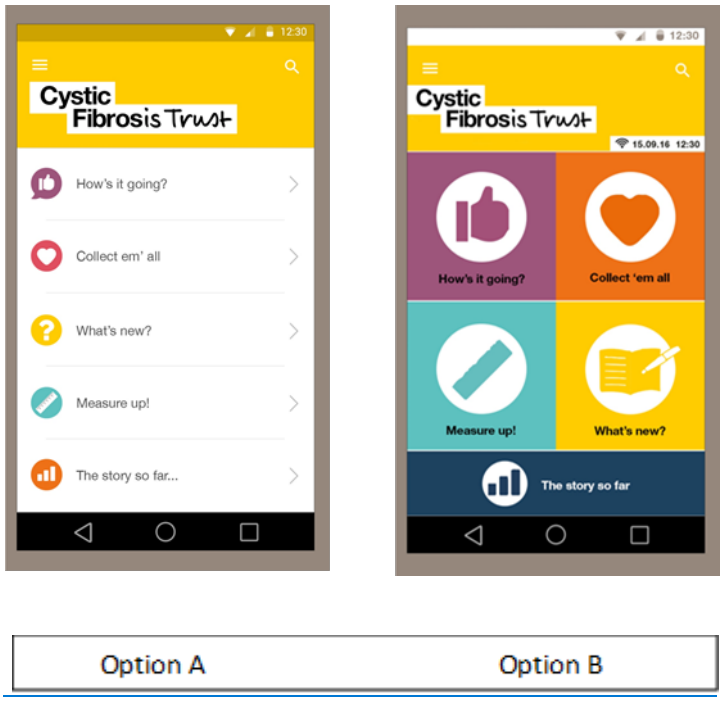


Figure 0-3. The sample screen shots of 2 home screen options voted on by testers and families from the CF Trust and the CF Trust's Youth Advisory Group.

Table 0-6 Responses to the two home screen designs from the CF Trust Youth Advisory Group Abbreviations F=female, M=Male. Number after F or M denotes age of person providing feedback.

YAG Feedback
'I prefer the look of B, it seems more straightforward with the squares and looks easier with more content (if that makes sense)' – F, 19
'I also prefer B, but they both look so good! I love the little face icons' – F, 22
'I'm in agreement with the option B preference, especially for the younger demographic' – F, 21
'I think option B too, both are really good, but B is probably more engaging for younger people. All about those emojis.' F, 18
'I like B best as well' F, 14

Table 0-7 Feedback from parents and children associated with the CF Trust. Number in bracket denotes age of young person providing feedback.

Option A	Option B	Additional comments
	A's Daughter (8)	If sticking with Option B, I'd suggest improving the measure up section to also show picture tiles, rather than in list format to match rest of app
A		I far prefer option A, I like its simplicity, clean lines and the fact that it isn't too gimmicky, but I also recognise that the kids would probably be more engaged with the second option
B's Daughter (13)		'A' is more clear, simple and user friendly really dislikes the 'cheesy titles' – catch 'em all (sounds too much like Pokemon Go)/measure up etc. etc. Finds them all patronising
	C's Daughter (9)	Like home screen of option B
	D's Daughter (14)	"it looks quite fun and funky" – "better graphics" – "much more modern"

Nine of the eleven people asked preferred the look of option B to option A. After this feedback option B was taken forward to the final app design. The submenus were designed based on the format of option B. These were designed during the last 2 weeks of October 2016.

Once the user interface requirements document was finalised and implemented there was a final round of testing before the release of the completed app. The completed app went live in January 2017.

In parallel to the app development and testing we also carried out development and testing of the user-facing and back-end of the website. This user-facing component included patient dashboards, the ability to add sites and participants, the ability to add participant data and the subsequent data

export. The back-end component of the webpage included the code that maintained the database for the duration of the study. It also included the permissions given to a user once they were set up on the website. This allowed access to either their own personal dashboard for participants, the participants at an investigator's own site, or an overview of all sites for myself and my research coordinator to help trouble shoot remotely. This was incorporated into the sprints and tested by myself and the business analyst from the CF Trust on a test website prior to being converted to a live website for the study. The final website is shown later in this chapter.

1.16.5.3 Site Selection, initiation visits and site contact

The CF Trust sent an expression of interest questionnaire to all CF centres in the UK, sites were invited to send forms back to the CF Trust if they wanted to be considered for the home monitoring arm of CLIMB-CF with an aim to recruit a minimum of 20 patients/ site. The questionnaire asked about staff availability, methods to identify participants, number of potential participants, other planned studies being undertaken at the site, access to WIFI and the access to at least internet explorer 6 on NHS computers in order to run the database. Ten sites (not including the Royal Brompton Hospital) returned expression of interest questionnaires. Three sites were unable to commit to enrolling 20 patients. The final decision was based on aiming to get spread across the United Kingdom: The final UK sites involved in the study were Royal Brompton Hospital London, Great Ormond Street Hospital (GOSH) London, Royal Alexandra Children's Hospital (BRN) Brighton, Alder Hey Children's Hospital (ALD) Liverpool, Great North Children's Hospital Newcastle on Tyne (NEW), North of Scotland Paediatric Respiratory Network (NOSPRN) (SCT) Scotland. In parallel to CLIMB-CF the Royal Alexandra

Hospital carried out a CF Trust funded site specific sub-study to explore whether it was possible to extrapolate respiratory rates from data recorded from a pulse oximeter.

Prior to the opening of the additional study sites involved in the study I set each individual study site up on the CLIMB-CF webpage, allowing them to see their participants only. I then carried out a site initiation visit (SIV) and training day and provided each site with a mobile phone with the app installed to allow sites to practice manoeuvring through the app prior to training participants. Each site was also provided with the SIV slides, a comprehensive site file, troubleshooting guides, and standard operating procedures for data entry, questionnaire delivery, and sample collection and labelling. They were also provided with contact details for myself and Nicole Westrupp (research co-ordinator).

In parallel with this, Cystic Fibrosis Canada (CFC) had approached the CF Trust to discuss the possibility of collaborating on a project investigating home monitoring. CFC were able to provide funding for two additional sites in Canada and were keen to be involved in a paediatric study. Approval was gained internationally, and I travelled to Canada and carried out SIVs in both Canadian sites (London, Ontario LON and Halifax, Nova Scotia IWK) and provided remote technical support.

1.16.6 **Ethical approval**

Ethical approval was granted by Queen's Square London Research Committee, UK (16/LO/1987), IWK Research Ethics Board, Halifax, Nova Scotia, Canada (1022312) and Western University HSREB London, Ontario, Canada (109185). Written informed consent was obtained from the participant's parents or legal guardians and, where age-appropriate, assent was obtained. Participants aged 16 or over consented for themselves. If a participant turned 16 during the study period, they then completed their own consent form.

1.16.7 Participant interventions

1.16.7.1 Setting up a participant for Arm 1 – Smart app and home monitoring in the study

Prior to enrolment we created anonymized Gmail email addresses for all participants at every site in Arm 1 – Smart app and home monitoring. These were provided to each site at their site initiation visit (SIV). Each email was also used to register a mobile phone and the CLIMB-CF app was preloaded onto every phone.

1.16.7.2 Study visits for participants in Arm 1 – Smart app and home monitoring and Arm 2 – Web based symptom diary

Each participant was enrolled for 6 months, a summary table of the study requirements can be seen in Table 0-8.

<u>The enrolment visit</u>

Once consent, and assent if applicable (aged ≥ 12 years), was obtained the participant was given a unique study number and enrolment data were obtained. Enrolment data were collected on a study specific proforma (Appendix 3). This proforma was used by the research team to collect the following data:

- *CFTR* genotype
- Co-morbidities including pancreatic status, cystic fibrosis related diabetes and cystic fibrosis related liver disease as well as non-CF related co-morbidities such as asthma
- Current medications and any changes to medications in the preceding 6 months
- Nutritional parameters: height, weight, BMI, and pancreatic status from the study start date and the previous 6 months

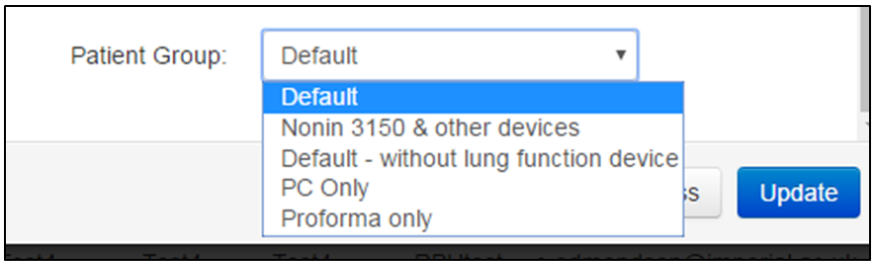
- Ethnicity as determined by the participant
- Postcode (from which Index of Multiple deprivation scores and environmental parameters can be assessed)
- Parental educational status
- Parental and participant self-reported smoking status
- Parental alcohol consumption
- Frequency of respiratory events requiring IV antibiotics or oral antibiotics in the previous 6 months
- All hospital admissions in the previous 6 months
- Spirometry from the previous 6 months (FEV_1 in L, FEV_1 % predicted, FVC in L, FVC % predicted)
- Height and weight for the study start date and the previous 6 months.
- Positive respiratory bacterial, fungal, viral, and nontuberculous *mycobacterial* cultures over the previous 6 months

The participant's study account was then set up on the study specific CLIMB-CF webpage (http://cftrust.fatfractal.com/climbcf/index.html#/). This involved signing into the CLIMB-CF website and clicking the user admin tab.

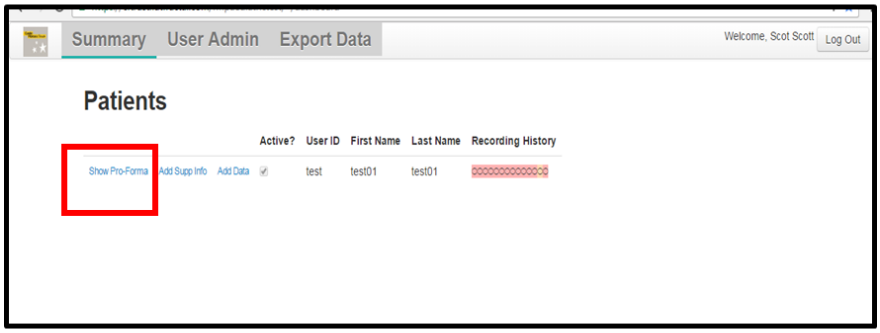
In order to ensure the data remained anonymous the first and last name sections were filled in with the study user ID. Age, in years and months, was completed but date of birth was left empty. Sex was also completed. The red boxes indicate the minimum that had to be completed for the system to register the user. These domains could also be edited after the user was created in case of a

mistake. There was a drop-down clinic menu, which allowed sites to attach the participant to their site so they could see their data.

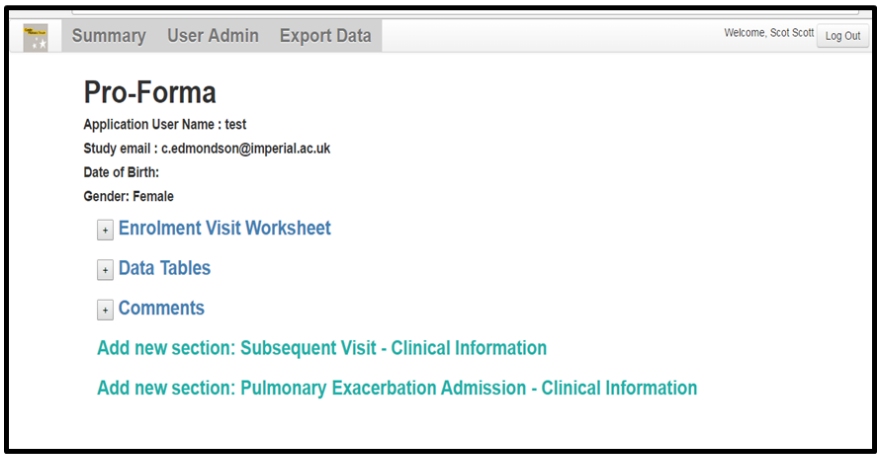
As the website was used by study teams at the Royal Brompton Hospital, who were recruiting to both arms, and all other study sites who were only recruiting to Arm 1 – Smart app and home monitoring- an option was required to allocate the participant to the correct study arm. There was also an option to record whether they were old enough to be provided with a handheld spirometer (Figure 0-4) as if they were too young the lung function option would not appear on their study app. "Default" was a patient who was completing all home monitoring including lung function, "Nonin 3150 & other devices" was specific for the Royal Alexandra Hospital (as the data from this device were being used by the Royal Alexandra Hospital study team to see if it would be possible to extrapolate respiratory rate from the pulse oximeter pleth recording, however the process to record oximetry measures was the same), "Default – without lung function device" was for participants under 5 or deemed by their enrolling site to not be able to do lung function at home, "PC only (PC=Personal computer)" were for participants from RBH who were in Arm 2. Once the participant was registered on the system their enrolment data were then subsequently entered onto the CLIMB-CF website in an anonymised format (Figure 0-4).



Panel a



Panel b



Panel c

Figure 0-4 Screenshots from the CLIMB-CF webpage showing selection of participant group when registering a participant (panel a), the link research teams would use to enter data (panel b) and the proforma they would complete which matched the paper proforma (panel c)

All parents were asked to complete the PHQ-8 for depression and the GAD-7 for anxiety (Appendix 4). If the participant was over two years of age parents were asked to complete the Strengths and Difficulties Questionnaire (SDQ) (Appendix 5), if 11 years old or over they also completed an SDQ. If

the participant was six years of age or over both the participant and parent completed the Cystic Fibrosis Questionnaire – Revised (CFQ-R) (Appendix 6) and the Knowledge of Disease Management – CF (Appendix 7). These questionnaires were scored locally by the study teams on excel scoring files provided with the questionnaires and transferred to myself. The results of the questionnaires will be explored in more detail in chapter 4.

Participants then received training either on the smart app and Bluetooth equipment if they were in Arm 1 or the web-based symptom page if they were in Arm 2. This training will be explained in more detail later in the chapter.

Clinic Visit two (at ~ two months)

At the second clinic visit a review of the clinical data was carried out including documentation of:

- Admissions to hospital
- Changes in treatment
- Any positive microbiology results
- Clinical lung function including spirometry was carried out as appropriate

This information was subsequently added to the CLIMB-CF study website. Participants and their parents completed the same questionnaires they completed at enrolment.

Clinic Visit three (at four months)

The frequency of routine clinics varied between sites, as such, clinic visit three was not compulsory. Clinical data were reviewed as before and submitted into the CLIMB-CF website. Clinic samples were collected if provided and participants delivered their home samples for storage.

End of study contact (at six months)

The final study visit was carried out at six months. Clinical data were again reviewed and submitted to the CLIMB-CF website. Parents and participants completed the same questionnaires as at enrolment and clinic visit one. If they were over six years old, they also completed My CF Treatments Treatment adherence questionnaire-CF (Appendix 7). Clinic samples were collected if the participant provided them, and home samples were stored by the study team. Parents and participants aged over six years of age completed a CLIMB-CF specific acceptability questionnaire (Appendix 8).

If a participant changed age group during the study, they continued to complete the same questionnaires they completed during their enrolment visit to ensure comparison. If a participant turned 16 during the study, they were re-consented to continue in CLIMB-CF. A summary of the study design is seen in Table 0-8.

Table 0-8 Summary table of interventions through CLIMB-CF. Arm 1 – Smart app and home monitoring (X) Arm 2 – Web based symptom diary (+) Subscript 1: if not done previously or participant symptomatic.

Investigations and assessments						
	Enrolment	First 2 months at home	Subsequent 4 months at home	Clinic visit at 2 months	Clinic visit at 4 months	End of study contact at 6 months
Smart app training	X					
Smart app and home device monitoring		X	X			
Web Symptom Diary training	+					
Symptom Diary		+	+			
Home collection biomarkers			X			
Knowledge of Disease questionnaire	X +					
CFQ-R	X +			X +		X +
PHq-8 GAD-7	X +			X +		X +
Strengths and difficulties questionnaire	X +			X +		X +
Adherence questionnaire						X +
Acceptability questionnaire						X +
Clinic spirometry	X +			X +	X +	X +
Clinic collection of biomarkers inc urine, throat swabs, DBS etc	X +			X +	X +	X +
Spontaneous/induced sputum	X +			X_1 +	X_1 +	X_1 +

1.16.8 **Arm 1: Smart app and home monitoring specifics**

1.16.8.1 Arm 1: - Enrolment visit specifics

In addition to the information listed above, each participant was provided with a Motorola Moto E, 2nd generation, mobile phone with the study app already downloaded. As the application was not freely available, each participant was also emailed an access link in case they needed to download the app again during the study. They were also provided with a rucksack with all the Bluetooth equipment and underwent an in-person training session by the study team covering how to use the phone, the app, and all the pieces of equipment.

The Vitalograph Spirometer is pre-set for an average adult male when it is first removed from the box. This meant that while the values for FEV_1 in litres would be displayed correctly the FEV_1 % predicted would be calculated on the adult pre-set and the results displayed would potentially be significantly lower than the participant expected. In order for participants to see FEV_1 % predicted based on their normative values rather than the pre-set values the study teams were required to set the spirometers to each individual participant. After a participant had carried out spirometry on the calibrated clinic spirometer study teams made note of the values recorded on the printout for a participant's FEV_1 in litres that equated to an FEV_1 % predicted of 100%, and peak expiratory flow (PEF) in litres per minute. They then were instructed to enter this data into the participants handheld spirometer. As the device would only allow data entered to the nearest 10 ml it was advised that data be rounded down prior to being entered into the device i.e., if a participant's FEV_1 was 2.67L it was entered at 2.6L in order to avoid underestimating. The sites used the spirometry software routinely used in their clinics and were asked to update the recorded values in the handheld spirometer as participants grew during the study.

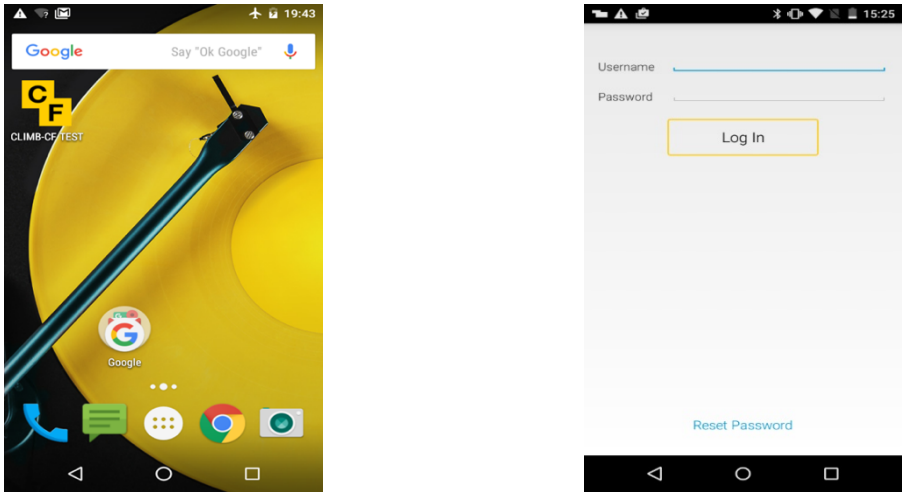
Participants and parents were then shown how to use the study specific app and the Bluetooth equipment as well as how to connect to WIFI on the phone provided. Each participant had a unique account created via the website and were provided with an app log in and initial password, which they could change, should they wish. After training, they were provided with a paper manual for guidance and a link to a YouTube video, filmed by myself and the CF Trust, which provided reminders of how to use the Bluetooth equipment (https://youtu.be/tuEqVVfcyeo). The mobile phone was provided without a SIM card but with a WIFI connection, so all functions of a normal smart phone were available. In view of this, parents were provided with information on how they could restrict the apps that their child could use, delete unwanted apps or restrict which apps could be downloaded by Google Play (https://support.google.com/googleplay/answer/1075738?hl=en-GB).

In this arm we were seeking to assess feasibility of both monitoring and sample collection for biomarker analysis; to allow an understanding of both separately, they were introduced in a staggered fashion: firstly, monitoring alone for the first two to three months, until their next clinic visit, followed by the introduction of sample collection to run in parallel with the home monitoring.

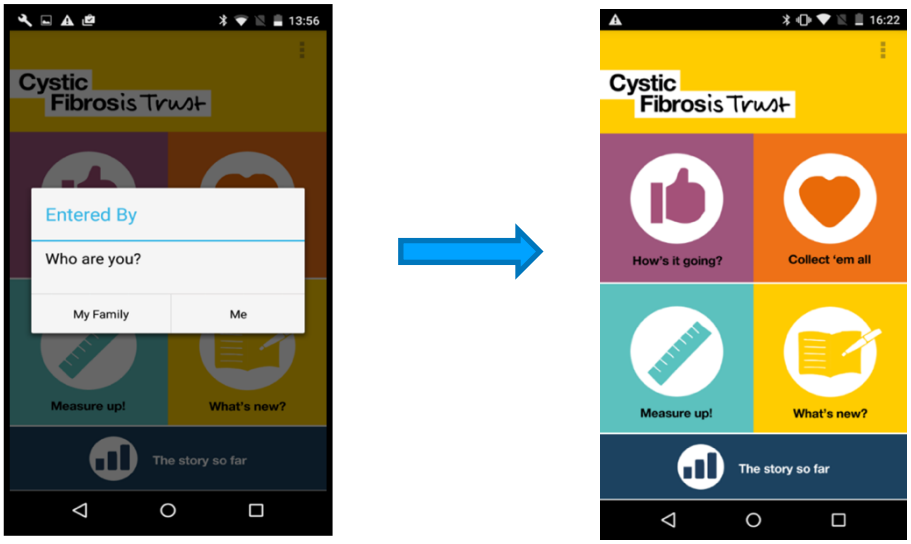
1.16.8.2 Home monitoring prior to next clinic visit (~2 months)

The thumbnail for the app was on the front page of the mobile phone; once selected, it asked for the participant's username and password (Figure 0-5). After a participant had signed in once, the app remained signed into that account, unless specifically logged out via the settings button. The first daily opening of the app resulted in a pop-up asking if the participant, or a family member would be entering data. Once this question was answered the participant would see the below home screen

(Figure 0-5) showing the 5 sub menu buttons, and also the last successful upload to the cloud in the top right-hand corner.



Panel a



Panel b

Figure 0-5 Screenshots from the CLIMB-CF app. Panel a shows two screen shots, the screen shot on the left shows the CLIMB-CF tile on the main phone screen, the screen shot on the right shows the log in screen for the app. Panel b on the left hand side shows the daily pop up that participants answered, once the pop up question was answered the app progressed to the CLIMB-CF home screen shown on the right side of panel b.

Participants and their parents were asked to complete the measures listed below, either daily or twice a week as indicated.

1.16.8.3 'How's it going?' tab

This tab opened a submenu including all the wellness questions that participants were asked to fill out daily.

Depending on the question selected, participants were offered different options ranging from, 'much better than usual' to 'much worse than usual', or 'no cough' to 'very bad cough' (Figure 0-6). They would select the emoji that related to how they felt that day, press ok and their answer would save. That emoji would then be the only one highlighted for that rating in the main submenu so they would know which questions they had answered and which they still needed to answer (Figure 0-6).



Figure 0-6 Screenshots from the 'How's it going?' submenu. The screenshot on the far left shows the whole 'How's it going?' submenu, the subsequent 2 screenshots show examples of the pops ups that a participant would see once they selected a question to answer. The

screenshot on the far right shows the 'How's it going?' submenu once all the questions were answered for the day. The selected emoji stays yellow and the other emojis are shaded out. The next day the menu resets and all emojis return to the yellow colour.

When a participant answered the sputum volume question, if they selected 'No sputum' then there were no further questions to be completed. If they selected any of the other four options an extra pop-up menu appeared, asking for sputum colour.

1.16.8.4 'Measure up!' tab

The second menu participants were shown was the measure up tab, which opened a sub menu showing the measures participants were asked to complete using their items of Bluetooth equipment (

Figure 0-7). Each tab provided step-by-step guidance for taking the appropriate measurement, with ticks showing which steps had been completed, and automatic progression to the next instruction (

Figure 0-7).

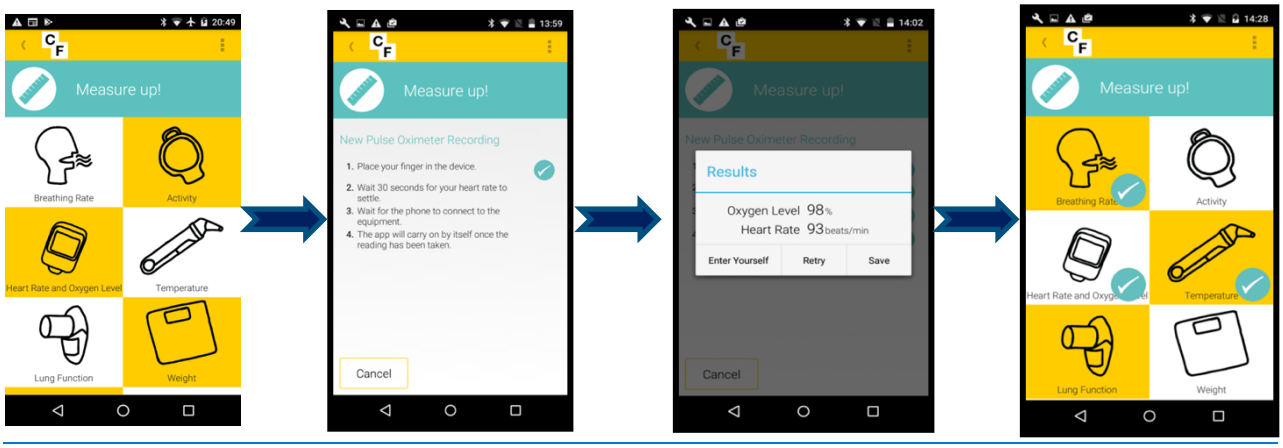


Figure 0-7 Screenshots from the 'Measure up' submenu. The screenshots show the stages a participant would go through to record a measure, the first screenshot on the left shows the multiple tiles participants could select to complete their measures. The next screenshot shows an example of the instructions they would receive then the subsequent results they could save or repeat. The final

screenshot shows an example of the submenu with some measures completed. When a measure was completed for the day a blue tick would appear. These would reset when the app was opened the following day.

If the phone was unable to connect to a device an option would pop up to allow the participant to try again, or to manually enter the data from the device. Whether a data point was entered manually, by the participant, or automatically, by the device, was recorded and included in the overall data export for later analysis.

Participants were asked to complete the below measures either daily or twice a week.

Daily

Participants were asked to record their temperature, from the external ear only, using a Pyle Health thermometer (PHTM20BT). After the ”Temperature” tile was selected from the menu the patient/carer was asked to turn the thermometer on and wait for it to connect. They then placed the thermometer into their ear and pressed and held the measurement button until a bleep sounded. The app would then carry on by itself and provide a reading on the screen. Participants were asked to check the temperature shown on the thermometer display with the number on the screen of the app, and press confirm if it was correct to upload the result. If the number on the screen was incorrect, they had the option to retry or enter manually themselves.

Heart rate and oxygen saturation were measured daily after at least two minutes of rest, via a finger probe Nonin 3230 bluetooth pulse oximeter (Nonin Medical B.V, Amsterdam, Netherlands). After selecting the “Heart rate and oxygen level” tile they placed their finger in the device and were asked to wait for 30 seconds for their heart rate to settle. The app would then connect to the pulse oximeter and the results would appear on both the oximeter and the phone screen. Participants were asked

to confirm the results matched to finalise the upload. If they did not match, participants were given the option to retry or to manually enter the data themselves.

Parents were taught to count participants respiratory rate for a 30 second period whilst the Nonin 3230 was recording. They then doubled this and entered the value manually by selecting the "Breathing rate" tile. They were taught to count the respiratory rate either by direct observation or by palpation by placing a hand on the back of the participant.

A Misfit Flash Personal Physical activity monitor (S90F00AZ, Misfit, Massachusetts, USA), was provided to be worn for the duration of the study. Participants could wear this either on their arm or belt. The Misfit would hold data for 7 days at a time, but participants were asked to enter data daily, through the "Activity" tile, in case of equipment malfunction. The first time they uploaded data the activity monitor was connected by pressing its face; once the app and the activity monitor were paired this process did not need to be repeated. The monitor would then automatically connect to the app and upload the steps from the day. Participants were given the option to retry if the device would not connect or to manually enter steps.

Participants were asked to select the sleep disturbances tile and enter the number of times in the previous night they had woken up.

<u>Twice a week</u>

Participants were asked to weigh themselves, on the same days of the week, if possible, while wearing light clothing, no shoes, using Pyle Health Digital Scales. They were asked to select the

"Weight" tile in the menu, step on the scale and wait for the weighing scales display to blink. The scales and the app would connect, and the weight would appear on the screen of the app. Participants were asked to check the weight on the display of the scale and the weight displayed on the app, and given the option to confirm the amount, retry the reading or to manually enter the data.

Participants aged five and above, unless assessed as unable to perform the technique by their research site, were provided with the Vitalograph Lung Monitor BT handheld spirometer (Model number 4000, Vitalograph, Buckingham, UK) and asked to complete spirometry twice a week. The spirometer was pre-set by the study team. Participants selected the lung function tile from the submenu. They were asked to sit down when using the device, then insert the mouthpiece and turn the device on. When the device connected to the app a blue tick appeared to let the participant know their attempt would be recorded. The lung function device also had a symbol on its display to show it was ready to test (). They were asked to take a deep breath in and then breathe out as hard and as fast and for as long as possible, aiming for a maximum of 6 seconds. The results were displayed on both the lung function device and the app. Participants were given the option to save the result, retry or enter manually. The patients were asked to complete the measurement 3 times each time they completed a recording. They were asked to complete the recordings at the same time of day each time and after physiotherapy if possible. The Vitalograph Lung Monitor BT had internal "quality of blow" indicators which would indicate on the screen of the spirometer if the attempt was of good quality. The spirometer would not compare the variation between the three attempts. The app then automatically picked the highest valid measurement from the day, which would be the one recorded for the participant to review in their history. They were requested to increase their measurement

frequency to daily if they developed respiratory symptoms. A nose clip was available in the spirometry pack, the participants were given the option of using the nose clip or not but were asked to be consistent for the duration of the study.

Participants were not requested to enter data at a specific time set by the study team, but they were asked to enter data at a similar time of day that suited them.

1.16.8.5 'What's new?' tab

Each participant was also provided with a diary component within the app called the 'What's new?' section, allowing participants to add data that was not collected within other tabs. We asked participants to record changes in medication but also stated they could record anything that was important to them, and they could utilise this section as they wished (Figure 0-8). They were made aware that the study team would be able to see anything written within this section.

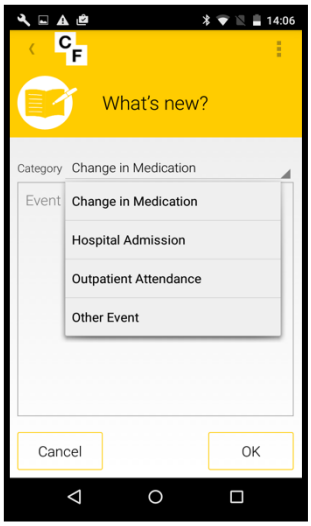


Figure 0-8 A screen shot showing the options participants could select within the 'What's new?' tab and the free text box they could fill in.

1.16.8.6 'The story so far' tab

This tab allowed participants to view their data either graphed over a week, a month or the whole data set as one. Each measure collected had its own tab, which would produce a graph (Figure 0-9). If the participant had added an event to their 'What's New' tab it appeared on the X axis of the graph as a yellow triangle. If the participant pressed on the triangle, they were able to see the entry to which the triangle corresponded.

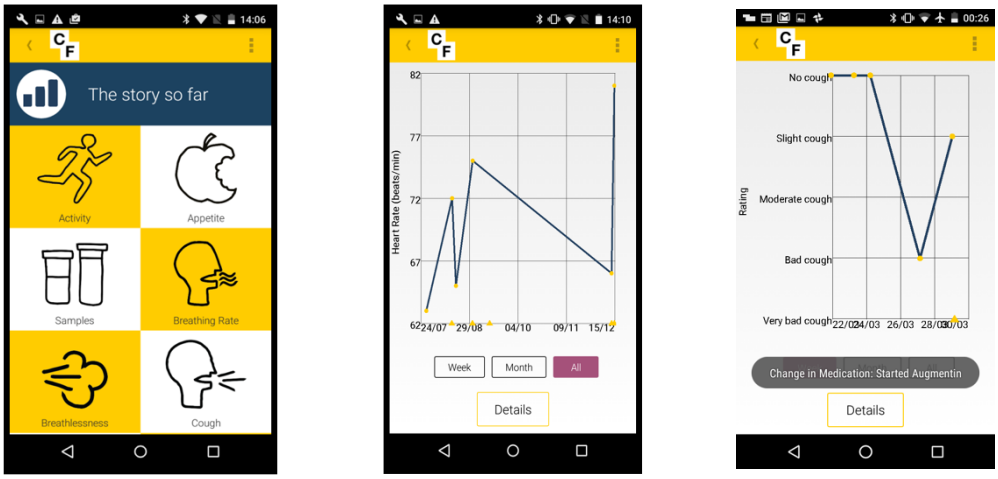


Figure 0-9 Screen shots showing 'The story so far' tile, the graphs participants would see and the pop up that identifies events participants have previously added to the 'What's new' tab.

1.16.8.7 Reminders

Participants were not reminded to complete the study automatically as we wanted to assess feasibility in real world usage. They were, however, provided with the ability to set both a daily reminder and a twice a week reminder for their lung function and weight if they wished as when surveyed by Hilliard and colleagues regarding user preferences in remote monitoring designs; the feedback was that people with CF would like to be able to set alarms/reminders based on their daily schedule (384).

1.16.8.8 Monthly phone calls

All participants and parents were provided with contact details for the research team at their site but monthly trouble shooting phone calls were also scheduled. Sites were given a proforma for the call (Appendix 9) and it was focused on troubleshooting the phone, app and equipment, not clinical concerns; participants were directed to talk to their clinical teams regarding any medical concerns they had.

1.16.8.9 Arm 1 Clinic Visit one (at ~ two months)

The collection of home samples was also discussed. Participants were given the choice of collecting any combination of urine, DBS, throat swabs, nasal secretions, or sputum at home. Participants were shown the "Collect 'em all' tab at their second study visit, as it was the section they were asked to use to record their sample collection at home. They were only required to record the samples they collected and were not required to add data to all the tabs (Figure 0-10).

They were asked to collect these weekly and to increase the frequency of collection to 2-3 times weekly from the onset of any respiratory symptoms until one week after symptoms resolution. Participants and parents were taught how to collect and label their samples, provided with printed Laser cryo baby cryo-tag labels (LCRY-1700, Diversified Biotech Massachusetts, USA) and a Sigma-Aldrich Fine Tip Lab marker (S5894, Sigma Aldrich, Missouri, USA). Participants were requested to freeze all samples as soon as they were collected at home in either their home freezer or if requested a tabletop freezer could be provided for them and bring them to their subsequent study visits frozen. Cool bags and ice blocks were provided at this clinic visit as well as a sample collection guide, and relevant pots and swabs. A freezer was offered for delivery if requested. Home sample collection will be discussed further in chapter 7.

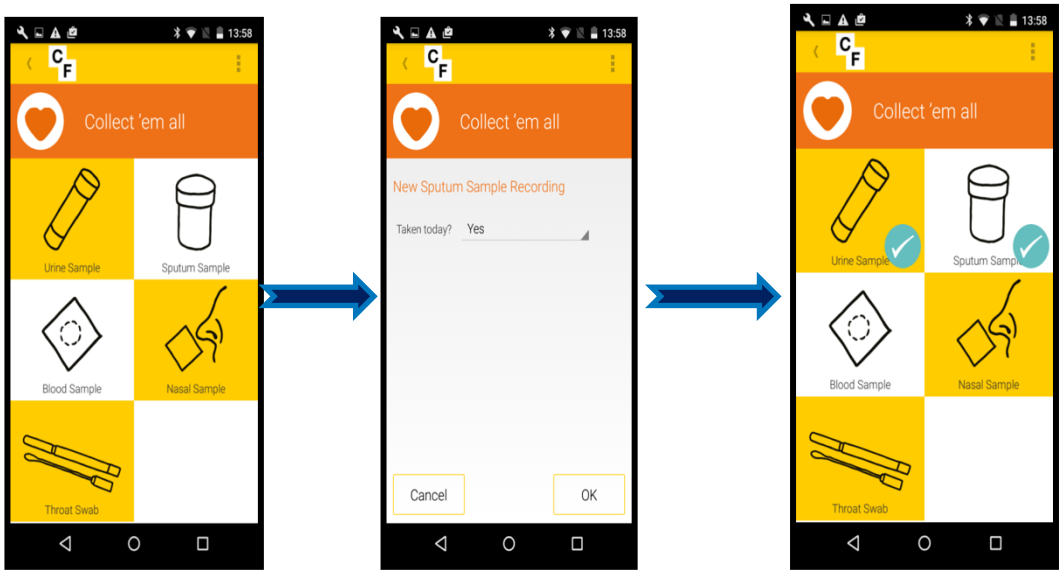


Figure 0-10 Screen shots showing the menus participants worked through to record their sample collection at home.

1.16.8.10 Home monitoring for months 3-6

For the subsequent four months, participants continued the home monitoring using the mobile phone app and Bluetooth equipment as well as collecting samples at home. Monthly phone calls with the study team continued.

1.16.8.11 Arm 1 End of study contact (at six months)

Home samples were collected, logged, and stored by the study team.

1.16.9 Arm 2 Web based symptom diary specifics

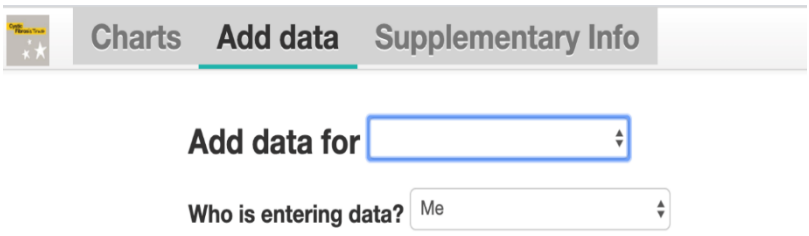
1.16.9.1 Enrolment visit

In addition to the enrolment visit documented above participants in this arm were provided with training on the web-based symptom diary, as well as a unique username and password, and a link to the webpage. They were provided with contact details for the research team.

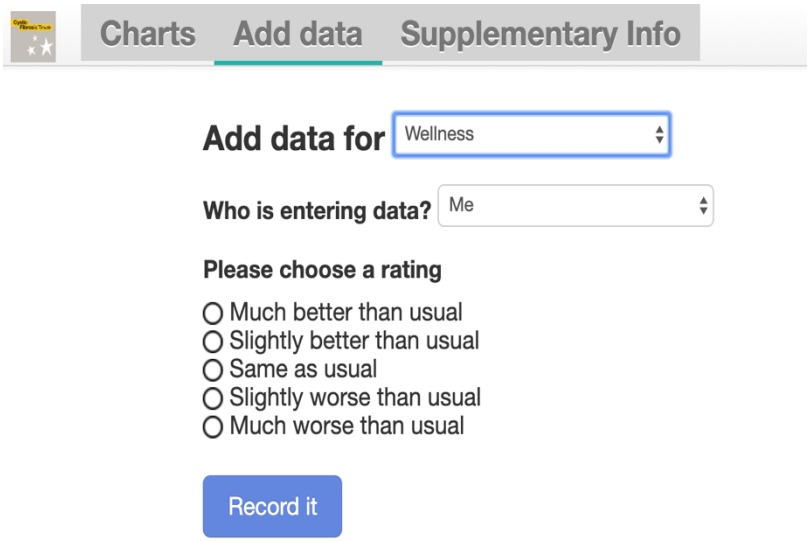
Participants were set up by the study team as documented previously with 'PC only' being selected as their patient group. They were emailed a welcome email to the CLIMB-CF study, which included a link to the webpage, their user ID, and a generic password with information on how to reset it to something personal.

Participant's home pages had three tabs along the top. The "add data" tab had two options on it, one to select if it was the participant or the parent adding data. The second drop down menu allowed participants to enter data for all the wellness questions included in the app (Figure 0-11).

Once an item was selected from the drop-down menu the rating score appeared, the participant could pick the radial button that matched the rating they wanted to select and then press "Record it" (Figure 0-11).



Panel a



Panel b

Figure 0-11 Screenshots from CLIMB-CF participants webpage. Panel a shows the question participants would answer regarding who was entering the data and panel b shows the options participants would have when answering questions selected from the 'Add data for' drop down menu. They would click on the radial button next to the answer they would like to select and press the record it button.

Participants were able to track their ratings on the "Charts" tab of the web page and see their trends (Figure 0-12).

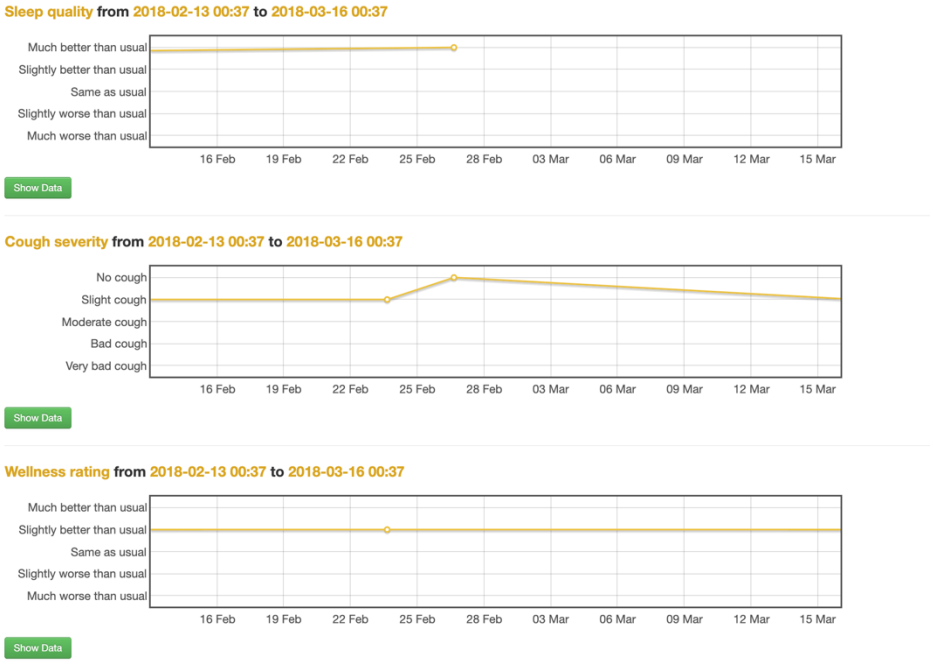


Figure 0-12 An example of the charts section of the CLIMB-CF web page.

The final tab participants had access to was the "Supplementary Info" tab, which allowed them to enter free text information, similar to the 'What's new?' section on the app. The entries would appear at the bottom of the charts page with a date and time, allowing participants to map it to their wellness charts (Figure 0-13).

Supplementary Information

	Date/Time	Category	Detail
Ignore	2017-02-03 11:21	Other Event	gone on holiday
Ignore	2017-02-03 11:22	Change in Medication	amoxycillian on 2/2/17
Ignore	2017-02-03 11:44	Other Event	school camp
Ignore	2017-02-03 11:44	Other Event	swimming
Ignore	2017-02-03 11:46	Change in Medication	started fluclox
Ignore	2017-02-03 11:49	Other Event	went to the zoo yesterday
Ignore	2017-02-03 11:50	Outpatient Attendance	induced sputum today
Ignore	2017-02-03 11:51	Other Event	school today
Ignore	2017-02-06 09:44	Other Event	weekend away to paris

Figure 0-13 The supplementary information as displayed on the charts section of the web page.

1.16.9.2 Completion of web-based symptom questions at home

Participants and their families were asked to complete the web-based symptom questions daily. The webpage was accessible on a personal computer, tablet, or mobile phone. Participants were not regularly contacted by the RBH study team but had the study team contact details for technical support and advice.

1.16.9.3 Clinic visits at ~ 2, 4 and 6 months

The clinic visits for the rest of the study are as documented above. Technical support was provided if participants were reporting difficulties with the webpage.

1.16.10 Data protection

All participants were given a unique study identity with deanonymized participant logs kept by the individual study site. No identifiable data was uploaded on to the CLIMB-CF website. All data received from the app was hosted by a UK hosting company called Memset. All data collected within this study is classified at 'OFFICIAL' level: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/715778/May-2018_Government-Security-Classifications-2.pdf and Memset met the requirements to host data of this level (https://www.memset.com/about/datacentres/).

Data were encrypted during transmission from the participant's device to the study website and database. The website was only available via https. Data in the database were strongly protected via role-based security as laid out in the study requirements document.

Passwords were not stored as supplied by the participant. They were stored as hashes using the PBKDF2 function, using SHA1-HMAC for its random number generator. This meant that neither the web developer nor the study teams could see participants personal passwords.

1.16.11 **Data handling**

Anonymised participant and sample databases were stored on a password protected computer in a secure office. Sample location logs were kept electronically and with paper back-ups in accordance with the Human Tissue Act 2004. Data handling was carried out by Nicole Westrupp and myself.

1.16.12 **Statistical analysis**

Throughout this thesis, unless specified specifically in a chapter statistical analysis was carried out as described in this section.

Data analysis and figure generation were completed using GraphPad Prism software version 9.0.1 (GraphPad Software, La Jolla, CA, USA) and Microsoft Excel 365. Data were assessed for normality using Schapiro Wilk testing. Data that were normally distributed have been described as means and standard deviation (SD), 95% confidence intervals (CI) have been presented where relevant. If data failed the normality test the results were summarized using median values and interquartile ranges (IQR). For non-parametric data subgroup analyses were performed using either the Mann-Whitney test (for 2 groups) or Kruskal-Wallis test corrected for multiple comparisons using Dunn's test (for more than 2 groups). For paired data the Wilcoxon Signed Rank test was used. Coefficient of Variation (CoV) is presented as a percentage (SD/mean x 100). P values of <0.05 were considered significant.

1.17 Recruitment figures and demographics

1.17.1 Recruitment

1.17.1.1 Recruitment to Arm 1- Smart app and home monitoring

The first site opened on the 16th of January 2017 and the last site opened on 9th January 2018, with the last patient visit being carried out on the 24th of October 2018. The number of participants recruited per site can be seen in Table 0-9. Each site was contacted by the lead study site (RBH) regularly during the recruitment period. One UK site expressed concern at managing to achieve their recruitment target, so the decision was made to over recruit at the Royal Brompton Hospital.

Table 0-9 Participant recruitment per site

CLIMB-CF Study site	Participants consented
Royal Brompton Hospital, London, UK	23
Great Ormond Street Hospital, London, UK	20
Alder Hey Children's Hospital, Liverpool, UK	20
Great North Children's Hospital, Newcastle upon Tyne, UK	19
North of Scotland Paediatric Respiratory Network (NOSPRN), Scotland, UK	20
Royal Alexandra Children's Hospital, Brighton, UK	13
IWK Health Centre, Halifax, Canada	13
Children's Hospital, London Health Sciences, London, Canada	20

Participants lived a median (IQR) of 18 miles (9.5-40.2) from their CF centre with the furthest participant living 359 miles away (Table 0-10). Figure 0-14 and Figure 0-15 show individual CLIMB-CF participants in relation to their study site.

Table 0-10 Median distance in miles of participants from their CLIMB-CF study sites

	Distance to study site in miles Median (IQR)
Whole cohort	18 (9.5 – 40.2)
Royal Brompton Hospital, London, UK	23.9 (13.2 – 50.1)
Great Ormond Street Hospital, London, UK	22.2 (11.1 – 41.6)
Alder Hey Children's Hospital, Liverpool, UK	9.1 (4.5 – 11.9)
Great North Children's Hospital, Newcastle upon Tyne, UK	12.4 (8.5 – 18.3)
North of Scotland Paediatric Respiratory Network (NOSPRN), Scotland, UK	26.1 (16.6 – 48.5)
Royal Alexandra Children's Hospital, Brighton, UK	12.4 (4.5 – 27)
IWK Health Centre, Halifax, Canada	65.4 (15.9 – 232.5)
Children's Hospital, London Health Sciences, London, Canada	28.7 (7.2 – 65.7)

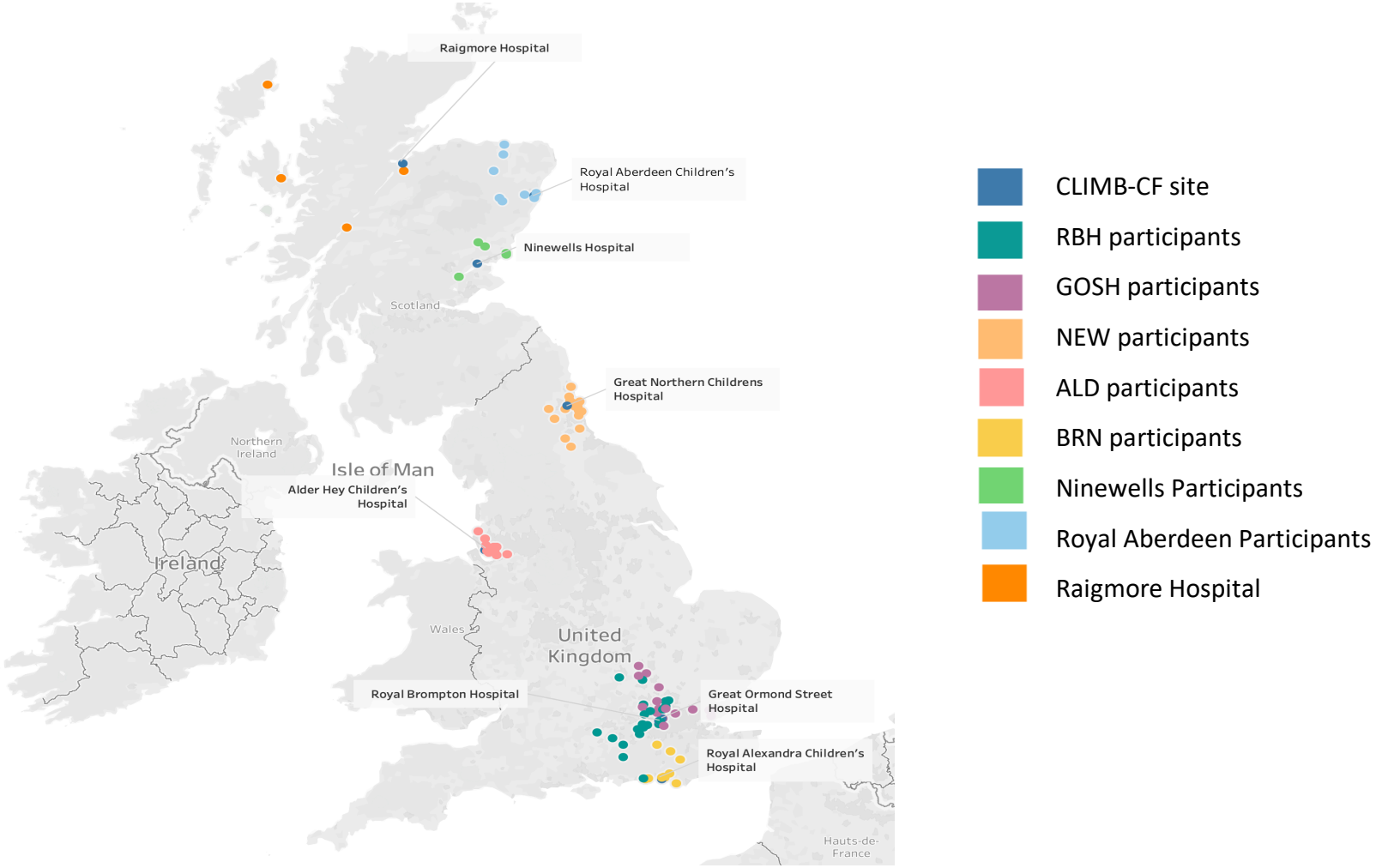


Figure 0-14 A map showing individual UK participants and their location from their CLIMB-CF study site.

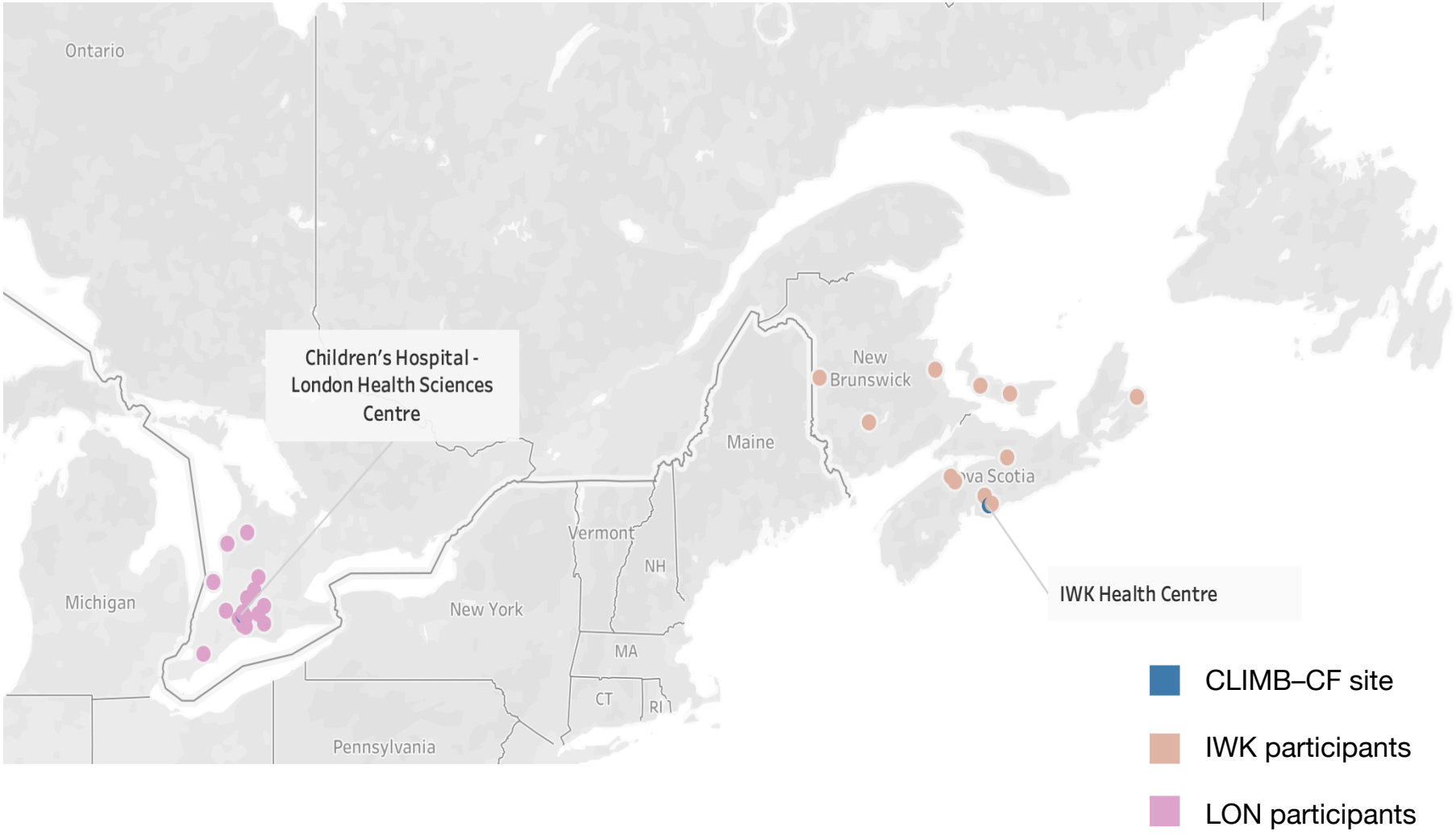


Figure 0-15 A map showing individual Canadian participants and their location from their CLIMB-CF study site.

1.17.1.2 Recruitment to Arm 2 – web-based symptom monitoring arm

The recruitment target to Arm 2 was 50 participants, however the decision was made to focus on over recruiting to Arm 1 at RBH, and to stop recruiting to Arm 2 due to a second CLIMB-CF centre failing to meet their Arm 1 recruitment target. 38 participants were recruited to Arm 2, 34 of whom provided data. Two participants failed to achieve clinical stability within the time period, one participant did not receive the enrolment email and one participant transferred their care to their local hospital.

1.17.2 Patient demographics

The patient demographics for participants recruited to both Arm 1- smart app and home monitoring and Arm 2 – web-based symptom monitoring are documented in Table 0-11.

*Table 0-11 Demographics of participants recruited to home monitoring arm 1 (app) and arm 2 (web) * defined as any sputum culture positive documented in medical notes by the site and not cultured during the study period. + defined as previously documented in the medical notes and not currently active/being treated during the study period. Ethnicity as selected by the participant from a provided list. Abbreviations: IQR: interquartile range, ppFEV1: Percent predicted forced expiratory volume in first second, ABPA: Allergic bronchopulmonary aspergillosis*

		App (N=144)	**Web (N=34)**
Sex		82 (57%) female	19 (56%) female
Age (years); median (IQR)		7.9 (5.2–12.0)	6.3 (4.3-9.5)
Weight z scores; median (IQR)		0.06 (-0.61 – 0.44)	0.11 (-0.5-1)
Ethnicity	Caucasian	140 (97%)	32 (94%)
	Other	4 (3%)	2 (6%)
Genotype	F508del/ F508del	92 (64%)	21 (62%)
	F508del/Other	46 (32%)	12 (35%)
	Other/Other	6 (4%)	1 (3%)
$ppFEV_1$; median (IQR)		91.8% (88.9-97.3%)	92.5% (82.3-97.8%)
Pancreatic insufficient		134 (93%)	32 (94%)
Cystic Fibrosis related diabetes		12 (8.3%)	6 (17.6%)
Liver disease (including fatty liver)		13 (9%)	4 (11.7%)
Current *Pseudomonas aeruginosa*		42 (29%)	7 (20%)
Previous* *Pseudomonas aeruginosa*		62 (43%)	18 (53%)
Previous* *Mycobacterium abscessus*		5 (3%)	3 (8.8%)
Previous^{+} ABPA		8 (6%)	3 (8.8%)

Intravenous courses of antibiotics in previous 6 months Median (IQR)	0 (0-1)	0 (0-1)
Oral courses of antibiotics in previous 6 months Median (IQR)	1 (1-2)	2 (1-3)

1.18 **Equipment issues and their consequences**

A participant enrolled at the Royal Brompton Hospital site contacted the study team on the 2nd February 2017 reporting an issue with the plug component of the phone charger. The family reported it had fused the electrics in the house and appeared scorched. The study team immediately contacted all seven active participants in the study at that time and advised them to stop using the provided charger and the decision was made to pause recruitment to ensure safety. Participants who had alternative chargers at home that were compatible with the study phone continued to enter data. All chargers were returned by the participants and discussed with trading standards. Trading standards subsequently tested one of the plugs on the 14th of February 2016 and concluded 'The sample complied with the requirements of the British Standards as tested. No departures were found that contravened the requirements of the Electrical Equipment (Safety) Regulations 2016'. Despite this the decision was made with the CF Trust and the study sponsor Imperial College London to purchase new chargers were purchased and distributed with a testing protocol as devised by clinical engineering. Recruitment was recommenced on the 4th of May 2017.

1.18.1 **Activity monitors**

The information provided with the Misfit activity monitors stated the activity monitor was waterproof and could be used during activities such as swimming. At the start of the study two participants reported the activity monitor not working after using it in water. The monitors were

returned to the Royal Brompton Hospital and the internal workings showed evidence of water, therefore advice to participants moving forward was to keep the activity monitor dry. 45 activity monitors were replaced in the UK arm of the study and one participant withdrew from the study based on frustration with this piece of equipment, in particular the difficulty with connecting the activity monitor to the app and uploading the results. In 2017 alternative activity monitors were explored with Fatfractal however it was not possible to integrate a different activity monitor into the app without the inclusion of third-party software.

1.18.2 **Weighing scales**

The weighing scales could be set to record weight in kilograms or stone but would only sync with the app if set to kilograms. Participants reported issues with the scales syncing and having to enter the data manually. Due to the weight of the scales, they could not easily be brought to centres for review by study teams so technical support was provided remotely, however, the individual items could not be reviewed by the study teams on study visits, but the amount of data manually entered during the study is explored in the next chapter.

1.18.3 **Thermometer**

The thermometer was found to have a short battery life. Replacement batteries were sent to families when requested but delays in receiving these may have affected the amount of completed data. In attempt to mitigate some of these delays every study site was supplied with spare batteries. All participants were requested to record their temperature in their ear. However, some participants contacted the study team reporting a perceived error due to an 'E' being visible on the screen. This

was the thermometer reporting it was on ear setting rather than an error. Subsequently advice was given to participants regarding this in their training session at the start of the study.

1.18.4 **Pulse oximeter**

It was noted that occasionally the pulse oximeter would give impossible results such as a heart rate of 666, further information regarding the frequency of these readings can be found in chapter 3. Participants were advised to cancel this reading and carry out another reading should this occur.

1.18.5 **Spirometers**

Cystic Fibrosis Canada bought the same equipment and mobile phones as the UK Cystic Fibrosis Trust. Despite the mobile phones running the same systems software and the same version of the CLIMB-CF app, some of the Canadian spirometers would not sync with the app. This occurred at both Canadian study sites and did not affect all Canadian participants. Trouble shooting by myself and Fatfractal was unable to identify the cause for this or fix the issue. In view of this Canadian participants were given information on how to manually enter their lung function data (results in section 3.3.1.5).

1.19 **Data Export**

Data were exported from the CLIMB-CF website for testing and analysis. Data exports of the participant proforma and the individual measures were available (Figure 0-16). Data were exported from the website in Comma Separated Values (CSV) format.

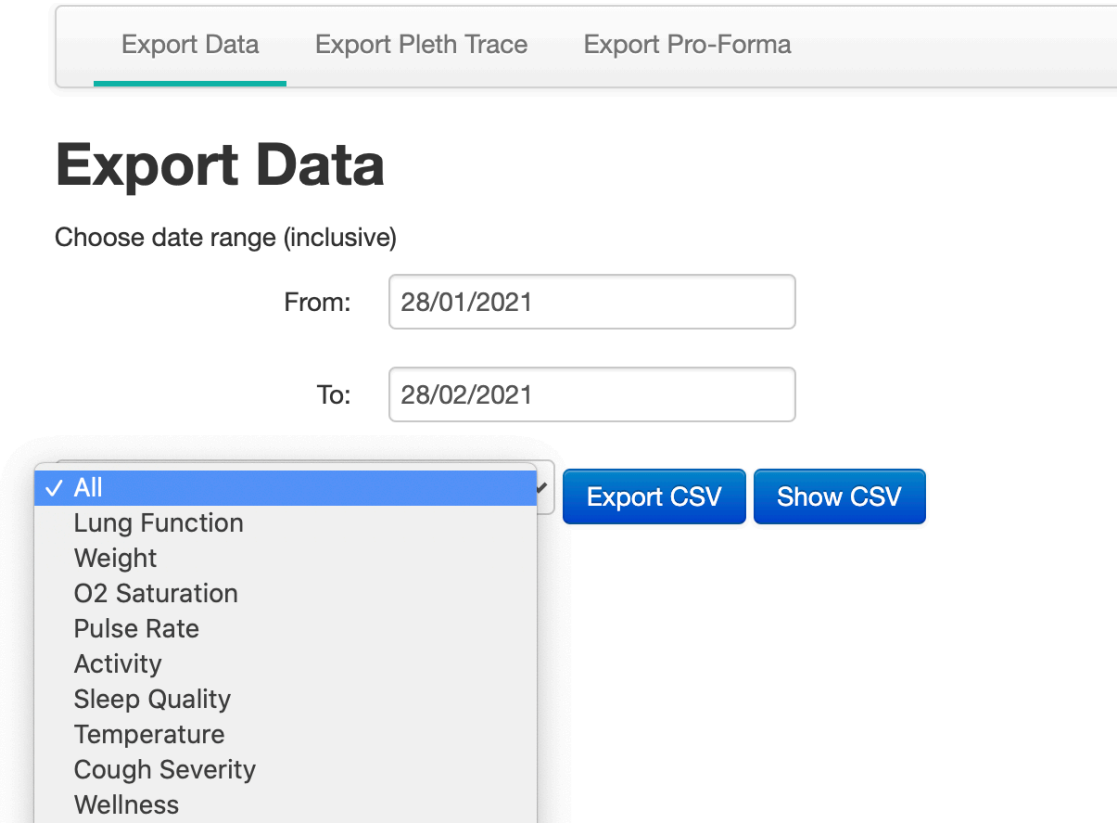


Figure 0-16 Screenshot showing Export Data page of website with options to export data per measure and individual participant proformas

1.19.1 **Export testing**

Data export testing was run in parallel to the live study using both a test web site and data from the live web site. Throughout the study modifications were made to the data export due to identified issues, the modifications were subsequently retested to ensure resolution. A summary table of the issues noted during data export testing is included below as well as discussion regarding the most significant problems experienced during testing (Table 0-12).

Table 0-12 Problems found during data export testing and the fixes implemented.

Data export problems found during testing	**Data export fix**
Back-end website producing individual identifiers on export not using participant IDs so export unidentifiable	Export fixed to pull through participant ID rather than back-end identifier number
Age and sex not mandatory on proforma import and therefore potentially missing from some participants	Both made mandatory fields to register a participant to ensure present on export
FEV_1 and FVC fields pulled through litres and percent predicted in the same cell, not allowing for easy differentiation between the numbers	Export adapted to export FEV_1 and FVC litres and percent predicted in separate columns
Proforma export exported as one large sheet with all sections and all participants on the sheet potentially making analysis hard	Proforma export changed to per participant with separate tabs for the different sections of the proforma
Test exports missing lung function data	Coding changed to ensure all lung function values pulled through onto data export
All measures for all participants were exporting on to one sheet and on testing with test data as the amount of data increased the export would timeout before completing the export	Decision made to export each requested measure as a separate export i.e., one export for heart rate, one for lung function and one for wellness etc.
Exports for individual measures not documenting on export which measure was being exported potentially allowing for errors in analysis	Title of each measure added to the column header of the result
The time the reading was taken was allocated a column in the export but did not have a header, so all subsequent column headers were off by one line	Additional header for 'time taken' was added next to 'date taken'
Wellness questions converted to numerical scale but initially exporting values from a ten-point scale	Converted to a five-point scale

The plan for the data export from the study specific webpage into a CSV file was that there would be a row of data per participant per date. Each row would then identify the result of the measure submitted by the participant or that the participant had not entered data for that day.

Initially on the data export, data for each individual were not capped by their specific start and end dates, rather by the start and end date of the study as a whole. For time periods outside of each individual participants start and end date the system prepopulated rows of data as if the participant had not entered data for that day. This meant that within the export there were significant lines of irrelevant data per participant from outside of their specific study dates. In order to isolate only data entered by a participant during their specific study dates manual deletion of data would have to occur. This would lead to a significant risk of human error. Once identified Fatfractal were able to code subsequent exports to only export by individual start and end dates.

In order to record the written scales used within the 'How's it going?' section of the app the back-end website data export converted the questions to a numerical scale as seen in Table 0-13. On testing the data export, it was noted that the export was exporting the score 0 as a blank cell rather than the number 0. In parallel to this, it was also exporting days when data were not entered by a participant as a blank cell. This meant that for the analysis I was unable to differentiate between days where data were not entered verses days when the participant had entered data but may have selected the worst option on the wellness questions rating.

After discussions around possible alternatives, Fatfractal's subsequent changes to the export meant on days where data was not entered the CSV cell was filled with the word NULL and wellness scores

of 0 exported as the number 0 in the CSV cell. All CSV files were converted to Microsoft Excel workbooks (Microsoft Office 365) to prevent data loss.

Table 0-13 Conversion of the 'How's it going?' scales options to a numerical scale

'How's it going?' scale option	Assigned number by back-end website
Much better than usual No cough Not Breathless No sputum	100
Slightly better than usual Slight cough Slightly breathless A little bit of sputum	75
Same as usual Moderate cough Moderately breathless Some sputum	50
Slightly worse than usual Bad cough Badly breathless Quite a bit of sputum	25
Much worse than usual Very bad cough Extremely breathless Lots and lots of sputum	0

During the export testing of live site, it was noted that there were occasional duplicates in the data from the UK. The app did not allow for multiple data points per day or for the editing of a data point once submitted but occasionally the export would duplicate the data point. I discussed this with Fatfractal who were unable to provide a web page back-end fix to prevent this. Subsequently I was able to identify these duplicates using a COUNTIFS formula on excel to identify any participant rows

that included the same participant ID and the same date. I used the COUNTIFS formula on the exports for each measure, however on examining the data I identified another issue. The presence of duplicates was rare in the data from UK participants, however there were significantly more double entries noted in data from Canadian participants (Figure 0-17) shows a screenshot of the excel file for sleep activity for participant IWK012. The COUNTIFS formula has identified a duplicate and highlighted it using the number 2 and the colour red. This is a true duplicate as the date and time stamp are identical, in this case 07/06/2018 21:34:02. Figure 0-18 shows a screenshot of the excel file for sleep activity for participant IWK012 where the COUNTIFS formula has identified a duplicate with the same date but a different time stamp and different ratings to their sleep quality. These duplicates were only identified on exports from Canadian participants and were caused by the website converting all times to London Greenwich Mean Time (GMT). In this example no data were recorded for 9/6/2018 but two data points were recorded for 10/6/2018, one just after midnight at 00:14:46 and one late in the evening at 22:05:18. These represent data entered late in the evening of the 9th of June in Halifax, Nova Scotia, Canada and the evening of the 10th of June. The database has converted both times to London GMT and the export has them both as 10/6/2018. Fatfractal were unable to correct this through the back end of the webpage, therefore I corrected the data once exported in excel.

8925	IWK012	Male	8	11	SleepActivityRecordin	06/06/2018	23:40:26	50	1
8926	IWK012	Male	8	11	SleepActivityRecordin	07/06/2018	21:34:02	50	2
8927	IWK012	Male	8	11	SleepActivityRecordin	07/06/2018	21:34:02	50	2
8928	IWK012	Male	8	11	SleepActivityRecordin	08/06/2018	21:05:28	50	1

Figure 0-17 Screenshot of excel file demonstrating true duplicate data with the same date and identical time stamp

8929	IWK012	Male	8	11	SleepActivityRecordin	09/06/2018	00:00:00	NULL	1
8930	IWK012	Male	8	11	SleepActivityRecordin	10/06/2018	00:14:46	50	2
8931	IWK012	Male	8	11	SleepActivityRecordin	10/06/2018	22:05:18	25	2
8932	IWK012	Male	8	11	SleepActivityRecordin	11/06/2018	19:00:15	50	1

Figure 0-18 Screenshot of excel file demonstrating data identified as duplicate data due to issues with the time difference between the UK and Canada

After corrections for conversion to London GMT were made duplicate data were deleted. For all duplicate data, the second entry on the export was deleted. Once the duplicates were deleted data were analysed in Microsoft Excel 365 and GraphPad Prism.

Further issues were found with the data export of the 'What's new?' section which needed to be taken into consideration. Entries that had been entered over more than one line appeared as multiple entries in the export.

1.20 **Summary**

This chapter details the development of the CLIMB-CF app, the CLIMB-CF study design and the recruitment process and issues identified during the study period. During the initial app development and subsequent testing strengths and weaknesses became apparent that will be informative for future study and app development. These are discussed in more detail below and summarised in Table 0-14.

Strengths and weaknesses

The CLIMB-CF app was developed using timelines and processes regularly adopted in the software developing community. The process of splitting development down into sprints allowed us to test the app and the equipment at multiple stages throughout the development process and fix problems throughout the development rather than once the final app had been developed. This process also allowed for the end user to contribute at the UAT and UI stages of development.

End users were used both in the testing phases as well as contributing to the design of the final app. The app, equipment and data export went through significant testing to identify errors and allowing for adaption of the app and data export as needed.

Despite rigorous testing of both the app and the equipment, we experienced issues with the equipment that both affected recruitment and was an ongoing issue within the feasibility study. The main issue affecting recruitment involved the concern raised by one participating family regarding the plug attached to the phone charging cable. Once notified about the potential issue recruitment was held and the other active participants were requested to stop using the plug while conversations with trading standards and clinical engineering occurred. There is no way of knowing how much data may have been lost during this period secondary to study phones running out of battery, but it was felt to be minimal as the 6 of the 7 families affected had alternative chargers at home that would charge an android phone. Subsequent investigation did not find an obvious fault with the plug once it was returned to the study site. The family in question did report ongoing issues with their electrical wiring at home, however the decision was made to source alternative chargers, and on discussion with clinical engineering a testing standard operating procedure was created for all sites moving forward. This did equate to a three-month delay in recruitment.

Throughout the study we had ongoing and unexpected issues with some of the pieces of Bluetooth equipment. Some of these issues were relatively easily rectified, however we were unable to resolve all of them. The activity monitor was a significant issue with the paediatric study and multiple devices had to be replaced at an unbudgeted cost. On discussion with the team that ran SmartCare CF, the number of activity monitors that required replacement in the CLIMB-CF study was significantly more,

perhaps secondary to the active nature of children while playing at home and in school. The other unexpected expense was the replacement battery requirement for the thermometers. Some participants within CLIMB-CF replaced the batteries at their own cost rather than waiting for replacement batteries to be dispatched to be able to continue data collection, however many participants were not able to absorb this cost and were reliant on the study sites providing replacements. When developing further research studies or clinical practices using Bluetooth equipment at home these additional costs must be considered, especially as many patients may not be in the position to cover these themselves. A recent study looking at the health care related costs related to the eICE trial found that the costs were higher in the early intervention arm (those participants provided with home monitoring), although this was not statistically significant. The costings, however, only included a one-off cost to provide participants with a spirometer and no additional costs for ongoing equipment maintenance/replacement (385). The initial costs in CLIMB-CF to provide each participant with a phone and the Bluetooth equipment was £484.13. This does not include the extra equipment purchased throughout the study. The results of our study suggest that both the initial set up cost and ongoing maintenance costs should be factored into future health economic calculations.

Completion of the CLIMB-CF data entry was designed to take five to ten minutes a day depending on whether spirometry was being collected that day (which increased the time required). This time will have contributed to the daily screen time of both the parent and participant. When designing future apps for young people, serious consideration needs to be given to the amount of time required to complete the requested measures and the contribution this time will have on the overall screen time of the young person.

Table 0-14 The strengths and weaknesses of the CLIMB-CF study design

Strengths of the study design	Weaknesses of the study design
Tested by both adults and children	Thermometer not tested on febrile people
Multiple sprints allowed for multiple testing points identifying potential errors in the app and equipment	Cough question did not allow for quantification of wet or dry
Identification of errors in the data export allowed to correction prior to analysis	Unable to incorporate a new activity monitor
There was end user contribution to both the testing and design phase	App usage contributes to screen time of participants
The app did not allow for back dating of data	The app did not allow for changing of data entry within the same day
Identification of potential costs to be incorporated into future study planning/service provision planning	Potential loss of data due to issues with the plug requiring extra testing

The next chapter will explore the amount of data received during the 6-month study and participant and parents' views on the acceptability of home monitoring.

Chapter 3-CLIMB-CF Study - feasibility data and acceptability data

1.21 Introduction

As described in the introduction the concept of home monitoring in CF is not a new one and has been described in the literature since the 1980s (338). Data completion in home monitoring studies has been highly variable, affecting feasibility and acceptability of these measures moving forward.

Feasibility of using remote monitoring equipment has been explored by interviewing adolescents and clinicians while trialling a home spirometer and symptom diary during a hospital admission (386). Five adolescents and three members of the medical team were enrolled and subsequently interviewed. Two further adolescents declined to take part, stating they did not have time. One participant's whole record was corrupted due to a technical issue. All participants stated they would not like a health worker supervising their readings. All participants reported they were satisfied with the remote monitoring set up and expressed no concerns about the safety of their data. They did, however, express concerns about how usable remote technology would be if there were significant technical issues. Comments were also made about how remote monitoring would be more convenient if you lived a significant distance from your CF centre. Interestingly the authors report the symptom diary was hardly used. The clinicians interviewed stated they thought remote monitoring would be a beneficial addition to routine clinical care and potentially could have a positive effect on their patients. Opposite to the participants, the clinicians stated they would prefer observed remote spirometry in order to ensure valid measurements are being achieved (386). Completion of remote monitoring data is highly variable (387) and in the paediatric population has previously only been explored in a small number of patients at a time.

This chapter will describe the feasibility of home monitoring and the amount of requested data completed and the acceptability of home monitoring to parents, participants, and staff (Arm 1). It will also describe, for comparison the feasibility of the web-based symptom monitoring webpage (Arm 2).

This chapter tests part of my first hypothesis namely that home monitoring will prove feasible and acceptable for patients and families by assessing the amount of requested data received, as well as the number of home samples received. Acceptability to both parents and participants will also be assessed in this chapter.

1.22 Methods

1.22.1 Daily and twice weekly data collection measures

As mentioned in the previous chapter, participants were asked to enter measures either daily or twice a week. Participants were also asked to increase the twice weekly measures to daily should they develop respiratory symptoms. They were able to set specific reminders within the app on certain days for their twice weekly measures if they wished.

1.22.2 Acceptability questionnaires

Study specific questionnaires were designed for parents, participants aged 6 to 11 years of age and participants aged 12 years and over. These questionnaires covered the phone and the Bluetooth devices themselves as well as acceptability of what they were asked to carry out at home, the perceived impact on daily life and mood and issues that were faced during the study period. The

questionnaires were a combination of five-point acceptability scales, ten-point Likert scales and free text boxes. Participants and their parents were asked to complete the questionnaire at the end of the study period. Participants who withdrew were also given the option of completing the questionnaire. For participants aged 12 and over, both the parent and the participant were given the option of completing the acceptability questionnaire.

A similar questionnaire was developed for parents and participants ≥ 12 years of age who were enrolled into Arm 2 – Web based symptom monitoring.

1.22.3 **Statistical analysis**

Subgroup analysis of three age groups (2-5 years of age, 6-11 years of age and ≥ 12 years of age) was completed. If a participant withdrew, their available data were included up to their official withdrawal date. Multiple regression analysis was performed using IBM SPSS Statistics version 26 (IBM Corporation, New York USA).

While 2 measures were only requested twice weekly when stable participants were able to enter data as frequently as they liked, however for the overall analysis data were capped at twice a week and extra data were not included. For analysis of the data around an exacerbation the number of measures in the seven days preceding the exacerbation – defined as the start date of antibiotics – were compared to the uncapped overall usage of the participant.

Coding for the free text 'What's new?' comments was completed using Nvivo 11 version 1.4.1 (QRS international, Cheshire, UK).

1.23 Results

1.23.1 Arm 1 Smart app and home monitoring

1.23.1.1 Participant withdrawals

10 participants formally withdrew (6.9%) at a median (IQR) of 68.5 days (34.5-118) into the study. Reasons provided included: becoming bored and no longer wanting to continue (n=1), families becoming frustrated with the equipment (n=2), in particular the activity monitor, reporting of inappropriate internet use by the participant (n=1), and a family bereavement (n=1). The other 5 participants failed to provide reasons.

1.23.1.2 Completeness of requested data over the 6 months

Data from 144 participants were included in the analysis. Median (IQR) requested data completion for the whole cohort over the six-month study period was 40.1% (13.6-69.9%). Twenty-one (14.6%) participants completed ≥ 80% of the requested data and 42 (29.2%) participants completed ≥60% of the requested data over the six-month study period. However, when divided by age group those aged 12 and over completed significantly less than the other two age groups (p=0.0002, Table 0-1).

There was no significant difference between the total amount of requested measures completed between males and females (40% [10.5-67.9%] compared to 40.4% [14.6-70.7%] p=ns).

Table 0-1 Percentages of requested measures collected over the six-month study period for the cohort as a whole and by three different age groups Reproduced with permission from Edmondson et al (388).

Total measures completed in 6 months by	N number	Percentage of measures completed Median (IQR)
The whole cohort	144	40.1% (13.6-69.9%)
2–5-year-olds	45	54.4% (20.5-77%)
6–11-year-olds	68	45.8% (27-71.6%)
12 years and over	31	15.6% (9.8-30%)

There was no significant difference seen in measures completed by participants during their 6-month study period when divided by study site (p=ns, Table 0-2, Figure 0-1).

Table 0-2 Percentage of requested measures collected over the six-month period by different study site

Total measures completed in 6 months by site	N number	Percentage of measures completed Median (IQR)
Royal Brompton Hospital	22	41.9% (16.6-73.4%)
Great Ormond Street Hospital	20	28.9% (11.8-47.7%)
Alder Hey Children's Hospital	20	51.2% (8.2-78.5%)
Great North Children's Hospital	18	21.8% (9.7-56.1%)
North of Scotland Paediatric Respiratory Network	19	49.5% (25.9-55.8%)

Royal Alexandra Children's Hospital	13	40.1% (15.9-77.6%)
IWK Health Centre	13	34.3% (20.8-72.9%)
Children's Hospital, London Health Sciences	19	25.9% (11.3-77.4%)

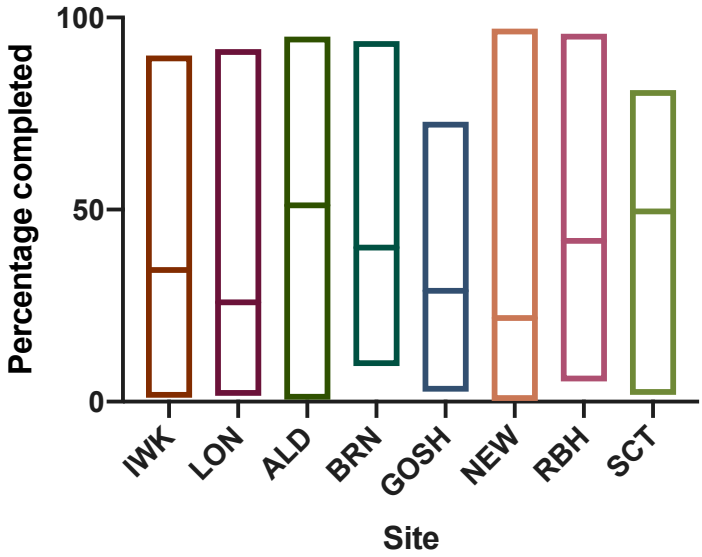


Figure 0-1 Percentage of requested data collected over the six months by study site as medians (minimum and maximum) Abbreviations : IWK- IWK Health Centre, LON - Children's Hospital London Health Sciences, ALD - Alder Hey Children's Hospital, BRN – Royal Alexandra Children's Hospital, GOSH – Great Ormond Street Hospital, NEW – Great North Children's Hospital, RBH – Royal Brompton Hospital, SCT – North of Scotland Paediatric Respiratory Network.

Most of the measures received (63.5%) were recorded as being entered by the participant themselves rather than by a parent.

1.23.1.3 Multiple regression analysis

Multiple regression analysis, using a stepwise approach, was performed to see whether percentage completion of home monitoring data related to age, sex, ethnicity, CFTR genotype, maternal and paternal education, FEV_1 % predicted at the start of the study, distance from site and social

deprivation scores. The two variables that statistically predicted percentage completion of home monitoring data were age and paternal education, $F(2,71)=7.98$, $p<0.001$. Increased levels of paternal education were positively associated with usage ($p=0.003$) and age was negatively associated with usage ($p=0.01$).

1.23.1.4 Device usage over whole study

The percentage of completed measures varied for different devices; the two measures requested twice weekly (weight, spirometry) demonstrating the highest completion rates. Sleep disturbances were completed significantly less ($p= <0.0001$, Table 0-3) than the other daily measures.

Table 0-3 Percentage completed of each measure over the 6-month study period. Abbreviations IQR - Interquartile range Reproduced from Edmondson et al (388).

Measure	Requested	Percentage completed over 6 months Median (IQR)
Lung function	Twice a week	58.3% (29.2-100%)
Weight	Twice a week	50% (22.9-89.6%)
Appetite, breathlessness, cough, tiredness and wellness	Daily	44.2% (13.7-75.1%)
Sleep Quality	Daily	44% (13.7-75.2%)
Sputum volume	Daily	43.1% (13.7-75%)
Heart rate and oxygen saturations	Daily	41.2% (12-77.7%)
Temperature	Daily	39.6% (11.4–73.4%)
Activity	Daily	31.5% (14-78.5%)
Respiratory Rate	Daily	26.2% (4.4-68.7%)
Sleep disturbances	Daily	19.2% (2.2-63%)

When looking at data entry per participant the pattern (as seen in Figure 0-2) was that if a participant signed into the app to complete a measure, they tended to complete most measures at that time point.

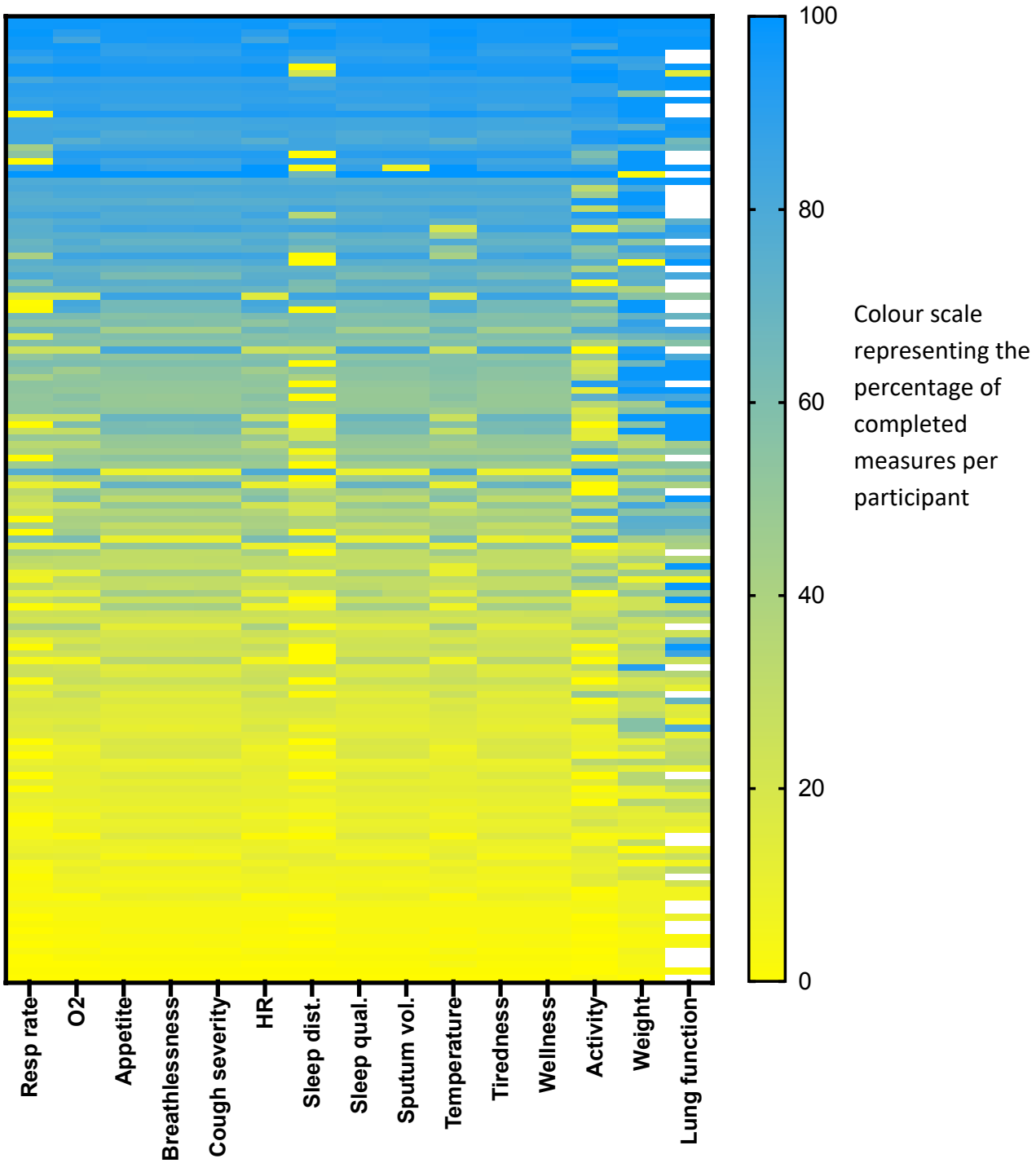


Figure 0-2 A heat map showing the total percentage of data entered for each participant for each measure. Each row on the heat map accounts for one participant and each column is a requested measure with the percentage scale on the right-hand side. The bluer the cell the higher the percentage of completion for the requested measure per participant. The white squares in the lung function column symbolise participants who did not have a home spirometer.

1.23.1.5 Measures automatically uploaded by the device compared to those manually entered

The Bluetooth devices gave the participant the option to enter the data from the device screen manually if the device did not sync correctly with the app. The activity monitor used in CLIMB-CF did not have a display on the device showing step count however step counts from alternative activity trackers could be manually entered. Most readings throughout the study were entered via the device Bluetooth connection (Table 0-4).

Table 0-4 Total number of readings over the study period and whether the reading was entered via the device Bluetooth connection or manually by the participant

Measure	Total no of readings	Total no of device readings (%)	Total no of manual readings (%)
Lung function	3577	2671 (74.6%)	906 (25.3%)
Weight	4335	3551 (81.9%)	784 (18.1%)
Heart rate and oxygen saturations	11084	10317 (93.1%)	767 (6.9%)
Temperature	10807	9126 (84.5%)	1681 (15.5%)
Activity	9842	8644 (87.8%)	1198 (12.2%)

1.23.1.6 Number of unreliable measures entered

The previous analysis included any registered reading from the remote monitoring regardless of the reading registered. For a selection of the measures that could either come from a device or be manually entered the quality of the data were explored (Table 0-5). For the purpose of analysis, measures outside of the below stated ranges were used:

- Heart rate readings outside 50 – 200 beats per minutes

- Oxygen saturations outside 80-100 percent
- Temperature outside 34-41 degrees
- Respiratory rate outside of 10-80 breaths per minute
- Weight outside 10 to 110 kilograms

Table 0-5 The number of unreliable readings registered per measure and the abnormal values registered and whether they were manually entered or entered by the device.

Measure	Total number of readings	Number of unreliable readings n (%)	Unreliable measures manually entered n(%)	Abnormal values registered
Heart rate	11084	186 (1.7%)	4 (2.2%)	1,18,31,41, 42, 44, 45, 46, 47, 48, 49, 201, 203, 205, 206, 220, 221, 255, 303, 317, 331, 511, 784, 949, 1005
Oxygen saturations	11084	134 (1.2%)	4 (3%)	0, 58, 62, 72, 73, 74, 75, 76, 77, 78, 79, 113, 123, 127, 5694
Temperature	10807	39 (0.4%)	34 (87.2%)	3.68, -83521.41, 3.72, 10, 24.2, 27, 32.1, 32.7, 32.8, 33.4, 33.8, 42.1, 42.1, 42.2, 42.2, 254, 359, 361, 362, 363, 364, 365, 366, 367, 368, 370, 372, 543, 982, 995, 3506, 3538, 11355
Weight	4335	36 (0.8%)	28 (77.7%)	2.17, 2.7, 3.21, 4.1, 5.3, 7.6, 8.4, 8.9, 9.6, 9.7, 110, 110.2, 110.9, 111, 111.8, 129.4, 130, 130.8, 131.2, 131.8, 132.2, 132.5, 132.6, 157.85, 221, 239, 240, 241, 246, 311, 331, 345.9, 412, 870
Respiratory Rate	9123	96 (1.1%)	N/A	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 81, 82, 84, 87, 88, 89, 93, 95, 96, 98, 99,100, 104, 105, 108, 129, 195, 201, 240, 244, 265, 283, 288, 296, 298, 329, 347, 868, 2222, 48464646, 56699888

1.23.1.7 Lung function usage around times of pulmonary exacerbation

Lung function usage around pulmonary exacerbations is explored in more detail in Chapter 5.

1.23.1.8 Arm 2 - Web based symptom diary usage

Data entry in Arm 2 via the web-based symptom diary was only a median (IQR) of 14 (2-50) % complete for the study period, significantly lower than data entered via the app in Arm 1 (p= 0.003 Table 0-6). Those participants aged ≥ 12 years completed very little data during the study period, median 0 (0-6) %. Due to the poor completion percentage of the web-based symptom measures it was concluded data collection via this interface was not feasible and no further analysis was undertaken.

Table 0-6 Percentage of data entered over the six months onto the web page by participants recruited to Arm 2 shown as the whole cohort and divided by age group

Total web measures completed in 6 months by	N number	Percentage of measures completed Median (IQR)
The whole cohort	34	14% (2-50%)
0-5 yr olds	16	22% (2-57%)
6-11 yr olds	13	29% (4-51%)
12 yrs and over	5	0% (0-6%)

1.23.1.9 Siblings

There were five sets of 2 siblings in Arm 1 of the study. The median (IQR) percentage of measures completed was 39.45% (7.7-57.2%) which was not significantly different from the whole cohort. When looking at the five sets individually there was no significant difference between the amount of completed data by sibling. As a family unit all five sets were consistent in the amount of data completed.

1.23.2 Completeness of requested data by month into study

Data completion in the study was not stable over the six-month study period, peaking at month 2 (54.7%) and then dropping significantly by month 6 (18.5%) (p=<0.0001). Participants aged 12 years and over showed a sudden drop off after month two which was not as pronounced in the other two age groups, it is unclear if this was impacted by the addition of home sample collection (Figure 0-3). There was, however, a decrease in data collection of the cohort, as a whole, after month 2, with data completeness falling to below that of month 1 after month 4.

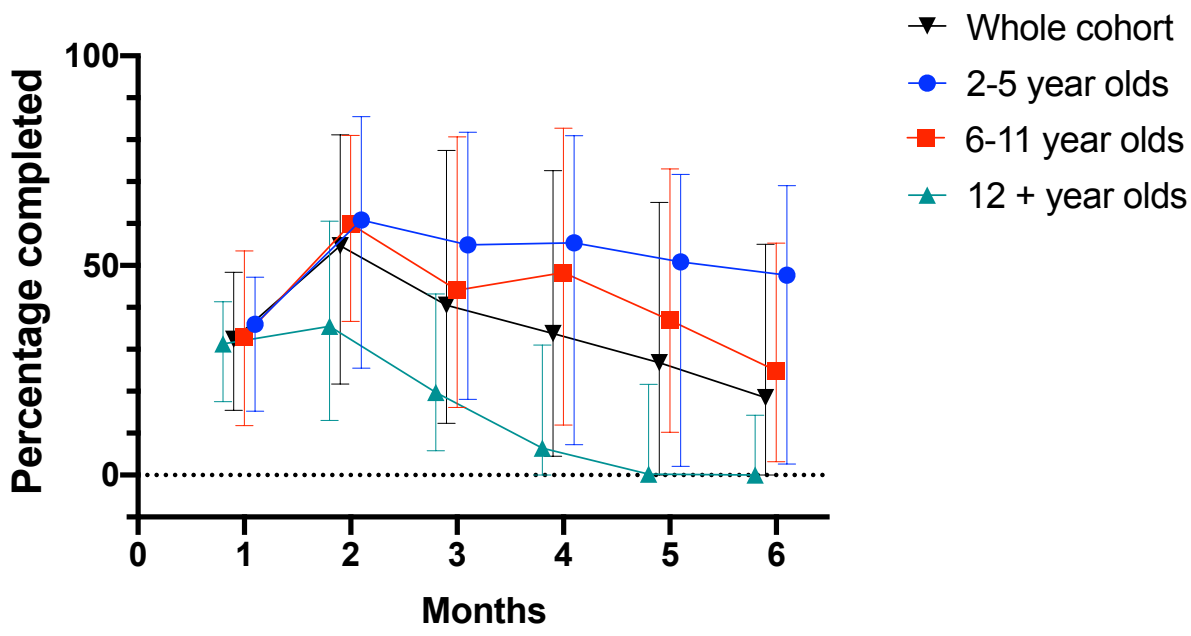


Figure 0-3 The percentage of completed data per month of the study for the whole cohort and the three different age groups (388)

1.23.2.1 Participant pattern of usage

Individual participant pattern of usage varied over the six-month study period. Some participants engaged with the study throughout the entire period and were relatively consistent with their data entry. Other participants failed to engage from the beginning. However, a selection of participants continued to collect data throughout the six months but self-modulated, possibly to a pattern that fitted with their lifestyles rather than daily as requested (Figure 0-4).

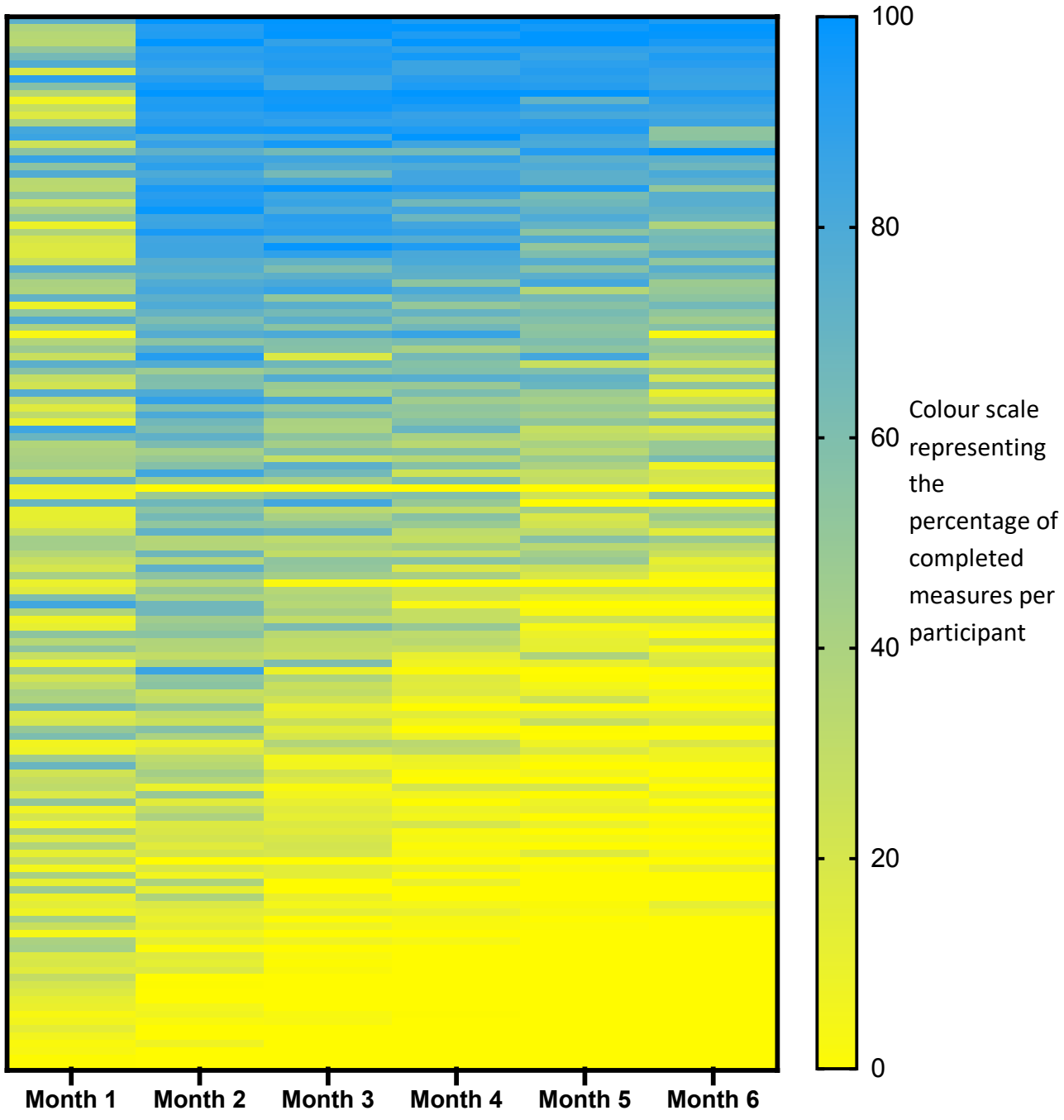


Figure 0-4 A heat map showing the percentage of requested data collected by each month of the study. Each row represents a participant, each column is a month of the study with the percentage scale on the right-hand side of the heat map

When looking at days of the week data were entered, it was distributed throughout the week with slightly less data being completed on a Friday or a Saturday (Table 0-7) (ns).

Table 0-7 The percentage of data completed by day of the week over the 6-month study period

Day of the week	Percentage of daily measures completed on that day
Monday	14.8%
Tuesday	15.2%
Wednesday	15.1%
Thursday	14.8%
Friday	13%
Saturday	12.5%
Sunday	14.6%

Figure 0-5 shows the percentage of completed data received for each month of the study by both males and females with no significant sex difference.

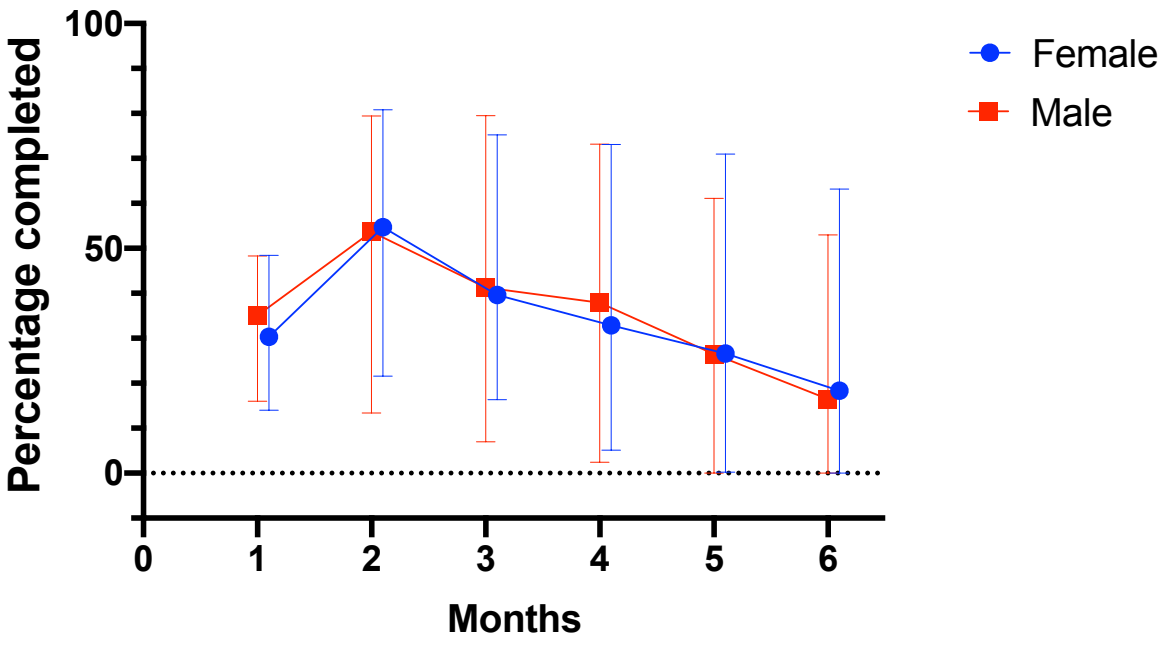


Figure 0-5 Data completion by males and females by month of study

1.23.2.2 Completeness of data over the study period by measure requested

Over the 6-month study period the completeness of data per individual measure generally tracked the same pattern as the monthly total data. The two measures requested twice weekly were proportionately recorded more consistently through the study. Sleep disturbances was consistently one of the least recorded measures each month and activity recording declined sharply as the study went on (Figure 0-6).

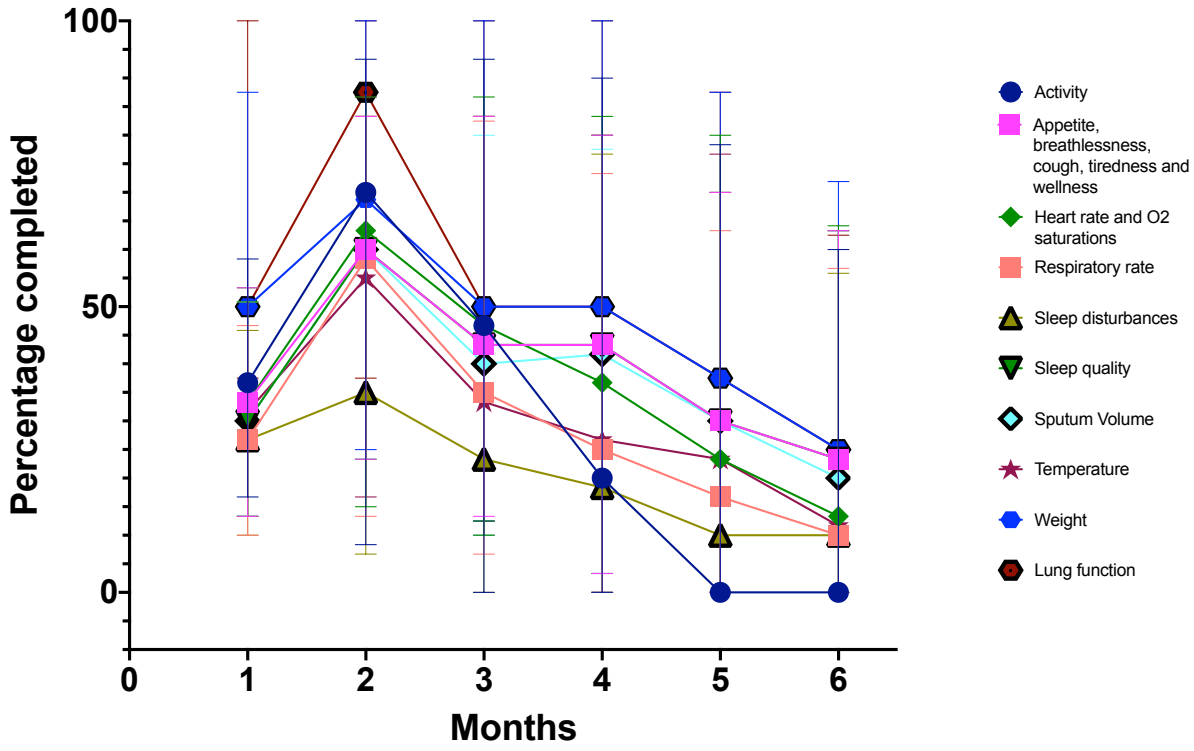


Figure 0-6 Percentage of individual completed measures by month. Measures with identical monthly usage have been combined if appropriate.

The completeness of data over the six-month period was not affected by whether the data could be entered directly into the app itself or whether it required an additional piece of equipment (Figure 0-7).

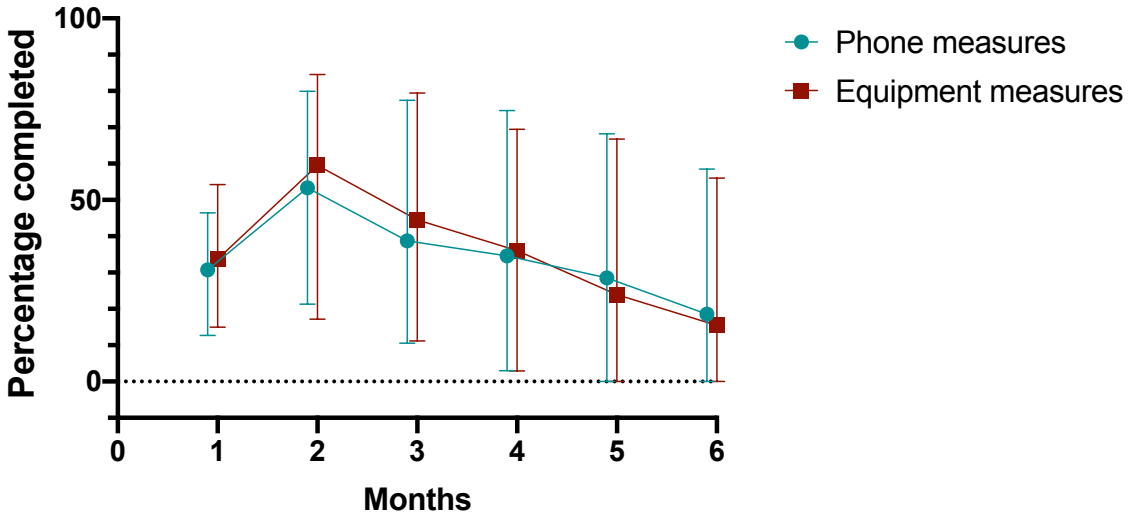


Figure 0-7 The percentage of requested measures completed per month of study by whether the answer could be directly entered into the app or whether the data required an additional piece of Bluetooth equipment

1.23.2.3 Completeness of data and distance from study site

There was no correlation between the distance from a participants' study site and the amount of data they completed.

1.23.2.4 'What's new?' types of data entry

Participants were not routinely requested to enter data into the 'What's new?' section. During the study period 2142 codable free text entries were entered from 122 participants. These were coded into four categories, clinical, equipment, exercise and social (Figure 0-8). A small number of entries were coded into more than one category (Table 0-8). Most entries were coded as clinical or were relating to study equipment, however a substantial number of entries, in particular by participants, where not related to their health, were focused on other important aspects of their lives. The most frequent words used can be seen in Figure 0-9.

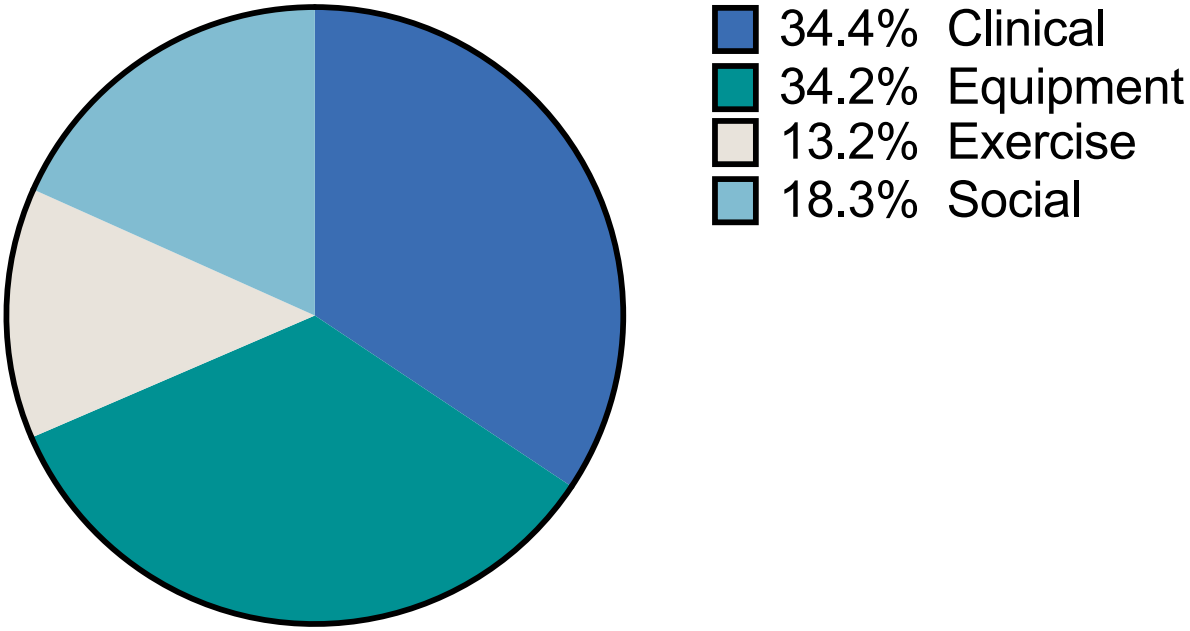


Figure 0-8 Percentage of comments in the 'What's new?' section coded to each category.

Table 0-8 Number of entries coded by more than one category for the 'What's new?' section

	Clinical	Equipment	Exercise	Social
Clinical		21	3	5
Equipment	21		11	42
Exercise	3	11		3
Social	5	42	3	



Figure 0-9 A word cloud showing the most frequent words used in the 'What's new?' section of the CLIMB-CF app. The larger the word the more frequently the word was used.

When looking specifically at the equipment comments 72% of them related to the activity monitor and issues associated with the piece of equipment such as it not syncing correctly with the app or participants forgetting to wear it for the day. Other comments mentioned difficulty uploading data on hospital WIFI or while on holiday.

Table 0-9 shows example comments coded as clinical or social from the 'What's up?' section of the app.

Table 0-9 Example comments coded to clinical or social categories from 'What's up?' section of the CLIMB-CF app. Comments altered to anonymise otherwise copied verbatim

Clinical comments
very ill night of 22nd right through till today. Therefore no measurements taken. No temp, vomiting and extreme pain below his chest which kept him up all night.
Sent home from school tired and whingy. Needing inhaler more as breathless. Full of cold.
Feeling very sick and I have woken up with bad joint pains in my ankles, my right knee my knuckles, my wrists, my elbows and shoulders
Still can't do lung function because productive cough
Sorry I haven't been doing it because I have been so tired
Phoned the hospital this morning as E has a productive cough, especially bad first thing in the morning. His appetite was also slightly reduced yesterday which is very rare for him. We are sending off a cough and nasal swab today (as he also has a heavy cold) and in the meantime the hospital has prescribed co-amoxiclav which he has started this evening.

Social comments
It's my birthday day
I'm going to a sleepover at a friend's house
school there is a talent show called e's got talent and I'm entering with my friends and we're doing cheerleading and they're lifting me up....hope we get through audittions
We're going on holiday 1 hour!!!!!! #YAY! I can't wait!!!
I also played with my guinea pigs in the afternoon. It was so much fun then and I did a little bit of dancing
Last night my big toy unicorn that is bigger than me pushed me out of bed then I pushed her out of bed

1.23.3 **The use of reminders**

I was unable to interrogate the data to explore whether participants had used the daily alarm feature, but I could explore whether participants had set reminders. Sixteen participants set reminders, 9 of whom sent reminders for the evening. Five set multiple reminders (each participant could set up to three separate reminders) and one participant changed the timing of their reminders 3 times during the study period. Half of the reminders were set to go off twice a week and the other half were set to go off every day. There was no significant difference in the percentage of completed measures between those participants who had set reminders and those who did not utilise the function.

1.23.4 **Home sample collection**

To identify a possible sample type for exploratory biomarker work, one year into the study I reviewed the home samples received from participants at RBH. 80% of the RBH participants were actively collecting urine samples, 70% were collecting throat swabs, 20% were collecting DBS (75% of these people had CF related diabetes, so were used to finger-prick samples), 20% were collecting nasal secretions and 15% were collecting sputum.

By the end of the study, I had received 2837 home samples from 106 (73.6%) participants, median (IQR) of 3 (2-3) sample types per person. Only 4 participants provided at least one sample of each sample type. Urine was the most collected sample type, making up 34% of all samples received. In terms of the other sample types, throat swabs comprised 33%, nasal secretions 23%, sputum 7% and DBS only 3%.

Urine samples were provided by 89 people with 961 samples over the 4-month period (mean of 10.8 samples per participant, SD 6.2). 86 people provided 918 throat swabs, 69 participants provided a total of 663 nasal secretion samples and 29 participants provided 204 sputum samples. Only 12 participants out of the 106 provided DBS samples although 91 samples were received (average of 7.6 samples per participant).

Home sample quality

DBS home sampling did also present an issue with quality. Below are examples of home DBS cards received during the study. For a DBS sample to be deemed to be of sufficient quality to be of use the blood spot must fill the dotted lined circle and should have no overlapping blood spots within it (389). This was explained to participants during their sample collection training if they expressed a wish to trial DBS sampling at home. The quality of the home samples received would need to be improved in order to meet the universally accepted criteria (Figure 0-10) (389).

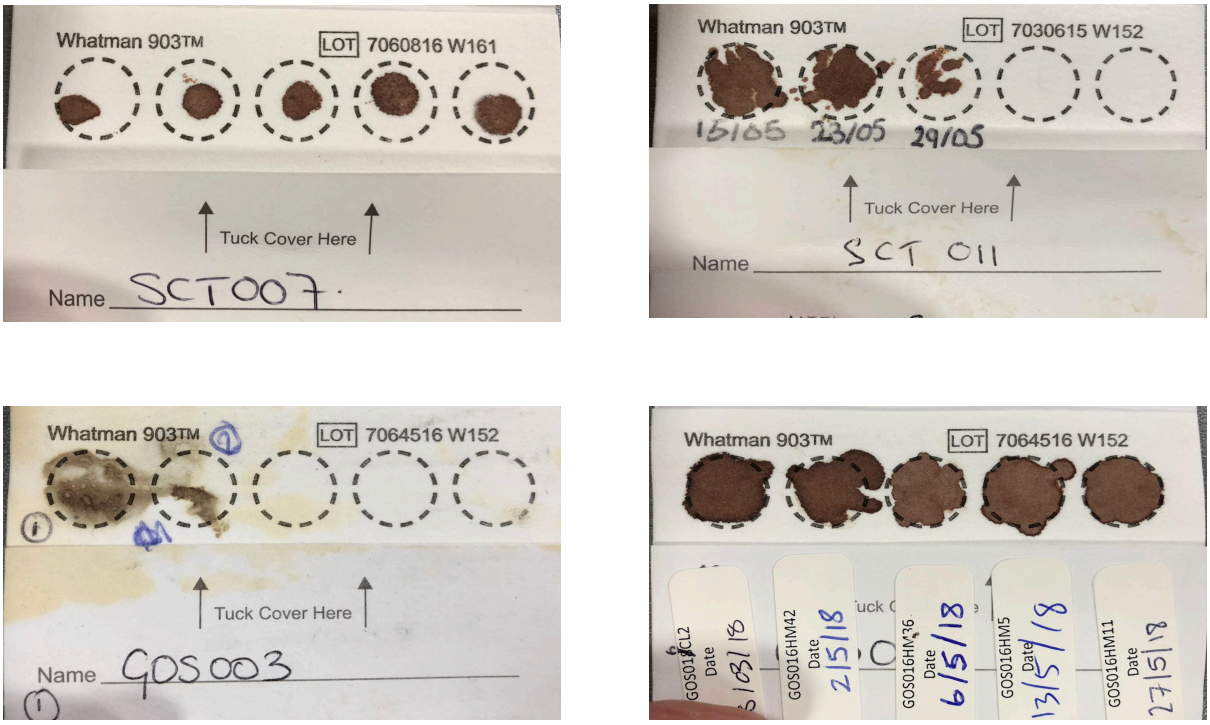


Figure 0-10 Examples of the quality of dried blood spot cards received during the 6-month study period from 4 separate participants

In view of the reported home sample numbers received a year into the study and ongoing discussions with a collaborator Mologic (Bedfordshire, UK), the decision was made to focus on urinary biomarkers. I would explore a biomarker in house and send samples Mologic to undergo testing on a wider biomarker panel, this will be discussed further in chapter 7. Another reason for this choice was that while blood sampling was viewed as minimally invasive, the quality of the samples received and the potential needle related anxiety connected with blood sampling made exploring a non-invasive sample type appealing (390).

1.23.5 **Acceptability of Arm 1 – Smart app and home monitoring**

We received acceptability questionnaires from 120 parents (94%) of the 128 expected (after accounting for the participants who withdrew and parents of siblings). They were completed by one parent per participating family. There were five sets of siblings in the study and their parents

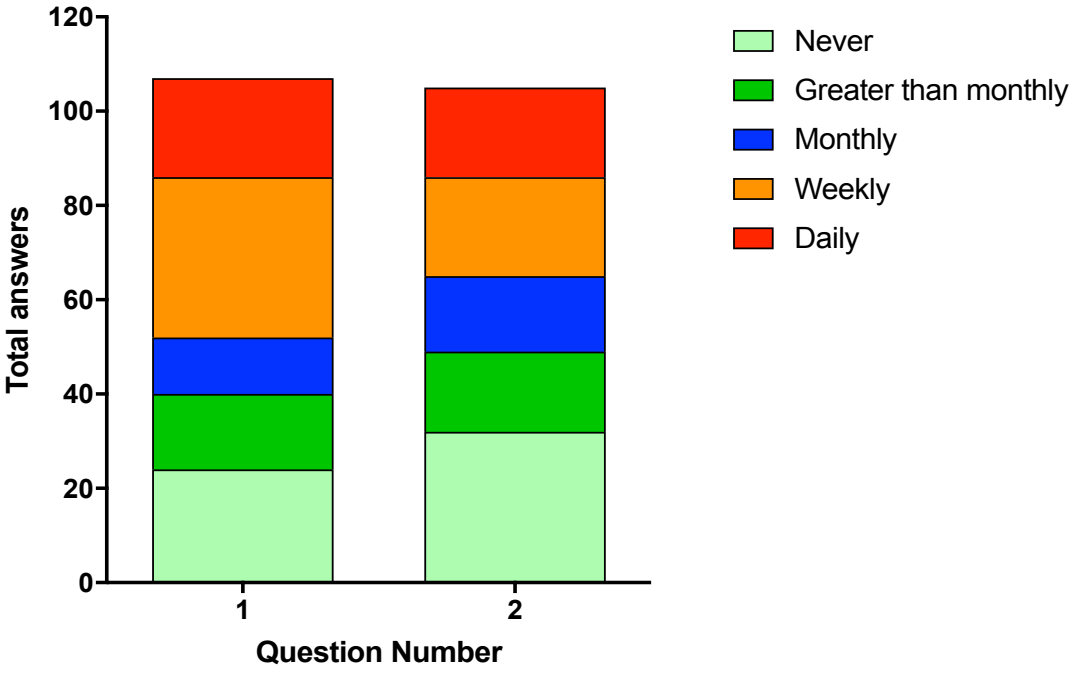
completed only one acceptability questionnaire. We received 31 (84%) acceptability questionnaires from participants aged 12 and over.

1.23.5.1 Parent and 12–17-year-old acceptability questionnaire results

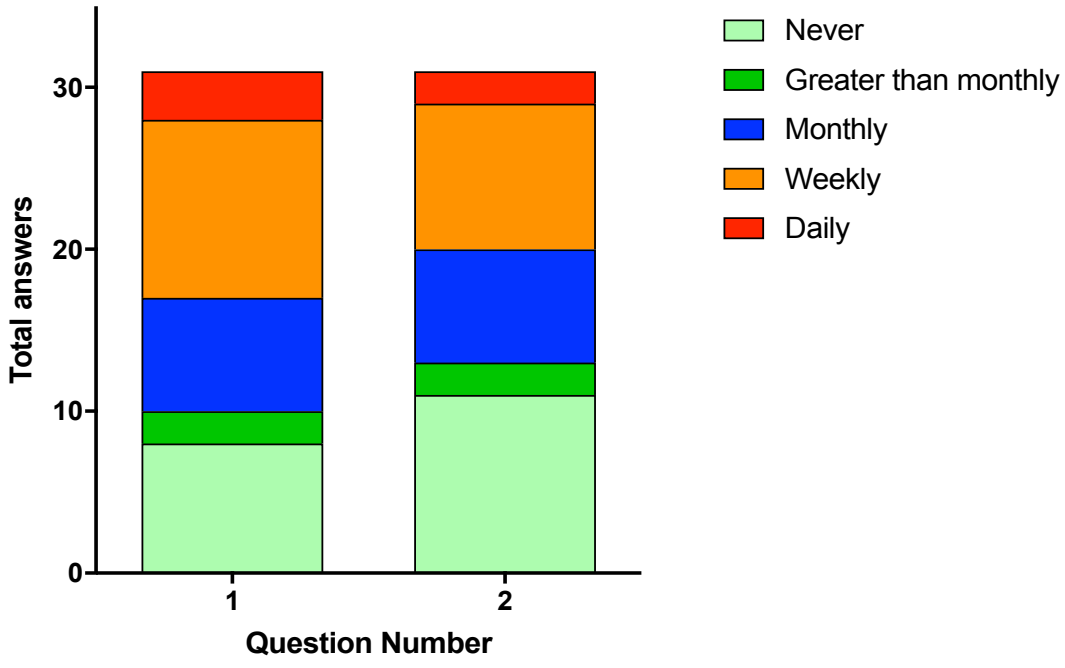
22% of parents and 25% of participants aged ≥12 reported never having a problem with measuring results compared to 29.6% and 35.4% respectively who reported never having a problem uploading results to the CLIMB-CF app (Figure 0-11). However, 19.4% of parents reported having problems daily with measuring results, this was lower (9.7%) in participants ≥12 years. There was no significant difference in total data completion between those who reported daily problems with either measuring results or data upload when compared to those who reported never having a problem with either for parents or adolescents.

Questions

1. How often did you have problems with measuring results?
2. How often did you have problems with uploading results?



Panel a



Panel b

Figure 0-11 CLIMB-CF acceptability questionnaires. Panel a shows parents responses and panel b shows the participants aged ≥12 responses to the two questions asked

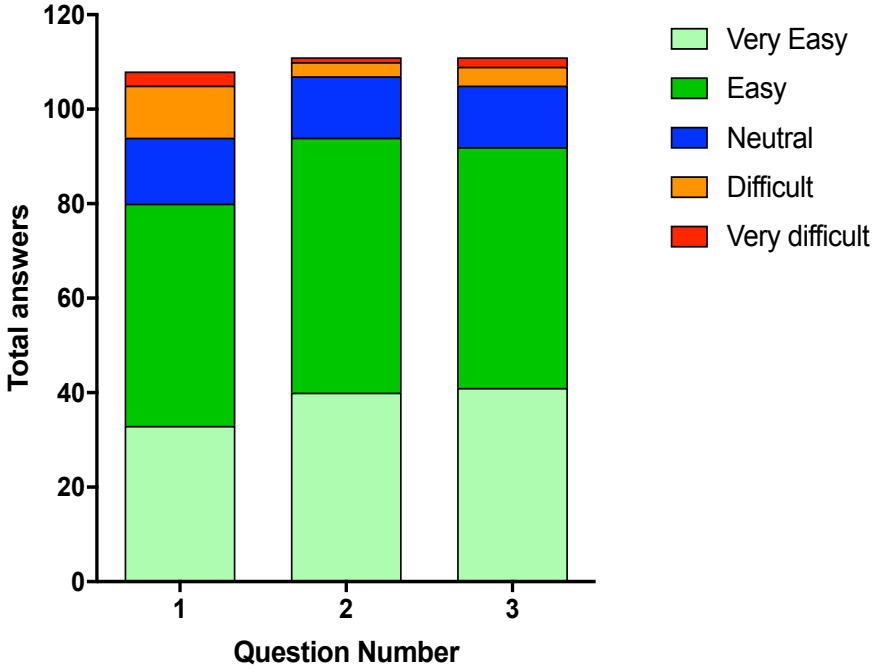
14 parents reported difficulties using the monitoring devices, 4 reported difficulties with the smart phone and 6 parents reported difficulties with the app, however only 3 participants aged ≥ 12 reported difficulties using the phone and only 1 reported difficulty with the app (Figure 0-12).

106 parents and 28 participants aged ≥ 12 answered the question regarding how much time the home monitoring took per day. The parents reported a median (IQR) time of 10 (7.5-15) minutes and the participants aged ≥ 12 reported the time taken to be 10 (8.1-15) minutes.

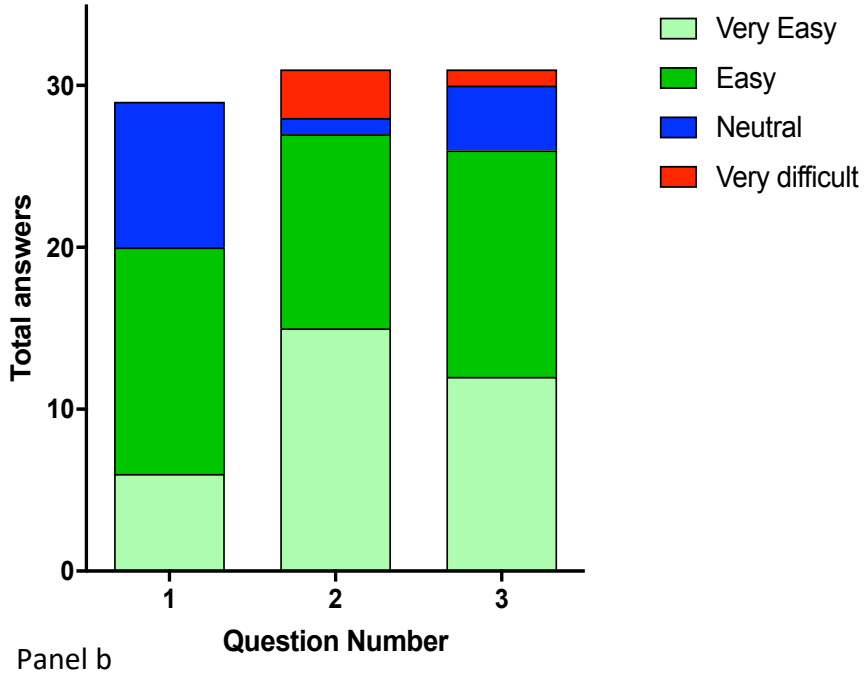
Most of the parents would prefer to complete home monitoring weekly and participants ≥ 12 years either every other day or weekly. Only a small percentage of both groups would like to complete home monitoring daily (Figure 0-13).

Questions

1. How did you find using the monitoring devices?
2. How did you find using the Smart phone?
3. How did you find using the Smart app?



Panel a



Panel b

Figure 0-12 CLIMB-CF acceptability questionnaires. Panel a shows parents responses and panel b shows the participants aged ≥12 responses to the three questions asked

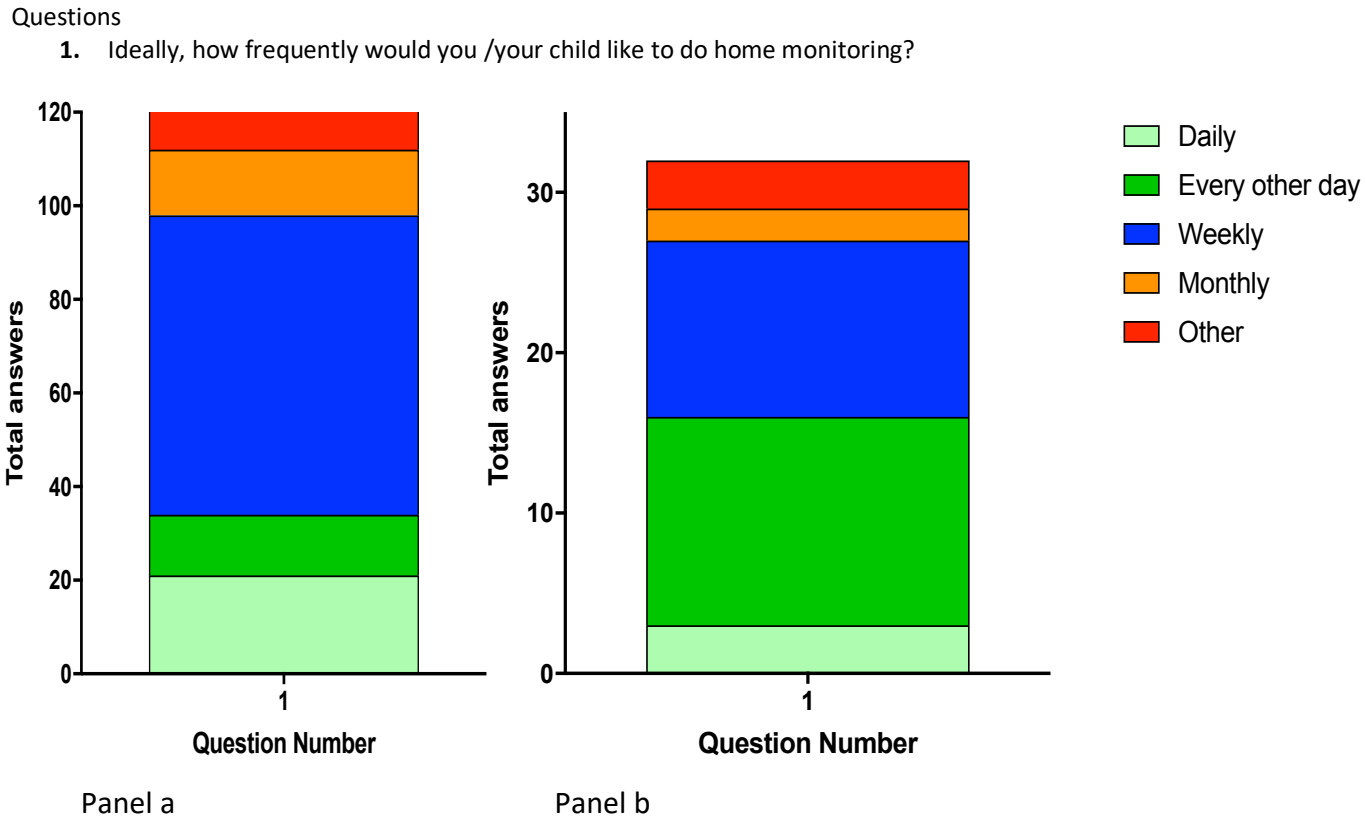


Figure 0-13 CLIMB-CF acceptability questionnaires. Panel a shows parents responses and panel b shows the participants aged ≥12 responses to the question asked

Wellness questions and oximetry were regarded to be the most acceptable measures to complete and spirometry and activity using the activity monitor were the least acceptable for both parents and participants ≥ 12 years.

When asked about the extent home monitoring interfered with usual daily activities, those parents (64%) who answered 'not at all' or 'slightly' interfered completed more measures over the six months than those parents who reported that home monitoring had a 'moderate' or 'extreme' interference with their daily activities (p=0.05). While a similar trend was seen in participants ≥ 12 years of age, this was not statistically significant, possibly secondary to the overall lower data completion in this group (Table 0-10).

Parents and participants were also asked their perceptions of usefulness. Those parents (71.6%) who responded, 'very helpful' or 'helpful' completed more data than parents who thought it was 'unhelpful' or 'completely unhelpful' (p=0.04). This pattern was not replicated in the participants ≥ 12 years (Table 0-10). Over the 6-month period, data entry from participants who felt it was not helpful declined from month 2 onwards (Figure 0-14).

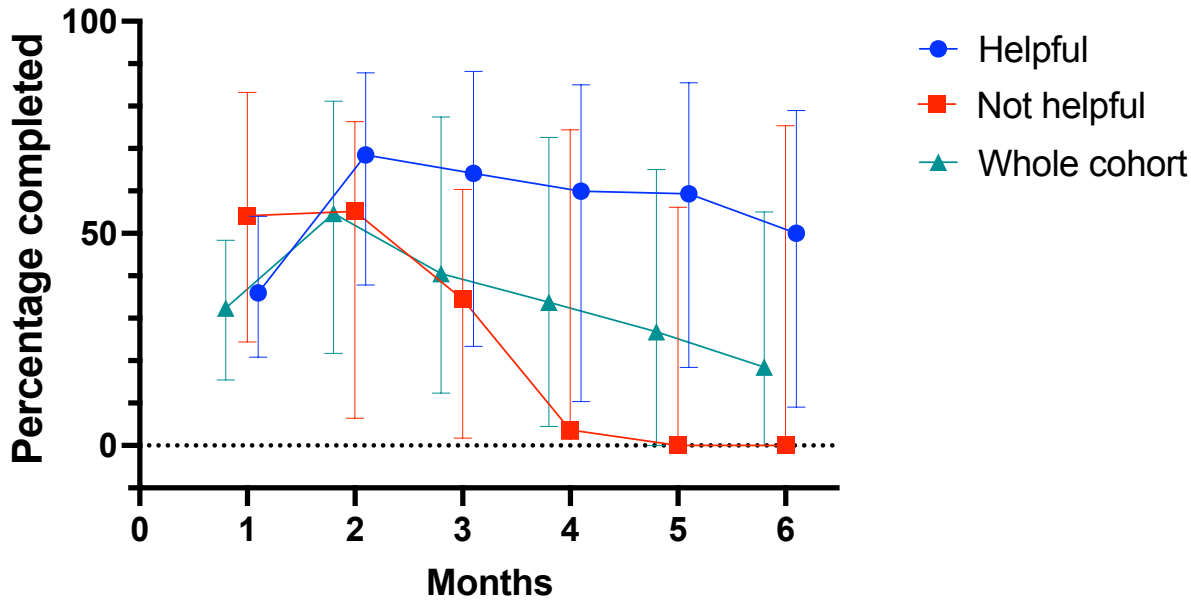


Figure 0-14 Data completion over the 6-month period by whether the participant reported remote monitoring was helpful in monitoring their health at home.

Table 0-10 Combined results from questions from the acceptability questionnaire and percentages of completed measures from parents and participants ≥ 12 years Reproduced with permission from Edmondson et al (388)

	Parent (N= 120)	Participant aged 12 years and over (N=31)
To what extent did daily home-monitoring interfere with your usual activities?		
Not at all	29 (24.2%)	6 (19.4%)
Slightly	48 (40%)	17 (54.8%)
Somewhat	21 (17.5%)	5 (16.1%)
Moderately	13 (10.8%)	3 (9.7%)
Extremely	9 (7.5%)	0 (0%)
Percentage of measures completed if answered 'Not at all' or 'slightly' Median (IQR)	52% (28.3-77.6%)	37.8% (14.5-73.2%)
Percentage of measures completed if answered 'Moderately' or 'Extremely' Median (IQR)	29.9% (9.2 – 74.5%)	9.6% (5.6-22.3%)
How helpful did you find being able to monitor your/your child's breathing, activity and weight at home?		
Very helpful	36 (30%)	7 (22.6%)
Helpful	50 (41.7%)	9 (29%)
Neutral	25 (20.8%)	9 (29%)
Unhelpful	1 (0.8%)	4 (13%)
Completely unhelpful	5 (4.2%)	1 (3.2%)
Did not answer	3 (2.5%)	1 (3.2%)
Percentage of measures completed if answered 'Very helpful' or 'helpful' Median (IQR)	48.3% (21.7-79.1%)	19.6% (8.1-44.5%)

Percentage of measures completed if answered 'completely unhelpful' or 'completely unhelpful' Median (IQR)	29.9% (7-36.9%)	20.4% (10.2-51.8%)

Parents and participants ≥ 12 years were asked to mark on a scale the impact home monitoring had had on their quality of life and anxiety levels. Most parents felt that home monitoring had had no impact on their or their child's quality of life or anxiety levels. This finding was replicated in the participants aged >12 years (Figure 0-15 & Figure 0-16).

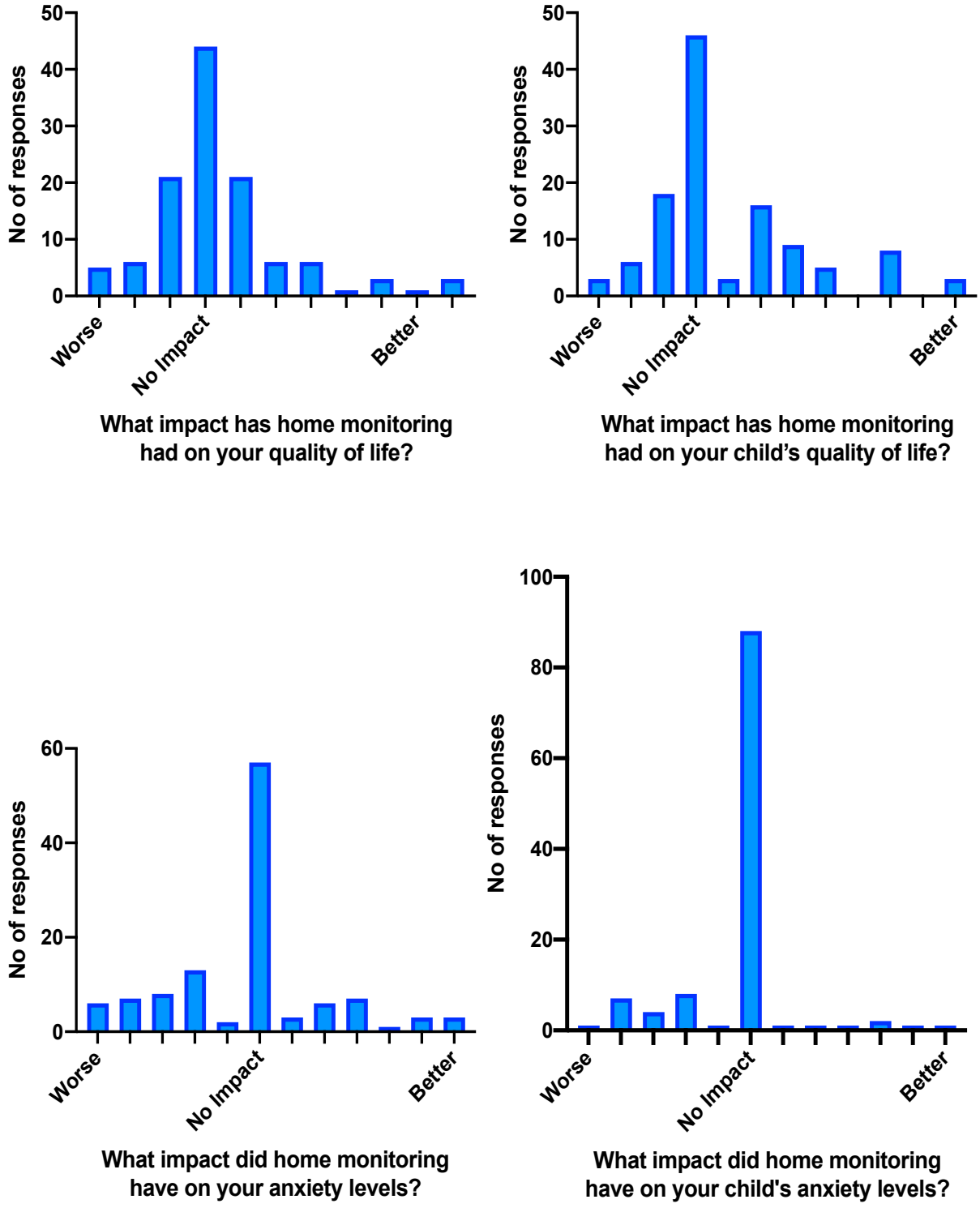
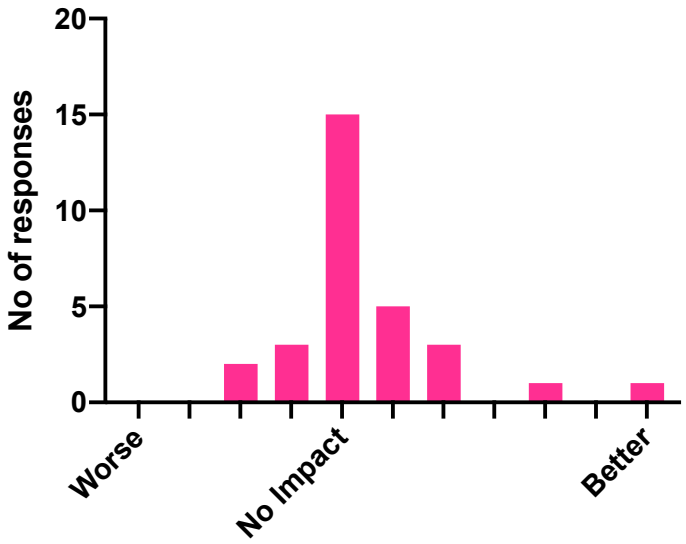
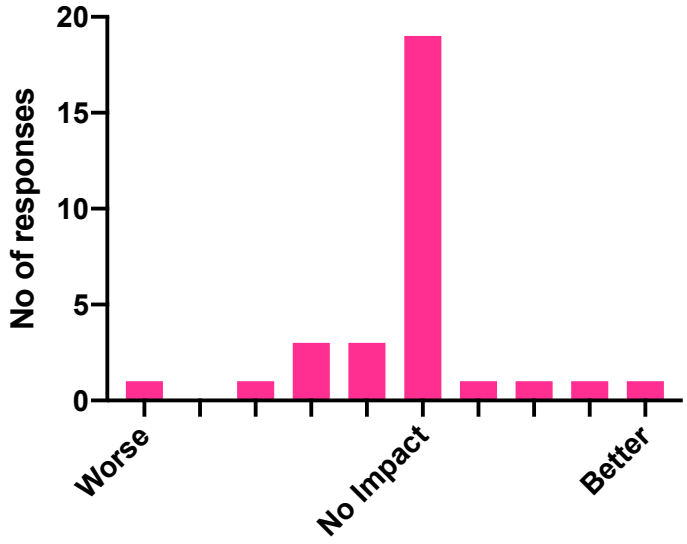


Figure 0-15 Results to the questions about the impact home monitoring had on quality of life and anxiety for parents and their children



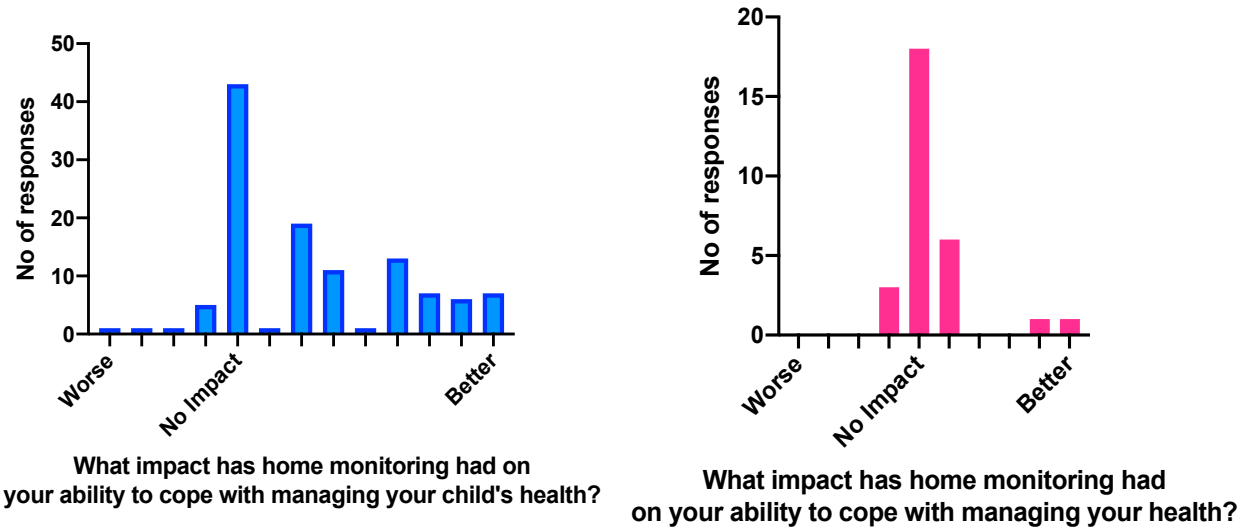
What impact has home monitoring had on your quality of life?



What impact did home monitoring have on your worry levels?

Figure 0-16 *Results showing the impact home monitoring had on quality of life and worry levels for participants aged 12 years and over*

When asked about the impact home monitoring had on the ability to either manage their child's health or their own health, the majority of respondents answered that it had no impact or a better impact than not carrying out home monitoring (Figure 0-17).



Panel a Panel b

Figure 0-17 *Panel a shows results from the parent acceptability questionnaire exploring the impact home monitoring has on the ability to manage their child's health. Panel b shows the results from participants aged 12 years and over and the impact home monitoring had on their ability to manage their health*

21 (4.7%) parents reported that home monitoring had a moderate or extreme impact on quality of life. Of those parents 62% reported that home monitoring had no impact on the anxiety levels of their child and 38% reported it had no impact on their anxiety levels (

Figure 0-18).

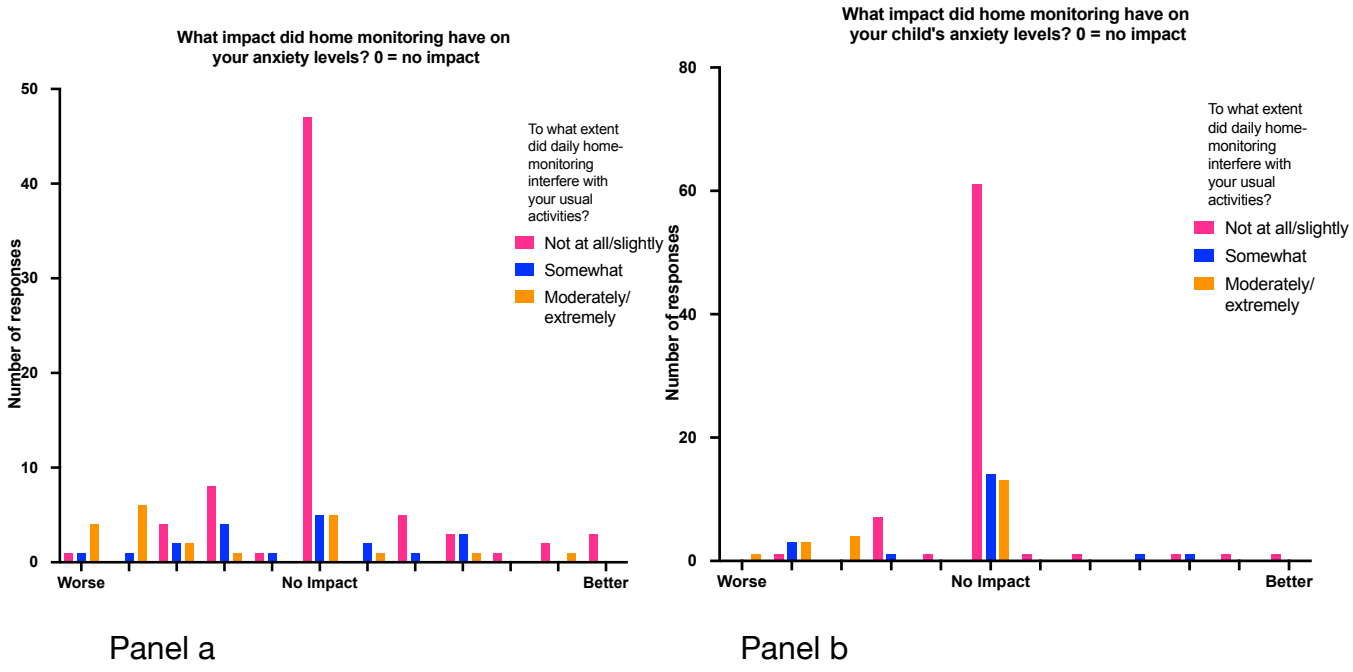


Figure 0-18 The combined results for the questions asking about the extent of interference from home monitoring and the impact home monitoring had on parental (a) and child (b) anxiety levels from the parental acceptability questionnaire

Despite some parents reporting that home monitoring had a moderate or extreme interference to their daily lives, they still reported that it improved their ability to cope with managing their child's health (Figure 0-19). Parents were also asked if they would prefer to use home monitoring and attend clinics less frequently. 36.5% stated definitely or probably and 21% were undecided, 42.5% would prefer to still attend clinics with the same frequency.

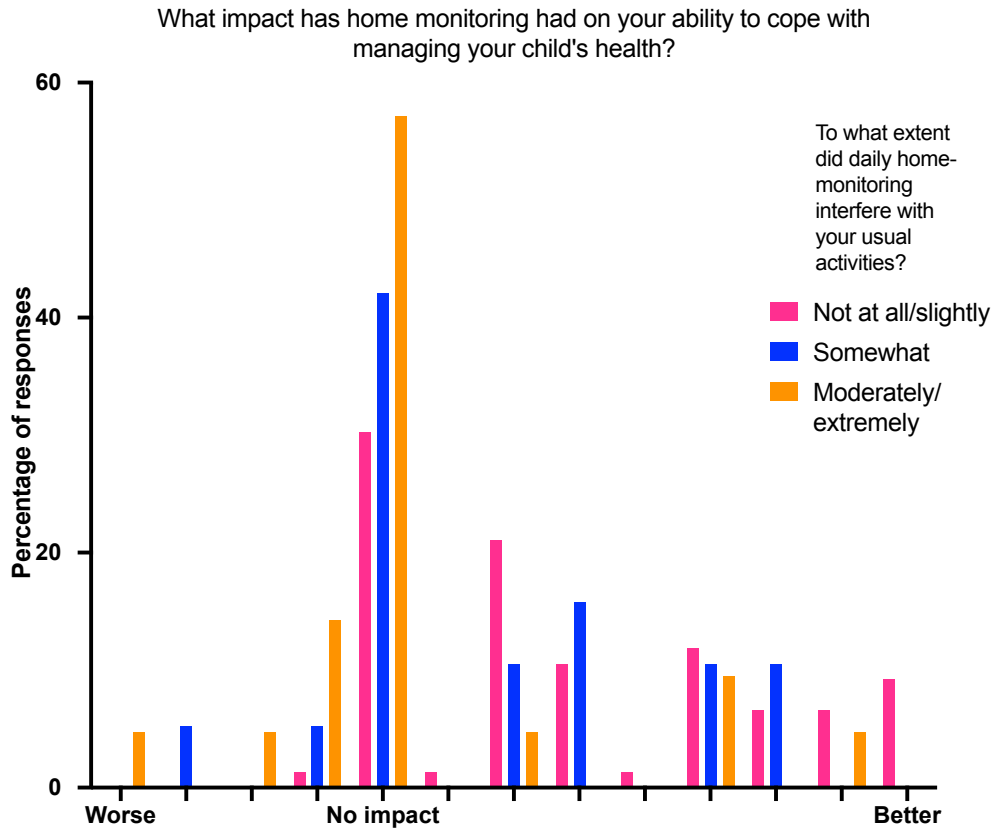
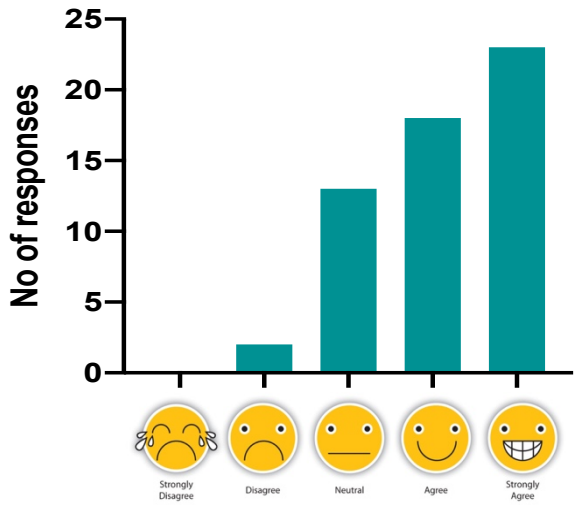


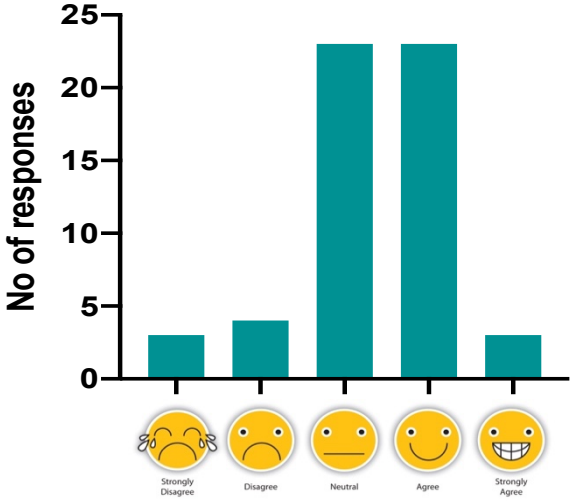
Figure 0-19 The results from two questions combined from the parental acceptability questionnaire.

1.23.5.2 Six- to twelve-year-old acceptability

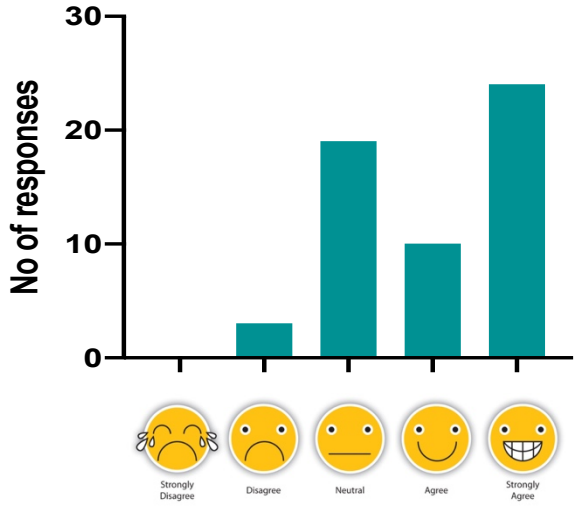
Completed acceptability questionnaires from 56 (92%) participants aged six to twelve were received. Most participants reported liking the look of the app, liked having the home monitoring checks done as home and did not feel sad having to do the home monitoring checks (Figure 0-20).



Did you like the look of the app?



Did you like having your breathing checked every day?



Did doing the checks at home make you happy?

Figure 0-20 Responses to three acceptability questions by six- to twelve-year-olds

1.23.5.3 Acceptability questionnaire free text comments

Table 0-11 shows a selection of the comments received in the free text comment section on both the parent and the participant ≥ 12 years of age acceptability questionnaire.

Table 0-11 Examples of free text comments received on the acceptability questionnaires by both parents and participants

	Free text comments
Parent	It would be good if there was an IOS app as the phone technology seemed dated and a little clunky. Having the app on your own device would be fantastic. The equipment is fantastic though
Parent	I think the app is a good tool, I like seeing the monthly progress data, but some days were harder to fit it into our already busy schedule
Participant	Irritating when activity monitor wouldn't connect/load but generally enjoyed being part of the study. Will continue to use app
Participant	Having the time was hard. The phone was a bit poopy
Parent	It was a brilliant opportunity for us to be able to keep checking his health, it's the best decision I have made
Parent	As I am a lone parent it impacted on my home routine and raised my anxiety

1.23.5.4 Contact with study team for technical help

77.5% of all participants contacted a member of the study team for technical help at least once in the 6-month study period. 22.2% reported the need to contact their study team more frequently than monthly. Frequency of contact was higher at the start of the study but did continue throughout the

6-month study period and was mainly focused on two items of equipment, the activity monitor, and the thermometer. Frustration over equipment (the activity monitor) led two participants to withdraw. Reassuringly 85% of participants who had to contact the study team found the process either very easy or easy.

1.23.5.5 Staff views

Members of staff from the CLIMB-CF study sites were given the opportunity to complete a staff acceptance questionnaire. Ten completed questionnaires were received, three completed by doctors and the rest completed by specialist nurses. Eighty percent of responders had used the technology themselves and everyone found it easy to use. Ninety percent of responders could see the potential benefit to both patients and members of staff. When asked if they felt the home monitoring technology had increased contact between the families involved in the study and the clinical team, three people replied yes. All three reported the increased contact was to support equipment failures or to provide troubleshooting advice for the equipment. No extra contact was due to clinical concern based on the readings participants were getting at home. Staff were also given the opportunity to add any free text comments they wished; comments received can be seen in Table 0-12.

Table 0-12 Free text comments received from members of staff at CLIMB-CF study sites

Profession	Comment
Nurse	Maybe not that feasible in whole age group
Doctor	Really empowered families and allowed for catalyst to great conversations
Nurse	Really helped one family open up about CF and how it made them feel
Nurse	May not be ideal for all already busy households
Doctor	While it is a benefit for the family and staff it may not be the easiest to incorporate, may benefit from just a few of the devices
Nurse	Mixed opinions as was burdensome to some families and none of the families voiced a positive impact to me. If living across geographical distance it may be helpful. Don't think it gives a true picture of a pattern of condition unless completed in full and consistently. Also subjective between parents and children
Nurse	Entering data on a daily basis over a long period of time could create an extra burden on a family. Useful having the equipment if child unwell and lives far from the hospital
Nurse	Potential benefit for staff if child is unwell and data is easily accessible. Could be problematic if the family are not technical with apps etc

1.24 **Discussion**

This chapter focused on the feasibility data and the acceptability data from all participants in CLIMB-CF. In summary I found that home monitoring appeared feasible for some and acceptable to the majority of participants and their parents enrolled in CLIMB-CF, however the amount of completed data over the six-month study period was highly variable and particularly low in teenagers.

The overall median amount of completed data collected over the 6 months was 40.1%, however there were wide interquartile ranges noted for the cohort as a whole, and fewer than 30% of participants completed ≥ 60% of the requested data. When the cohort was split into 3 separate age

groups, those aged two to five years had relatively consistent data collection over the six months, likely due to data being collected by the parents. Those aged ≥12 years entered significantly less data than the other two age groups. This is the time period that has previously been shown when parental supervision of CF medical treatments declines to the point where by 15 years of age, young people with CF are looking after 90% of their treatments with a negative impact on their adherence (307). This was regardless of whether or not they felt data collection had an impact on their daily lives and despite that fact young people with CF were involved in the user interface design of the app. While this may not be surprising, it is very concerning as adolescence is a known time of vulnerability in CF and is associated with an increased rate of loss of lung function (110, 391). This age range may benefit most from closer monitoring but requires better engagement from patients for that to be successful. Reassuringly there was no difference in completion of data between sexes. Also, although there were only a small number of siblings in the study group, their median data collection did not differ significantly from the cohort as a whole, which is reassuring should home monitoring become more widely used as many families have more than one child affected.

Data completion increased during the second month of the study. This could be related to the end of month one phone call with the research team potentially addressing issues or uncertainties with the CLIMB-CF app and pieces of equipment. It may also be attributed to families becoming more familiar with the equipment and integrating it into their routines. When exploring the separate age groups, the uplift was less marked in participants aged ≥ 12 years. After the uplift it then declined in the 6–11-year-old group and ≥ 12-year-olds. No difference in data entry over weekdays compared to the weekend was noted in this cohort which is different to previous studies that have shown decreased engagement in monitoring around weekends (308).

Sample collection did not appear to affect frequency of home monitoring in the short term, however greater study fatigue with the combination of home monitoring and sample collection compared to home monitoring on its own cannot be ruled out. The drop off in home monitoring from month two, in particular in the 6-11year olds and the ≥12 year olds, could limit the usefulness of home monitoring in the medium and long term unless the ability to show efficacy or possibly the use of gamification can increase engagement.

Spirometry was reported to be one of the least acceptable requested measures, however it was the measure completed most often. This could be due to the fact it was requested twice weekly, which families found more acceptable or possibly because the device provided a result families are familiar with from clinic attendance (FEV_1 % predicted). This may be particularly important in the participants aged ≥ 12 years whose overall adherence was poor to remote monitoring. The fact they found spirometry unacceptable may impact ongoing engagement. The use of home spirometry is not new, it has been used for over 20 years in lung transplant patients. When asked, only 65% of post-transplant adults felt that their home spirometer was reliable (392) and in a yearlong study exploring adherence to home spirometry only 37.5% of participants were satisfied with their spirometer (393). While it has been shown to lead to earlier detection of bronchiolitis obliterans, it has not been shown to improve outcomes, as there was no effect on overall post-transplant survival (394). Adherence to home spirometry in CF has been reported to be between 19-77% (341, 346, 348, 395). Adherence in CLIMB-CF was 58.3% for the whole cohort, with adolescent engagement being particularly challenging. The addition of gamification with spirometry to promote engagement, in particular in adolescents, has been explored in a small pilot study in paediatric asthma. They found that nearly

100% of participants would play games designed to involve the spirometer and no one stated they would prefer to use the spirometer on its own (396).

The 'What's up?' free text portion of the app was not part of the measures requested during the study however 84.7% of participants decided to use it at some point in the study. During the enrolment visit participants and parents were shown how to enter data into this section and the 'flags' it would produce on their graphs when they looked at their data trends. They were informed they could use this section as they wished. The majority of entries referred to clinical signs or symptoms and were entered by parents. However, many participants used this section more as a diary of important events in their day or events they were keen to document that had no direct relevance to CF. This emphasizes the need for future home monitoring apps or interventions to be co-designed with the end-user to ensure data collected are of relevance and importance to both the patient and the health care provider.

The results from the home sample collection portion of this study suggest that collection of most non-invasive samples at home is feasible and that urine may be a promising sample type for biomarker exploration as 84% of participants who provided home samples provided urine samples during the study period. It should be noted though that as participants had the option to try collecting different sample types at home and to change their mind during the study period, exact percentages of actual samples received to the potential total number of samples collected over the 4 months cannot be presented.

The overall official withdrawal rate from the study was low at 6.9%. A selection of participants who formally withdrew provided reasons to their study teams. The main documented reason for withdrawal involved frustration with some pieces of equipment not working as expected, in particular the activity monitor. One family cited inappropriate internet use as a reason for withdrawal. The study phone would function as a normal phone when attached to the WIFI and would allow streaming and downloading of other applications. Due to the age ranges involved in the study the decision was made to provide information to families to set parental controls on the mobiles as they saw fit. It is unclear if the controls were not set on the study phone for this participant or if the level of controls provided by Google Play were not sufficient, but consideration should be given to this aspect of home monitoring in the future. In particular, if the technology is being supplied by health care professionals, appropriate support should be available to set the required parental controls.

Some participants did not formally withdraw from the CLIMB-CF study but stopped completing the requested home monitoring measures, with 32% of the remaining participants recording no data in month 6 of the study. Other participants continued collecting measures for the majority of the study time period but reduced the frequency of data collection. If participants and their families felt that home monitoring was helpful, data collection tended to continue over the 6-month study period. This matches the results of the acceptability questionnaire at the end of the study. There is the potential that in the future if there were clear indications of utility to remote monitoring which people found helpful usage would increase.

Most parents and older participants reported preferring to complete home monitoring measures either every other day or weekly. Currently there is no evidence relating to how often home monitoring data needs to be collected to help guide clinical decisions, reduce the number of in person clinics or to predict exacerbations. There is the potential that the fact this was a feasibility study with no beneficial outcomes to participants medical care had an impact on the answer to this question. If a participant and their family were actively benefiting from their home monitoring data collection, they might consider collecting data more frequently.

The results from the acceptability questionnaires show that for the majority of parents and participants the initiation of additional home monitoring had no impact on their daily activities, quality of life, or anxiety levels. Parents who felt it did not have a significant impact on daily life tended to complete more measures. This was not replicated in participants aged ≥ 12 years, this may be because they did not see home monitoring as a significant impact to their daily activities or quality of life as they were not entering data.

One of the difficulties in exploring feasibility in relation to percentage of completed data collection is that many studies have requested data over varying periods of time (from daily to weekly) which can make comparison hard. The median data collection of the CLIMB-CF cohort was lower than previously documented in a similar age group of children with CF (mean age 10.3) (346), although in that study data were only requested three times a week and in a smaller cohort of patients with a higher dropout rate than CLIMB-CF (n=37 analysed from 49 recruited). In adults the eICE study reported only 19% of their early intervention (home monitoring) participants entered data twice weekly over the year as requested (341) and in asthma when adults were asked to complete spirometry daily for three

weeks, only 27% adhered, interestingly nearly all participants completed symptom diaries daily during the same period (397). Completion of data weekly have also been shown to be highly variable with reported completion rates between 59.5 and 97% in CF (343, 348, 359).

Historically, good medication adherence has been quoted as being 80% (398), and this percentage has subsequently been used in CF remote monitoring studies as an indicator of good adherence, although it has not been shown to improve outcomes (341). If this is extrapolated to our study only 14.6% of participants achieved this. Van Horck *et al* arbitrarily used 70% completion of requested measures over the year to define good adherence and found that 54% of their participants achieved this. This is higher than participants in CLIMB-CF (24.3%). However, in van Horck's study participants who had not provided data for 4 weeks prior to an exacerbation, did not have four weeks of stability data prior to the selected exacerbation or had not used the home monitoring device were excluded potentially influencing the higher percentage of adherence seen (346). All these studies show that requests for data in study protocols and completion of home monitoring is highly variable and identifies the need for further research exploring the required amount of home monitoring data to be clinically relevant and the barriers to engagement.

This chapter aimed to answer the hypothesis that home monitoring is feasible by presenting the amount of requested data received and the participants' and their parents' views on home monitoring. The highly variable pattern of data collection over the 6- month study period and the comments received by participants, their families and health care professionals suggests that home monitoring should not be a 'one-size-fits-all' solution. Home monitoring systems should perhaps be available in various forms either to allow for some individual choice or potentially to allow use in

some specific patients only rather than the whole patient cohort, suggesting the hypothesis can be partially accepted. The next chapter presents the results from the patient reported outcomes used to monitor depression, anxiety, and quality of life through the CLIMB-CF study.

Chapter 4- CLIMB-CF patient reported outcomes

1.25 Introduction

The International Committee on Mental Health in Cystic Fibrosis suggests the use of the PHQ-8 or PHQ-9 to screen for depression and the GAD-7 to screen for anxiety in caregivers of people with CF (277). Varying studies report differing levels of depression and anxiety in caregivers of people with CF; reports of depression range from 20-37% and anxiety levels 36-48% (273, 399). These screening tools ask the person completing the measure to refer to the previous 2 weeks. There is no accepted MCID for either of these measures in CF, however there is an accepted MCID of a change of score of ≥ 3 for the PHQ-8 (400) and a change of score of ≥ 4 for the GAD-7 (401) when being used to monitor depression and anxiety in the general population.

The CFQ-R is one of the most widely used patient reported outcome measures and has been shown to be reliable in the CF population (282). While there are questions based around several domains, there is only one validated and accepted MCID published: within the respiratory domain a change of ≥ 4 in a score is deemed to be clinically significant (283). The higher the score reported for a domain the less of an impact the domain is having on quality of life. The CFQ-R has been validated in children ≥ 6 years of age and asks about events over the preceding 2 weeks (278).

The strengths and difficulties questionnaire (SDQ) is a test of psychological adjustment for children, which can be used as a screening tool, for clinical assessment, to assess response to treatment or in research. It has been shown to be reliable and valid in the general population (402). While not validated specifically in CF, total difficulty score means and standard deviations for the UK are

available by age group at www.sdqinfo.org. Mean (SD) total difficulty score, as scored by parents for children aged 5-15 is 8.4 (5.8), and self-reported total difficulty scores for those aged ≥ 11 years are 10.3 (5.2). For those children aged less than 4 the mean (SD) total difficulty score was 7.3 (5). There are no accepted normative data for Canadian children on the SDQ website. In a small group of Italian children with CF (n=13) the mean (SD) total difficulties score was 18.5 (5.2) (288). There is no accepted MCID but current views are that when using SDQ as an outcome measure as the 'cut off' scores for categories can change with age, absolute change in absolute scores should be explored (403). The SDQ does not have a defined period over which the questions should be considered.

Several factors have been shown to impact adherence to treatment including knowledge of disease management (404). In view of this the Quittner group advise the combination of the validated Knowledge of Disease Management-CF (405) and the My CF Treatments Treatment adherence questionnaire (289, 406) to assess adherence and possible barriers to it.
(https://www.psy.miami.edu/ksa_measures/index.phtml)

This chapter explores the hypothesis that the addition of home monitoring will not adversely affect mood or quality of life. This will be assessed by analysing the responses received by both parents and, where applicable, the participants to questionnaires delivered at certain predefined time points within the study and tracking the change over the duration of the study.

1.26 **Methods**

Completion of all questionnaires were requested at the enrolment visit, visit ~ 2 months, and the end of study visit. The same parent was asked to complete the measures at each clinic

appointment. The parent was given a paper copy of the questionnaire with their child's study ID and date documented on it and were left in a quiet room to complete the questionnaire.

Participants were also requested to complete a selection of questionnaires as documented below. If a participant changed age bracket during the study, they were requested to continue completing the same questionnaire type they had started at the start of the study.

For all questionnaires changes in score from enrolment visit to end of study visit were analysed. In the event of a significant change, further analysis using the intermediate time point would be carried out to help understand the change over time. Questionnaire results were excluded from the analysis if not completed by the same parent.

Each site was provided with the scoring sheets for each questionnaire which they completed and then transferred electronically to me for analysis.

1.26.1 **PHQ-8 and GAD-7**

The PHQ-8 and the GAD-7 were completed during the CLIMB-CF study up to 3 times by all parents regardless of the age of the participant. The questionnaire was then scored immediately by the study team according to the instructions on the questionnaires and the scores actioned if required.

The PHQ-8 has 5 total score-based depression severity categories:

- 0-4 – No/minimal depression
- 5-9 – Mild depression
- 10-14 – Moderate depression
- 15-19 – Moderately severe depression
- 20-24 = Severe depression

The GAD-7 has 4 categories of anxiety severity categories:

- 0-5 – Mild anxiety
- 6-10 – Moderate anxiety
- 11-14 – Moderately severe anxiety
- 15-21 = Severe anxiety

Guidelines were given to study sites to offer psychological support to any parent who scored ≥ 10 on the PHQ-8 and ≥ 11 on the GAD-7.

There is no MCID for either measure in CF, therefore I explored the change in median scores of the cohort. I also explored the number of parents whose scores changed during the 6 months by the accepted MCID in the general population for depression and anxiety. I compared the amount of requested data completed with parental depression and anxiety scores at both enrolment and the end of study visit.

1.26.2 **CFQ-R**

The CFQ-R was only given to participants if aged ≥ 6 years at their enrolment date. Parents of participants aged ≥ 6-13 years also completed a CFQ-R questionnaire. There were 4 questionnaires provided to the sites and sites were asked to use the age appropriate one. The four questionnaires available were:

- Children ages 6-11 years- completed with an interviewer asking the questions and the participants selecting an answer using the orange and blue cards provided.
- Children ages 12 and 13 years- completed by self-report
- Adolescence and Adults (patients 14 years old and older)- completed by self-report
- Parents/Caregivers (Children ages 6 to 13 years old)- completed by self-report

If the participant was aged 6 to 11 years, the research team went through the questionnaire with the participant following the instructions within the questionnaire and using the coloured cards provided.

While parents were allowed to remain present, they were asked not to answer any of the questions and not sit within the eye line of the child. The study sites were provided with the CFQ-R scoring manual (available via https://qol.thoracic.org/sections/instruments/ae/pages/cfq-cfq-r.html) and the CFQ-R 2014 scoring- Multiple time points (MTP) excel sheet. The sheet has tabs for each of the above questionnaires and the ability to add multiple scores per participant and parent into the same sheet. Study sites were advised to save a CFQ-R 2014 MTP scoring sheet per participant and transcribe the data from the questionnaire to the relevant section on the scoring sheet. The CFQ-R 2014 MTP scoring sheet would automatically calculate the scores for each domain. While only the respiratory domain has an accepted MCID (283) for the initial analysis, enrolment and final visit scores completed for all domains by the participant and the same parent were analysed.

1.26.3 **Strengths and difficulties questionnaire**

The Strengths and Difficulties Questionnaire (SDQ) was given to all parents and to participants aged ≥11 years. There were 3 separate questionnaires depending on the age of the participant at enrolment. Again, if a participant changed age bracket during the study, they continued completing the same questionnaire type they had started at the enrolment visit. The questionnaires were:

- parent of 2–4-year-old,
- parent of 4- 17-year-old
- participants aged 11-17 years

A total difficulties score was calculated based on the questionnaire results:

2–4-year-olds parent scores: 0-12 close to average, 13-15 slightly raised, 16-18 high, 19-40 very high.

5–17-year-olds parent scores: 0-13 normal, 14-16 borderline, 17-40 abnormal

5-17-year-old participant scores: 0-15 normal, 16-19 borderline, 20-40 abnormal

While participant and parent results for one visit could be saved on a shared excel sheet, new sheets were created for each visit. Completed SDQ scoring excel sheets were sent to myself for analysis

1.26.4 **Knowledge of disease management questionnaire and adherence questionnaire**

The knowledge of disease management questionnaire was given to participants aged ≥ 6 years at their enrolment visit and their parents. There were 4 versions of the questionnaire depending on the age of the participant.

- Child version (6-10 years)
- Parent of child version (children aged 6-10 years)
- Adolescent version (11-20 years)
- Parent of Adolescent version (adolescent 11-20 years)

Each study site was provided with 2 excel scoring spreadsheets downloaded from (https://www.psy.miami.edu/ksa_measures/index.phtml), one to score the parent and child 6-10 years questionnaires and one to score the adolescent versions. The completed files were then sent to me for analysis.

At the end of study visit the My CF Treatments Treatment adherence questionnaire was provided to the participant and parent and was completed by the person who took primary responsibility for treatment. They were asked to consider the last week of treatments specifically. They were advised they only had to answer for the treatments they were actually taking. The questionnaire scanned to me for scoring using the scoring sheet provided at www.pys.miami.edu/ksa_measures/Self_report

In parallel to this the study team completed the prescribed treatment plan at the end of study visit documenting what treatments the participant was currently prescribed, including doses and frequencies.

1.26.5 **Statistics**

Correlation between home monitoring data completeness and depression and anxiety scores at the enrolment visit and end of study visit was carried out using GraphPad Prism 9.2.

1.27 **Results**

1.27.1 **PHQ-8 and GAD -7**

Questionnaires were expected from 139 parents (parents of the 5 siblings only completed the questionnaire once). In total, there were enrolment and end of study visit PHQ-8 scores from 111 (80%) parents. Questionnaires from enrolment and end of study visit were missing from the 10 participants who withdrew, a different parent attended the enrolment visit when compared to the end of study visit in 10 cases and 8 parents failed to. fully complete one of the PHQ-8 questionnaires provided at a visit. The median (IQR) score at enrolment was 2 (0-4) and the end of study median (IQR) score was 2 (0-3) the difference between which was not statistically significant. When looking only at changes in score from only those parents who at least scored high enough to be in the mild depression category at one of the two testing points, 10 parents' scores increased by ≥ 3 and 8 parents scores decreased by ≥ 3 (the accepted MCID (400)) (Figure 0-1). No parental score worsened enough to move them into the most severe category for depression. 10 parents were offered referral to local psychological support services, 7 at the enrolment visit and 3 at the end of study visit. The

outcome of these referral offers are not known to me as it was confidential information about the parent. 22% of parents scored high enough to fall into the mild depression category or higher at one of the testing points.

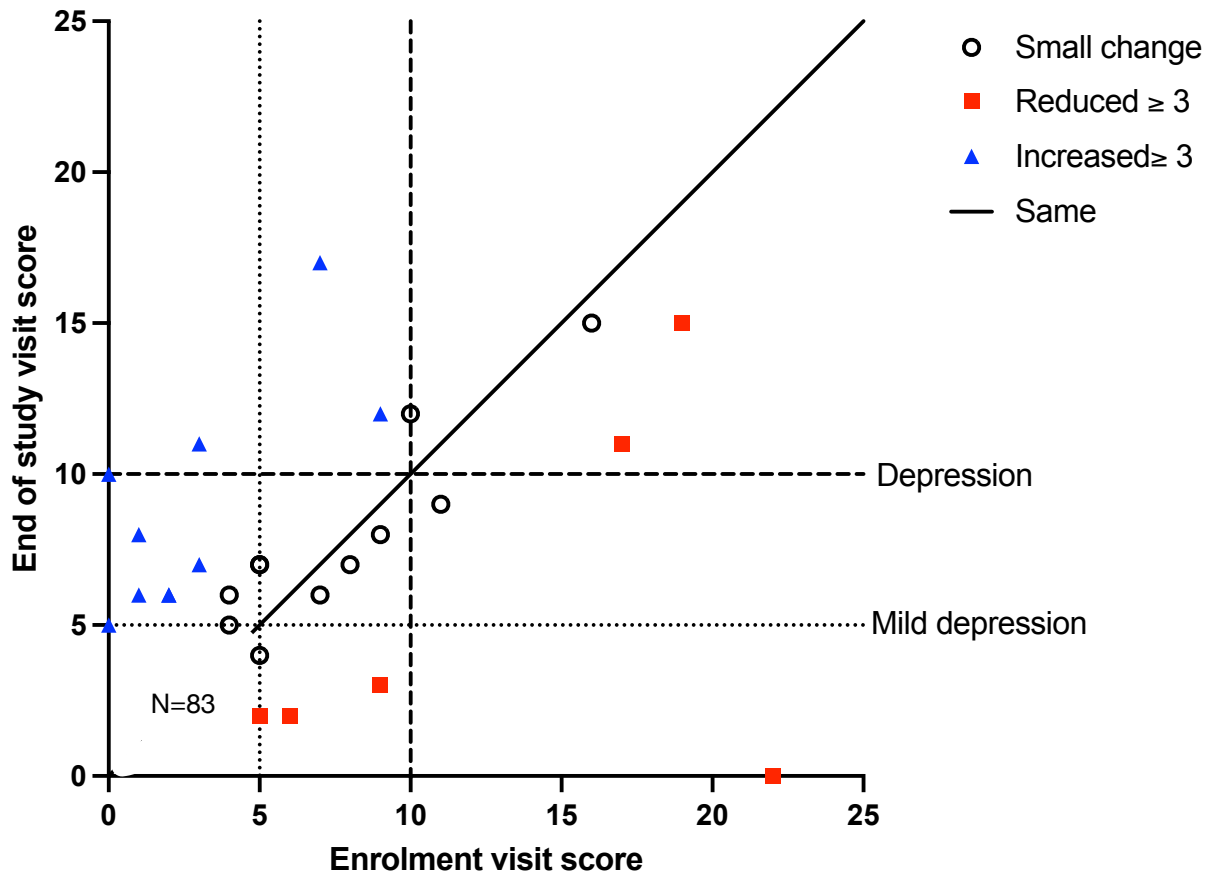


Figure 0-1 Changes in PHQ-8 depression scores between enrolment visit and end of study visit based on the MCID accepted in the general population for depression. 83 parents (lower, left-hand box) had both scores below the cut off for mild depression.

There were completed enrolment and end of study visit GAD-7 scores for 107 (77%) parents. Again 10 questionnaires were missing from the parents of the participants who had withdrawn, a different parent attended the enrolment visit when compared to the end of study visit in 10 cases and 12 parents failed to fully complete one of the GAD-7 questionnaires provided at a visit. The median (IQR) enrolment visit score was 2 (0-5) and the median (IQR) end of study visit score was 2 (0-6); there was

no statistically significant difference. When analysing scores from parents who scored high enough to at least be in the mild anxiety category, on one or both occasions, 11 parents' scores increased by ≥ 4 and 11 decreased by ≥ 4 (the accepted MCID in the general population) (Figure *0-2*) (401). Again, no scores worsened enough to move a parent into the severe anxiety group. 11 parents were offered referral to psychological support services, 9 at the enrolment visit and 2 at the end of study visit, again the outcome of these referral offers are not known to me as it was confidential information. 27% of parents scored high enough to fall into the mild anxiety category or higher at one of the testing points.

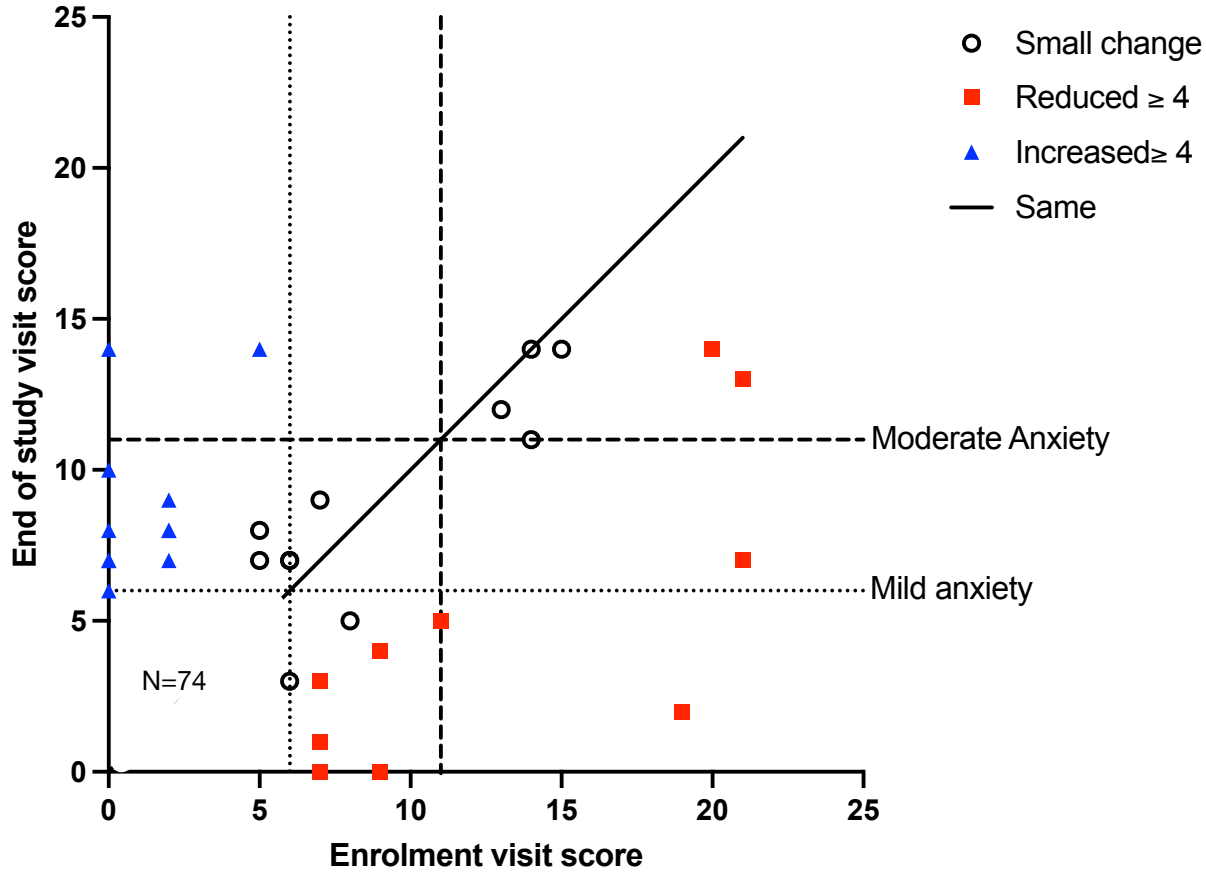


Figure 0-2 Changes in GAD-7 anxiety scores between enrolment visit and end of study visit based on the MCID accepted in the general population for anxiety. 74 parents (lower, left-hand box) had both scores below the cut off for mild anxiety.

Of note 5 parents scored in the moderately/severe and severe depression categories at their enrolment visit. All 5 also scored in the moderate/severe or severe anxiety categories as well. 2 parents remained in both of these categories at the end of study visit.

I then analysed the correlation between home monitoring data completion and parental depression or anxiety score at enrolment and at the end of the study visit. There was a negative correlation between the end of study GAD-7 and data completeness ($p<0.002$) with the higher the anxiety score recorded for the parent, the lower the percentage of completed data; no other correlations were seen (Table 0-1).

Table 0-1 Correlation between depression and anxiety scores at the enrolment visit and end of study visit and amount of requested data completeness

	Spearman r correlation between enrolment visit score and data completion	p value	Spearman r correlation between end of study visit score and data completion	p value
PHQ-8	-0.17	0.06	-0.16	0.07
GAD-7	-0.11	0.24	-0.29	0.002

1.27.2 **CFQ-R**

There were completed, paired enrolment visit, and end of study visit CFQ-R questionnaires from 52 (71%) parents, 51 (70%) children and 23 (92%) adolescents. The adolescent group recorded the largest change in respiratory scores from their enrolment visit (Mean [SD] score change of -3.6 [14]) although this did not meet the established MCID for this measure (4). There was no significant difference between the respiratory scores recorded by the three groups. Data for the enrolment

score and the end of study score for each group and the mean change in scores for all the domains of the CFQ-R is shown in Table 0-2.

Table 0-2 Enrolment and end of visit scores with mean change (SD) of the score between visits for each domain on the CFQ-R divided into parent, adolescent, and child respondents. Grey squares indicates that the category was not on the relevant questionnaire. Abbreviation SD – standard deviation ns-not significant.

	Parent				Adolescent				Child			
	Enrolment	End of study	Mean (SD) Change		Enrolment	End of study	Mean (SD) Change		Enrolment	End of study	Mean (SD) Change	
Physical	93	94	-0.57 (9.6)	ns	89	83	-6 (12)	ns	83	86	3 (17)	ns
Vitality	75	75	-0.09 (12)	ns	62	59	-2.5 (17)	ns				
Emotion	86	86	0.71 (11)	ns	77	78	0.85 (10)	ns	77	74	-2.1 (16)	ns
School	84	85	-0.32 (13)	ns								
Eating	77	79	-1.3 (13)	ns	91	86	-4.5 (14)	ns	81	81	-0.67 (21)	ns
Treatment Burden	64	62	1.9 (15)	ns	61	63	2.5 (14)	ns	77	78	1 (19)	ns
Health Perceptions	80	82	-2.7 (18)	ns	77	69	-7.6 (21)	ns				
Social					77	74	-3.1 (12)	ns	73	72	-1.5 (12)	ns
Body Image	83	85	-1.5 (15)	ns	87	86	-1 (15)	ns	87	93	5.7 (16)	ns
Role					87	81	-5.2 (16)	ns				
Weight	69	62	7.2 (31)	ns	83	87	4.8 (26)	ns				
Respiratory	87	87	-0.12 (16)	ns	85	81	-3.6 (14)	ns	84	85	1 (11)	ns
Digestion	82	83	-1.4 (14)	ns	85	89	1.1 (13)	ns	78	81	2.8 (26)	ns

1.27.3 **Strengths and difficulties questionnaire**

There were paired enrolment visit, and end of study visit questionnaires from 111 (80%) parents and 39 (81%) participants aged ≥ 11. The mean (SD) total difficulties score, as scored by the parents, was 9.9 (4.9) at enrolment and 9.4 (5.3) at the end of study visit with no significant difference between the two study visits. The participants ≥ 11 years old mean (SD) enrolment score was 12.15 (5.6) and 12.2 (5.6) at the end of study visit (ns) (Figure *0-3*). Of note, based on the parental responses at enrolment, 37 children's total difficulties scores were outside of the normal range with 11 in the abnormal category and 26 participants scoring in the borderline range. At the end of study visit time point 31 children continued to have scores outside of the normal range with the same 11 remaining in the abnormal category.

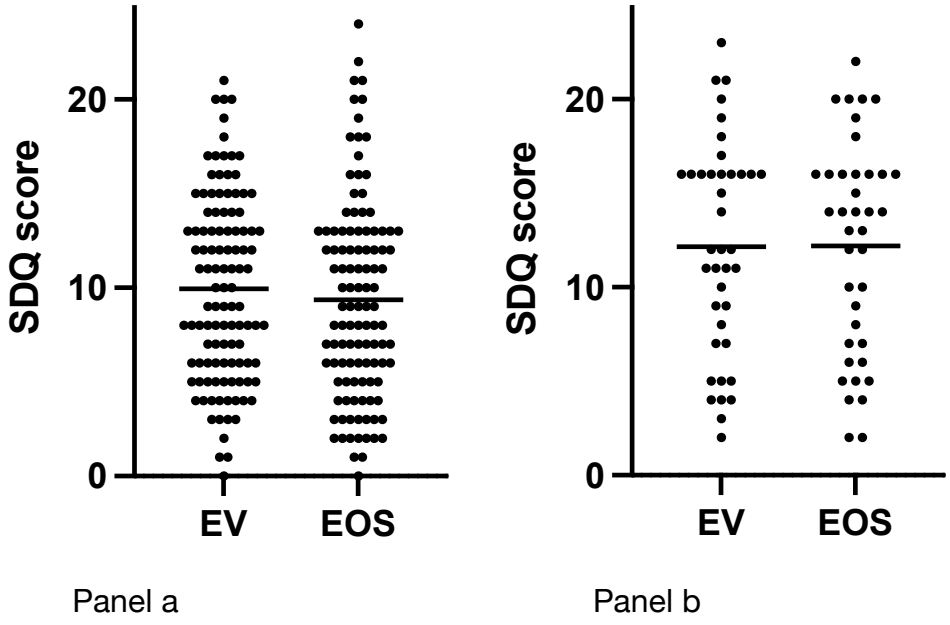


Figure 0-3 *SDQ scores for enrolment visit and end of study visit for parents (panel a) and children (panel b). The mean for each group is depicted with a horizontal line. Abbreviations: EV - enrolment visit, EOS - End of study visit.*

1.27.4 **Knowledge of disease management questionnaire and adherence questionnaire issues**

During the study, we noted that the most up to date My CF Treatments (Treatment adherence) questionnaire we were using included disease modifying medications such as ivacaftor, but this was not included on the score sheet available online. Another discrepancy noted was that insulin was on the score sheet but not on the updated version of the questionnaire. I contacted the Quittner Measures team via their website and email, and they were unable to provide me with an updated scoring sheet, so these measures were not analysed.

1.28 **Discussion**

This is the first study exploring the effects of home monitoring on quality of life in children and young people with CF and anxiety/ depression in their caregivers. In the group as whole, reassuringly, there was no significant change in parental depression and anxiety scores over the 6-month study period. There was a trend to worsening quality of life scores in the adolescent group within the respiratory CFQ-R domain, although this did not reach the MCID for this measure (283). This was not mirrored in the younger children either on self or parental assessment. There was no significant change in the strengths and difficulties scores for the cohort over the 6-month study period. Reassuringly none of the known reasons for formal withdrawal were connected to the mental health of the parent or the participant.

Anxiety and depression levels within our cohort as whole were not affected by the introduction of home monitoring, which is similar to results seen in post lung transplant patients after the initiation of home monitoring (407). It should be noted, however, that while the anxiety and depression levels as a cohort did not change, screening did identify parents who were experiencing symptoms of depression and anxiety. While it is difficult to make direct comparisons as each study uses a different

cut off to represent depression and anxiety, here I have reported any patient who scored in the mild depression or anxiety group at any point. The levels recorded in caregivers in CLIMB-CF are lower than previously reported levels of anxiety and towards the lower end of reported depression levels (290, 399). They are higher than reported levels in the UK general population. NICE Common mental health guidelines quote that the proportion of people who are likely to experience major depression in their lifetimes is up to 10% and 5.7% will experience a generalised anxiety disorder. However, the caveat is the fact that both are likely underdiagnosed in the community as many people will not seek help; this seems particularly true for anxiety disorders (408). It is clear that screening will identify individuals who may require further psychological support and CF centres need to have provisions in place to be able to make the appropriate referrals (277). This is particularly relevant to parents who score in the moderate/severe depression category and may, as demonstrated in our study, also score highly for anxiety. Those parents who score highly for depression and/or anxiety may warrant regular screening in the future should home monitoring be instigated for longer periods of time as there is the potential that home monitoring may exacerbate symptoms. This may be particularly true for those parents who have high anxiety levels as GAD-7 scores at the end of the 6 months was the only correlation to completion rates that could be found. It should be noted though, that while the correlation was statistically significant the spearman r was -0.29, therefore I would suggest the clinical relevance warrants further investigation in future studies, especially as the GAD-7 only represents the preceding 2 weeks at the point of completion. It should also be noted that results were not correlated to the self-reported anxiety reports in chapter 2 as it was felt that due to the low number of parents will high levels of anxiety on validated measures it would not be possible to draw meaningful conclusions.

While there was a trend to worsening adolescent CFQ-R respiratory domain scores, these did not meet clinical or statistical significance (277) and were not reflected in the adult or child CFQ-R scores. Previous studies in asthmatic children have shown that home monitoring may improve quality of life, although the same studies have also shown that increased exacerbation alerts or triggers can worsen quality of life (335, 336).

The SDQ scores showed no significant change over the 6-month period. As a cohort the scores received were higher than the accepted normative data for the UK although they do include scores from the Canadian children for whom there are no data. Our scores (in a larger cohort) are also lower than those previously published in CF children (288).

Unfortunately, during the study, it became apparent it would be impossible to score the My CF Treatments treatment adherence questionnaire and to utilise the results from the Knowledge of Disease Management questionnaire within this study. Therefore, I have been unable to analysis and present the adherence data for this cohort in this thesis.

This chapter provides evidence to support the hypothesis that the home monitoring used in this study did not negatively impact quality of life or mood in children or young people with CF or their care givers using the assessment tools described above. Screening however does identify parents with higher levels of anxiety and/or depression who may warrant further support should home monitoring be instigated for longer periods of time. It should also be noted that there is the potential that changes in the monitoring type or frequency may impact have a different impact and measures of mood and quality of life may need to be incorporated into future studies. It should also be considered

that in the future if people with CF feel better or are healthier on CFTR modulators there is the chance that worsening in signs or symptoms recorded using home monitoring may have a more substantial impact on their mood and quality of life. The next chapter presents data recorded around periods of stability and periods of pulmonary exacerbations and explores variations in the reported measures.

Chapter 5 – Clinical pulmonary exacerbation data

1.29 Introduction

Although not a primary aim of this feasibility study, one of the major benefits of home monitoring could be considered the early detection of- and intervention for- episodes of ill health. In the context of CF, there has been much interest in whether home monitoring could be used to pick up pulmonary exacerbations in a timelier manner, possibly even pre-symptomatically. As described in the introduction (Chapter 1) there is no clear definition of a CF pulmonary exacerbation nor a definitive way to diagnose one. Definitions and indeed treatments can vary significantly between CF centres.

Delay in diagnosis of pulmonary exacerbations is common, yet despite home monitoring in CF being around in some guise or another since the 1980s it has not been adopted into mainstream care (125). This lack of adoption may be because, currently home monitoring for pulmonary exacerbations has yet to show clinical utility, with the largest study to date (eICE) not meeting its primary outcome despite home monitoring detecting more potential exacerbations (341). The lack of consensus on how to treat a pulmonary exacerbation may have contributed to the eICE findings (342) and adds strength to the argument that detection alone is not enough (125).

In 2010 Sarfaraz and colleagues published data from 19 people with CF aged ≥ 12 and over in the UK (mean age 26.2 years, SD 1.2) who took part in home monitoring of lung function and symptom scores for 6 months (355). This was a proof-of-concept study to assess the feasibility and validity of this approach. They defined a device-identified pulmonary exacerbation when home monitoring readings met one of three criteria: “(i) an increase of at least one point of three symptoms scores

over three successive days (ii) a decline of at least 10% of FEV_1 alone for 3 successive days (iii) an increase of at least 1 point of 2 symptoms and a decline in FEV_1 of equal to, or more than, 10% for 3 successive days". If a participant's home readings met these criteria, they were contacted by the study team, invited to hospital for review and started on antibiotic treatment if the clinician and the participant felt it was appropriate. Participants could also contact the study team for a review if they felt unwell, regardless of their home monitoring readings, this was termed a patient-identified pulmonary exacerbation. During the study there were 53 pulmonary exacerbations reported by the study team, over half were patient-identified pulmonary exacerbations (all presenting with increased symptoms not satisfying the above criteria) and only 47% met the device-identified pulmonary exacerbation predetermined criteria. Of the 25 device-identified pulmonary exacerbations only 2 were identified based on decline in FEV_1 alone, whereas 18 were identified by only change in symptom score. All possible pulmonary exacerbations were treated with antibiotics after hospital review with 51% of them being treated with oral antibiotics. This was a higher percentage than the previous and subsequent years at this site. The authors postulated this was because of earlier detection using home monitoring. Interestingly 51 patients were recruited and provided with home monitoring equipment, of the 33 who were withdrawn 6 were withdrawn due to clinical reasons and 27 were withdrawn as they did not provide enough data for analysis.

The machine learning results from SmartCareCF, a UK adult home monitoring study found that of the measures requested, the symptom features (especially general wellness) provided a better prediction value for an upcoming exacerbation than the recorded physiological measures such as lung function, heart rate or oxygen saturations (344). The highest predictive value obtained was with the combination of five measures: wellness, cough, FEV_1, heart rate and oxygen saturations (area

under ROC curve of 88.6%). Although interestingly the combination of just wellness, oxygen saturations and heart rate were nearly as predictive, leading the authors to postulate FEV_1 may not be required in future home monitoring studies. They noted they were able to detect a pulmonary exacerbation 10 days prior to the recorded start date of antibiotics in their study.

There are less data on detection of a pulmonary exacerbation remotely in a paediatric cohort and, to date, paediatric cohorts have been smaller. Home monitoring data (consisting of symptom scores and lung function) from 49 Dutch children (mean age 10.3 years, SD 3.6 years) were retrospectively analysed around clinically diagnosed pulmonary exacerbations (346). Using multiple logistic regression analysis, they showed that the combination of FEV_1 % predicted and the mean of symptom scores over the preceding 4 weeks gave a sensitivity of 92.9 % and a specificity of 88.9 % for pulmonary exacerbation prediction. To date this model has not been used in a prospective study. Again, it should be noted that of the 49 children, nine children were excluded from the analysis as they did not provide enough data.

In this Chapter I explore the hypothesis that home monitoring may aid in the detection pulmonary exacerbations remotely by reporting physiological variability during periods of clinical stability and explore signals from data collection around exacerbation time points in the CLIMB-CF cohort.

1.30 **Methods**

1.30.1 **CLIMB-CF definition of a pulmonary exacerbation and clinical stability**

Study sites entered changes to participant medication on the CLIMB-CF study specific website with a start and end date as well as a reason for the change. For the pulmonary exacerbation analysis, the

start date of a pulmonary exacerbation was defined as the study specific website-documented antibiotic start date with pulmonary exacerbation given as the reason. Clinical stability was defined as periods of time with no documented treatment with acute antibiotics and participants were not seeking additional contact from their clinical teams.

1.30.2 Amount of lung function data received around periods of pulmonary exacerbation

Participants were asked to increase the frequency of lung function measurements from twice weekly to daily around periods of increased symptoms.

For the analysis in chapter three as lung function was only requested twice weekly when stable even though participants were able to enter data as frequently as they liked, the overall data were capped at twice a week, and extra data were not included. For analysis in this chapter of the data around an exacerbation the number of measures in the seven days preceding the exacerbation – defined as the start date of antibiotics – were compared to the uncapped overall usage of the participant to determine a participants percentage change. This was to account for if a participant used their spirometer more frequently than requested even during periods of stability.

1.30.3 Analysis of data around periods of pulmonary exacerbation

Data were extracted and cleaned of duplicates as described in Chapter 2. For exploration of data entry around periods of pulmonary exacerbation, data were extracted for all participants who had provided greater than 80% of the requested data over the 6-month period and mapped to their documented periods of pulmonary exacerbation (if experienced during their 6-month study period). This is because for the analysis presented within this thesis the data has not been inputted into a

machine learning algorithm, however as it is suggested that machine learning algorithms require data to be as complete as possible and advised 10 times the number of parameters requested per person during the initial stage of machine learning which is would be calculated as 77-83% of the requested data over the 6 months (depending on if spirometry is recorded by a participant) (409-413). For this analysis, compared to the feasibility analysis, significantly abnormal values were removed e.g., oxygen saturations of 124%.

For the objective measurements obtained from the Bluetooth equipment, the results recorded from the piece of equipment during periods of stability were compared with results recorded during periods of pulmonary exacerbation. Measures analysed were activity, heart rate, oxygen saturations, weight, lung function and temperature. Results were analysed as a group and an individual's results during stability were compared to their results during their pulmonary exacerbations for each measure. Data were regarded as connected to the pulmonary exacerbation if collected in the week prior to the start date of the exacerbation and during the 2 weeks after the start date of the exacerbation.

1.30.4 **Data presentation**

Data were combined and analysed in Microsoft 365 Excel and Graphpad Prism 9.2 and presented using Tableau Desktop Professional Edition 2021.2.1 (Seattle, Washington State).

1.31 Results

1.31.1 CLIMB-CF pulmonary exacerbations

97 of the 144 participants (66.6%) had exacerbations that met the above criteria. 86 (88.6%) of those participants had at least 1 exacerbation treated with oral antibiotics. 10 (10.3%) participants had both at least 1 exacerbation treated with oral antibiotics and 1 exacerbation treated with IV antibiotics. One participant had an exacerbation treated with IV antibiotics only. There were 211 incidences of courses of oral antibiotics with a median (IQR) of 2 (1-3) courses per participant and 14 courses of IV antibiotics documented in the 6-month study period. The maximum number of oral courses of antibiotics received by a single participant in the 6 months was 7.

1.31.2 Lung function collection around times of pulmonary exacerbation

In the cohort of children with spirometers at home (n=99), 73 (73.7%) subjects recorded 151 periods of pulmonary exacerbation (median [IQR] per person 2 [1-3]). In contrast to what had been requested, lung function measures did not increase in frequency prior to or during periods of exacerbation (median [IQR] percentage change in number of measurements 0.17% [-0.9%-0.2%]).

1.31.3 CLIMB-CF data entry during stability and periods of pulmonary exacerbation

21 participants (14.5%) provided ≥80% of the requested data over their 6-month study period. During that time 14 (67%) of these participants had at least 1 pulmonary exacerbation (range 1-7) requiring treatment with oral antibiotics and 7 (33%) participants received no additional treatment for respiratory symptoms. None of these participants received a course of IV antibiotics during the study period. Below are example graphs of data entries for each measure for the 6-month period for 2

participants who were stable during their study period and 2 participants who received additional antibiotics for pulmonary exacerbations.

Stable participants (i.e., no treatments received for pulmonary exacerbations)

The first participant is a 7-year-old female (Figure 0-1, Figure 0-2,Figure 0-3,Figure 0-4). Figure 0-1 shows results of her wellness questions, it can be seen on the graphs that there is variation on her wellness ratings over the 6-month period. These periods of worsening rating of symptoms were also associated with worsening in overall wellness. There appeared to also be associated drops in lung function. The best lung function recorded was an FEV_1 % predicted of 99.2% with a mean (SD) over this time of 77% (11%), but as can be seen in Figure 0-3, there were 2 occasions on which a large drop was recorded for more than a single measurement. The first appears to start on the 4th of March with the lowest recorded FEV_1 % predicted logged a couple of days later at 53.5%, the second drop starts on the 18th of May with the lowest recorded FEV_1 % predicted in that episode of 42.8%. These episodes correspond to changes in a selection of the wellness questions as seen in Figure 0-1. At the first episode in March there are worsening ratings seen in cough, sputum volume, wellness, and appetite. In the second episode there are corresponding drops in cough, sputum volume and wellness. During the 6-month study she did not receive treatment with antibiotics hence the label of a stable participant however her recorded data would imply she was not clinically stable. It is not clear if the participant and her family felt these changes were normal variation for her, either they did not contact her clinical team to discuss her changing symptoms, or the clinical team chose not to treat, but there is the potential that these episodes are missed pulmonary exacerbations that should have been treated. This participant's self-reported sleep disturbances graph is not included as there were significant missing data for this measure only.

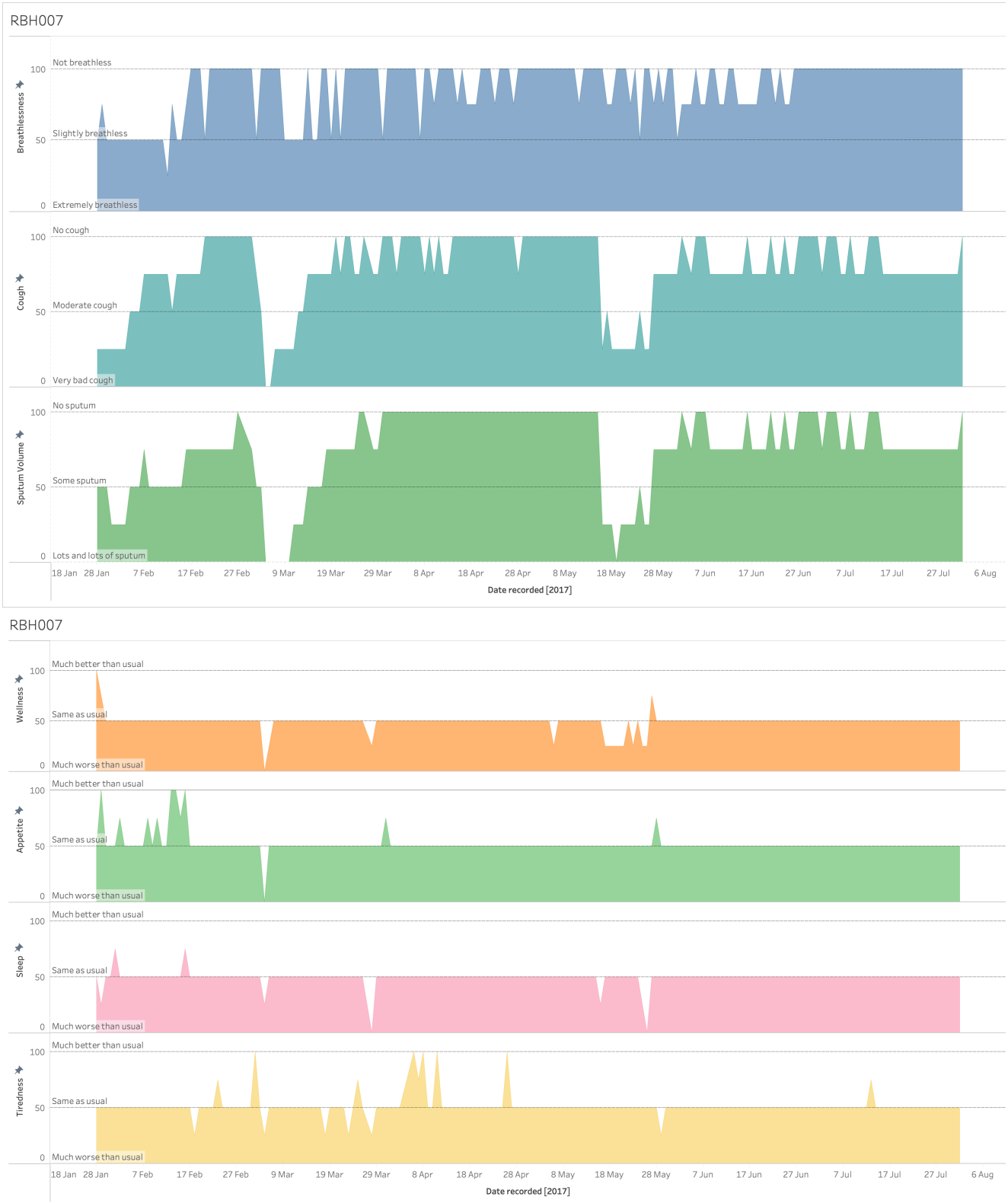


Figure 0-1 The results of the 7 wellness questions answered by RBH007 during her 6-month CLIMB-CF study period. Documented on the y axis are the wellness options she had the option of choosing from. Improvements in score are associated with readings higher up the y axis.

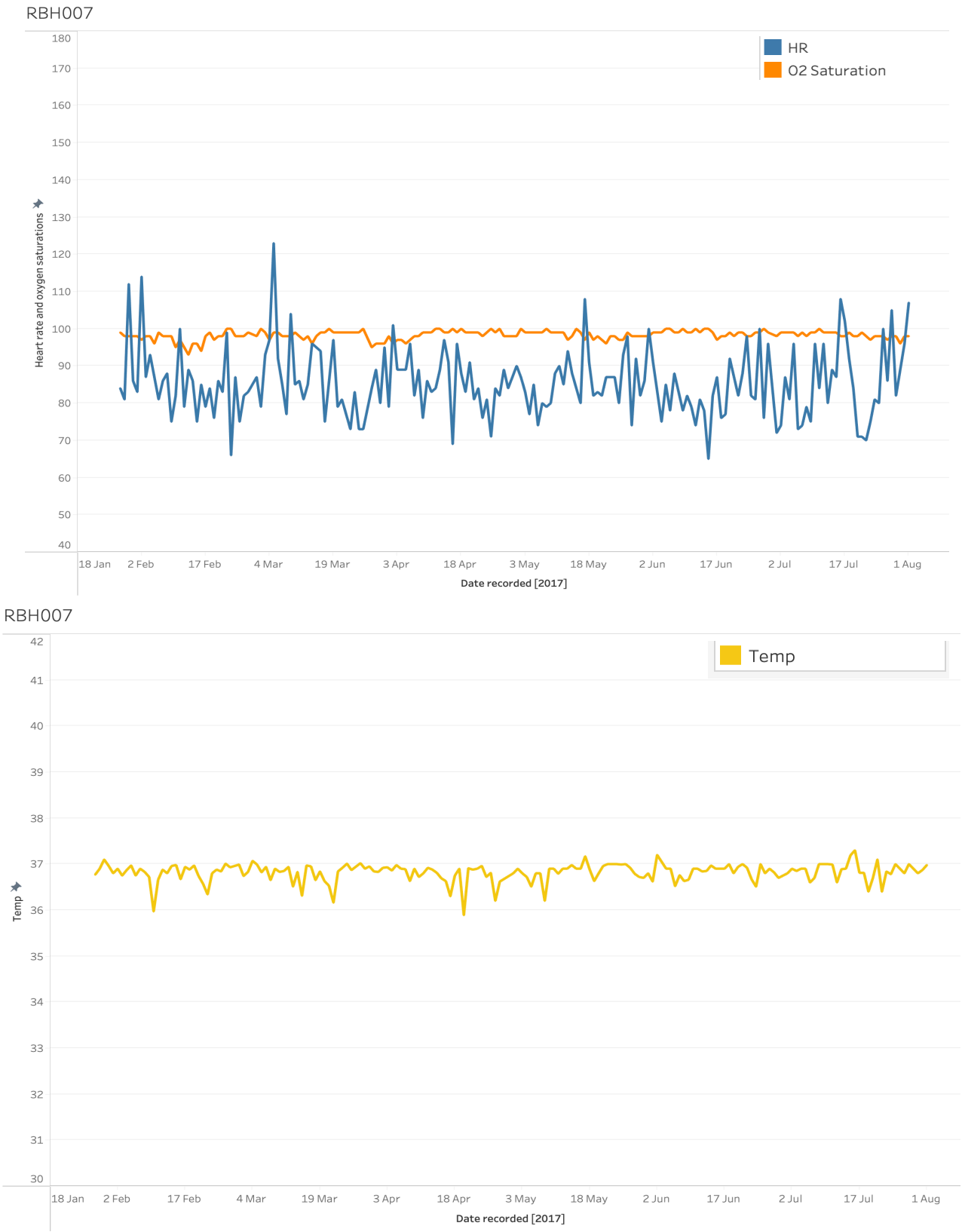


Figure 0-2 Heart rate, oxygen saturations (top graph) and temperature readings (bottom graph) for RBH007 during her 6-month study period

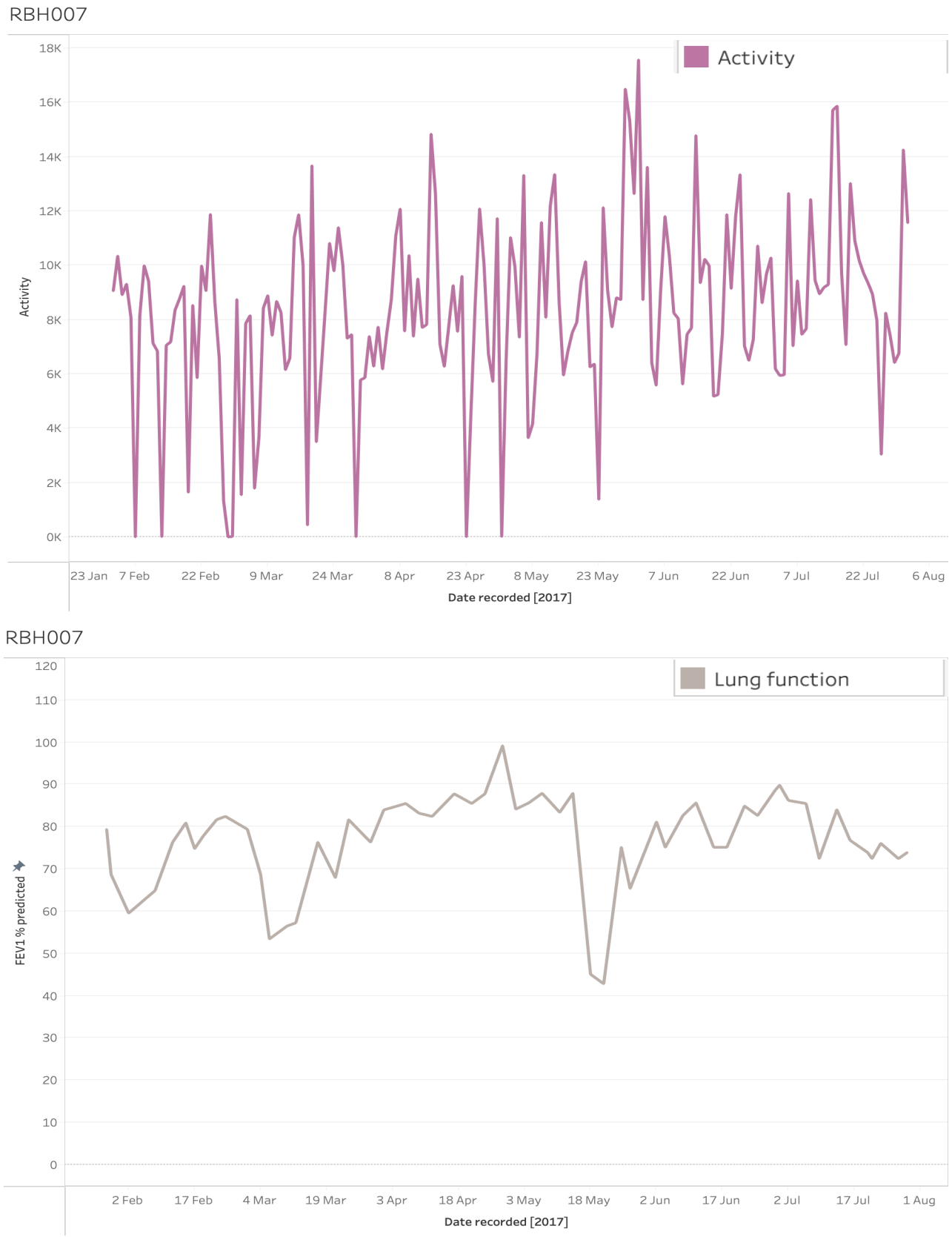


Figure 0-3 Activity in steps per day (top) and lung function as FEV_1 % predicted (bottom) for RBH007 for her 6-month study period

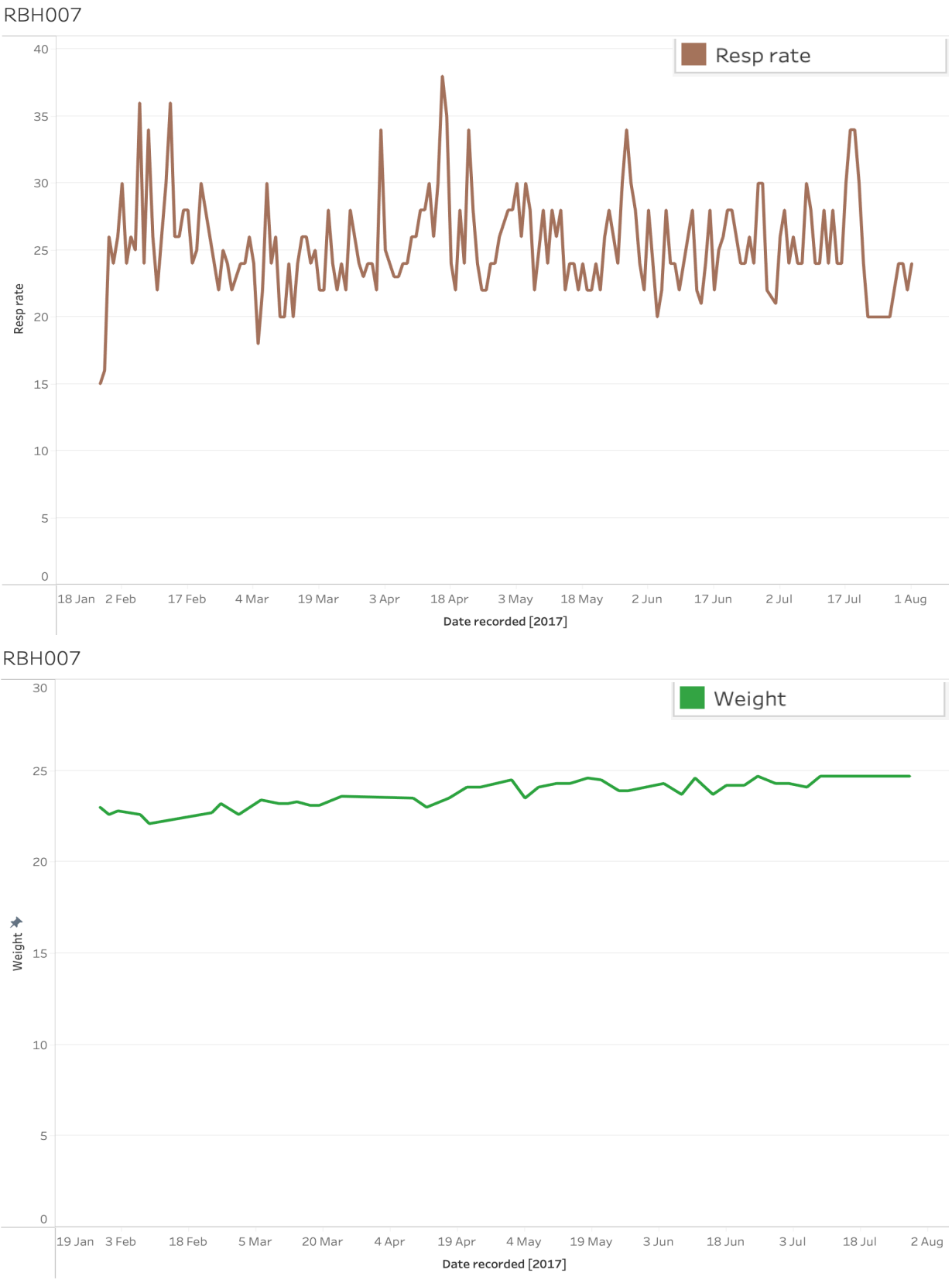


Figure 0-4 Respiratory rate in breaths per minute (top) and weight in kilograms (bottom) for RBH007 for her 6-month study period

The second stable participant is a 11-year-old male, and his result graphs are below (Figure 0-5, Figure 0-6,Figure 0-7,Figure 0-8,Figure 0-9). Throughout the 6 months there is variation within his answers to all the wellness questions, however the variation in a measure appears to be independent of the other measures. His lung function readings appear more stable than the previous participant with no significant dips and a mean (SD) FEV_1 % predicted of 75.5% (8%) and the lowest recorded reading documented at 65%.

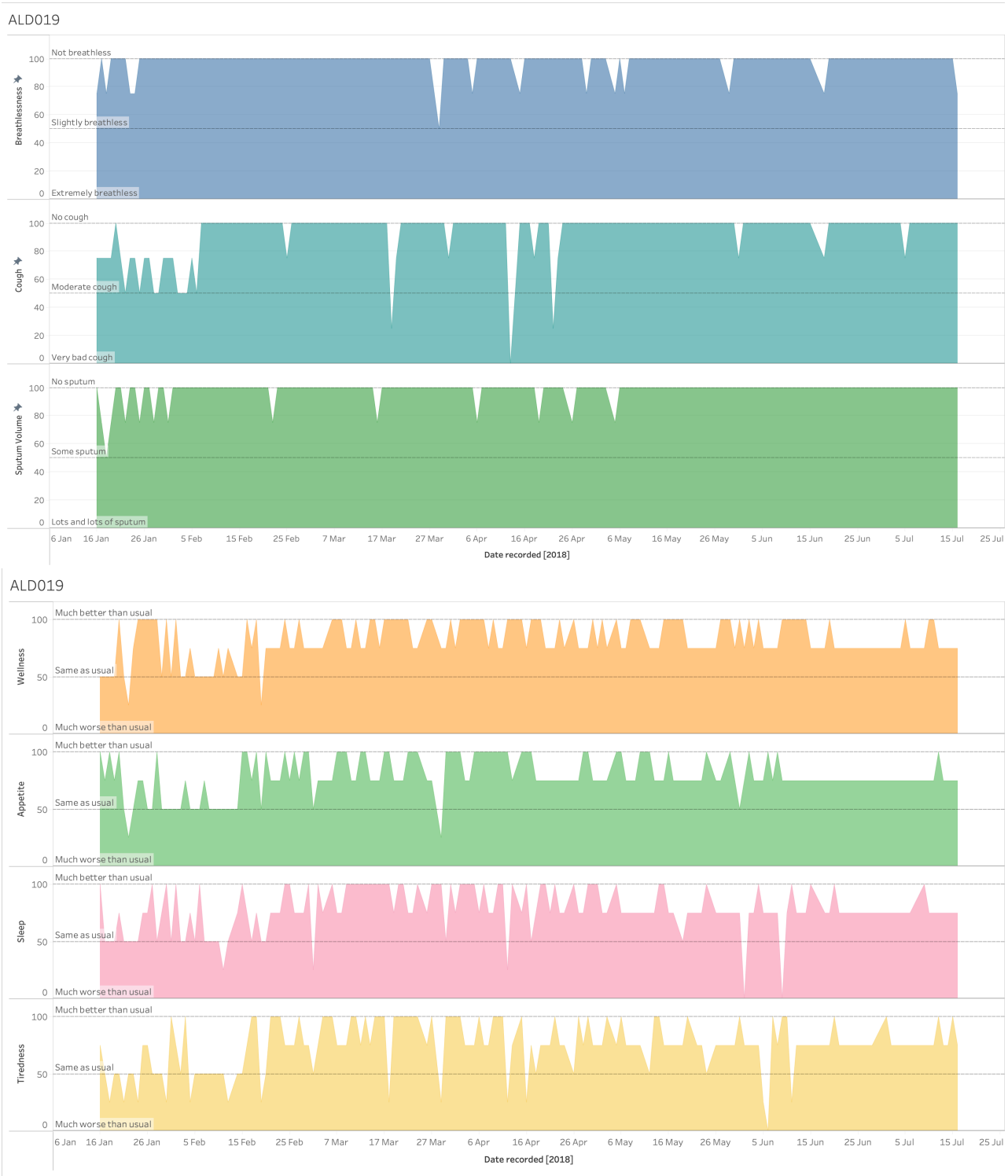


Figure 0-5 The results of the 7 wellness questions answered by ALD019 during his 6-month CLIMB-CF study period. Documented on the y axis are the wellness options he had the option of choosing from. Improvements in score are associated with readings higher up the y axis.

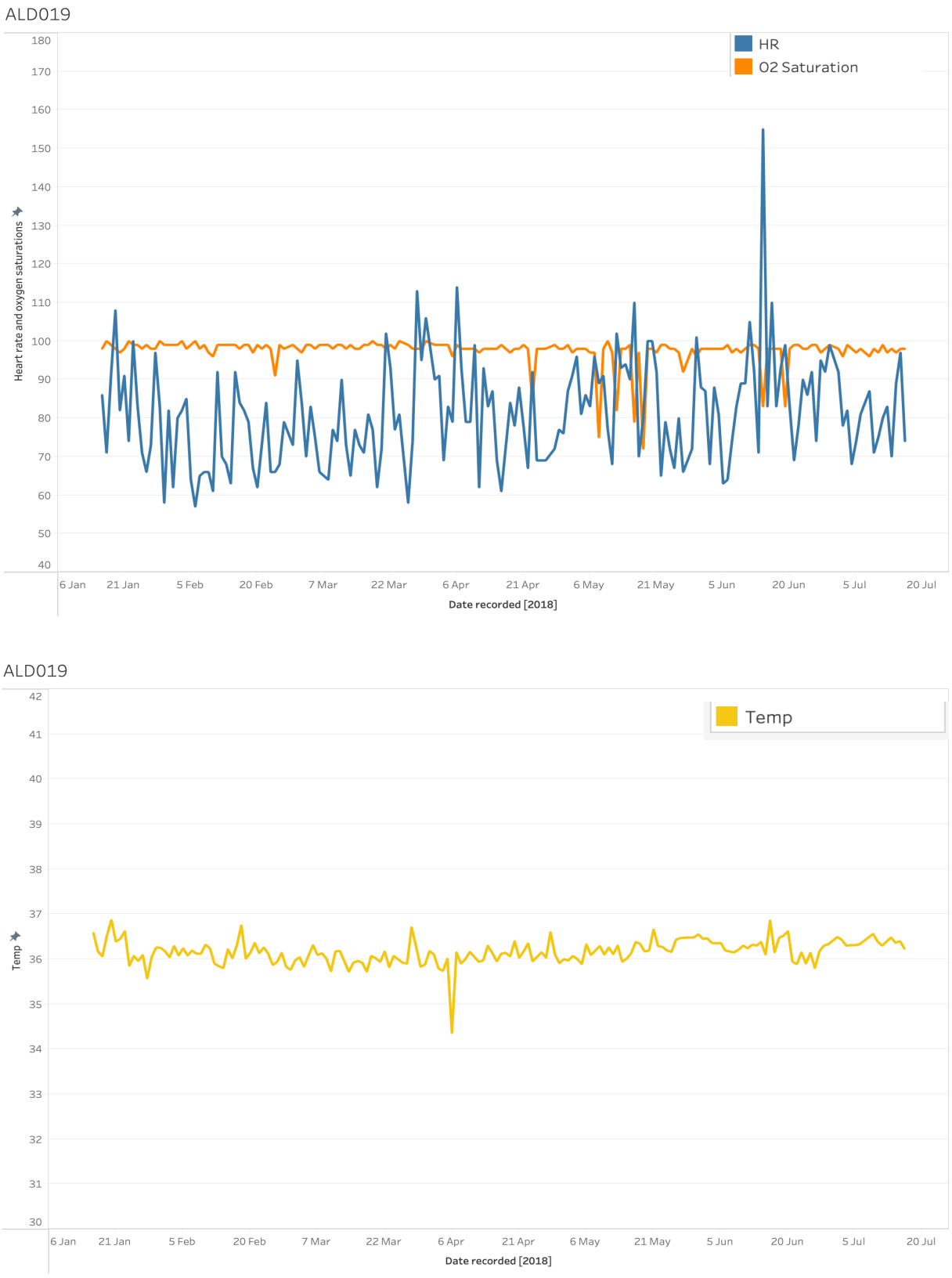


Figure 0-6 Heart rate, oxygen saturations (top graph) and temperature readings (bottom graph) for ALD019 during his 6-month study period

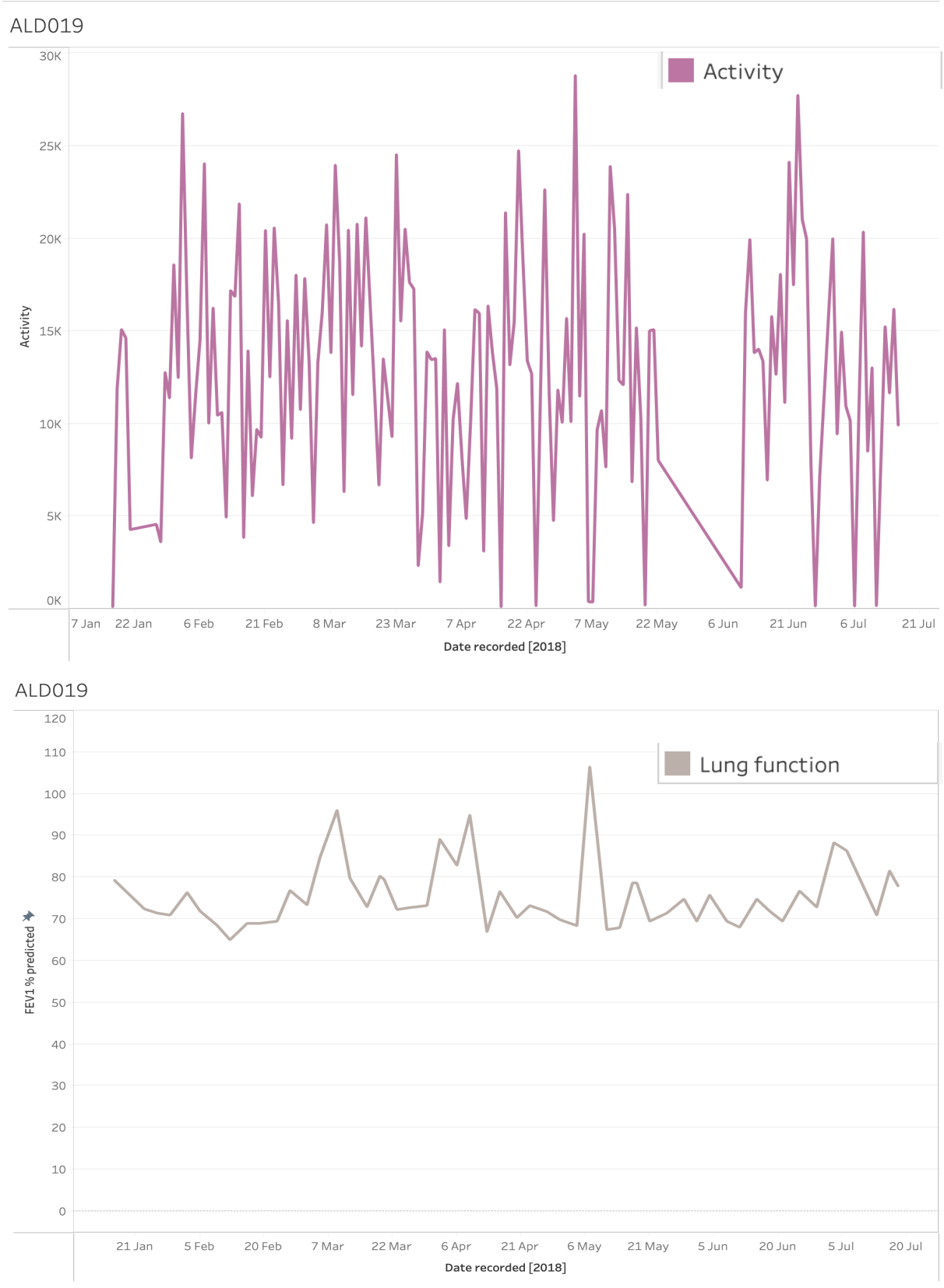


Figure 0-7 Activity in steps per day (top) and lung function as FEV_1 % predicted (bottom) for ALD019 for his 6-month study period

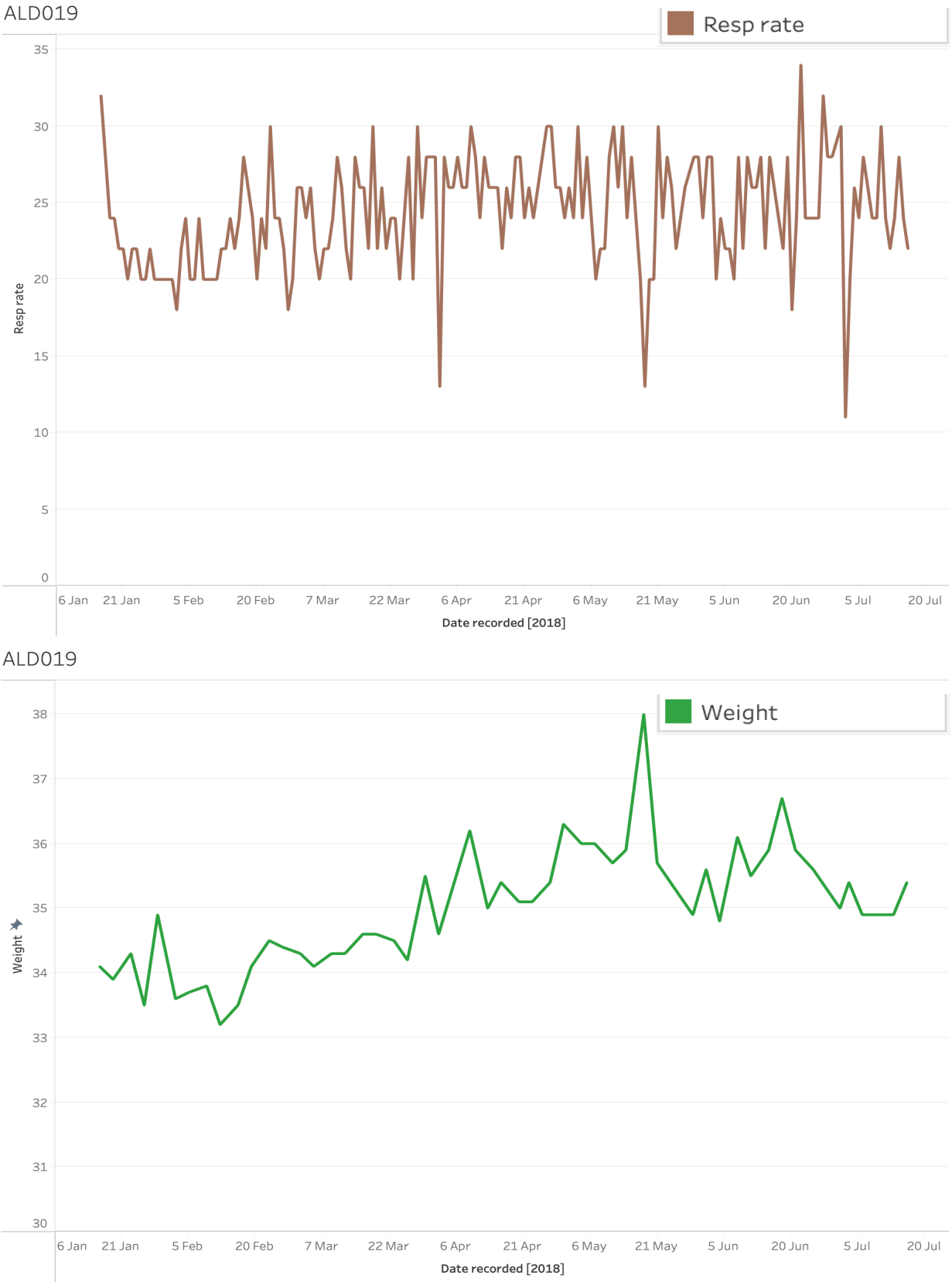


Figure 0-8 Respiratory rate in breaths per minute (top) and weight in kilograms (bottom) for ALD019 for his 6-month study period



Figure 0-9 The number of sleep disturbances reported per night for ALD019 for his 6-month study period

Participants who experienced a pulmonary exacerbation

The graphs below provide examples of the results entered by 2 participants who had pulmonary exacerbations during the 6-month study. The first is from BRN017, a 4-year-old female who received 5 courses of oral antibiotics during the study period. The exacerbation start date (the date antibiotics were started) is shown on the below graphs as a red arrow (Figure 0-10, Figure 0-11, Figure 0-12, Figure 0-13). There does appear to be some change with the start of an exacerbation, in particular worsening ratings in cough, wellness, and tiredness, however there are also periods of change not associated with treatment for an exacerbation (Figure 0-10).



Figure 0-10 The results of the 7 wellness questions answered by BRN017 during her 6-month CLIMB-CF study period. Documented on the y axis are the wellness options she had the option of choosing from. The red triangles depict the start date of a pulmonary exacerbation. Improvements in score are associated with readings higher up the y axis.

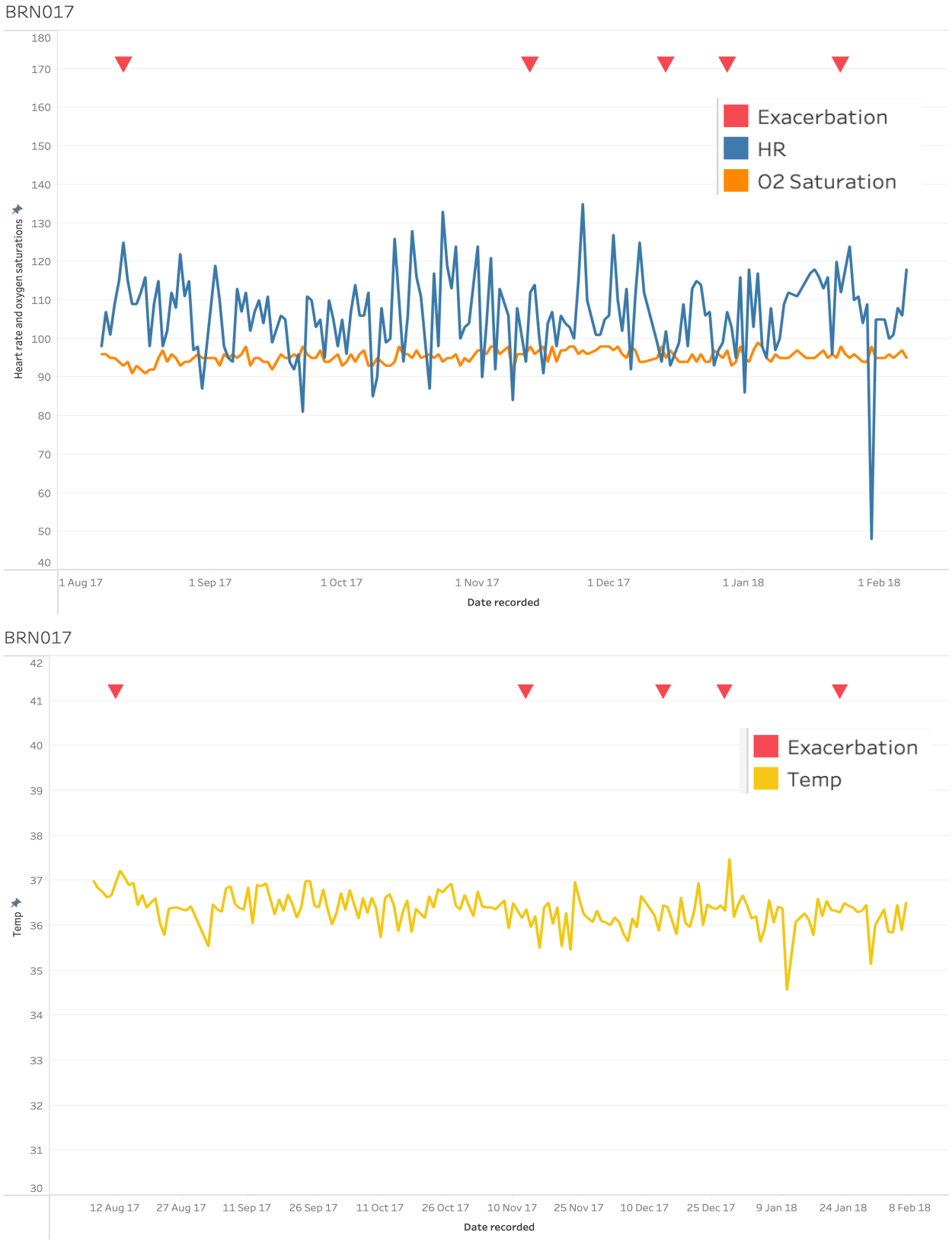


Figure 0-11 Heart rate, oxygen saturations (top graph) and temperature readings (bottom graph) for BRN017 during her 6-month study period. The red triangles depict the start date of a pulmonary exacerbation.

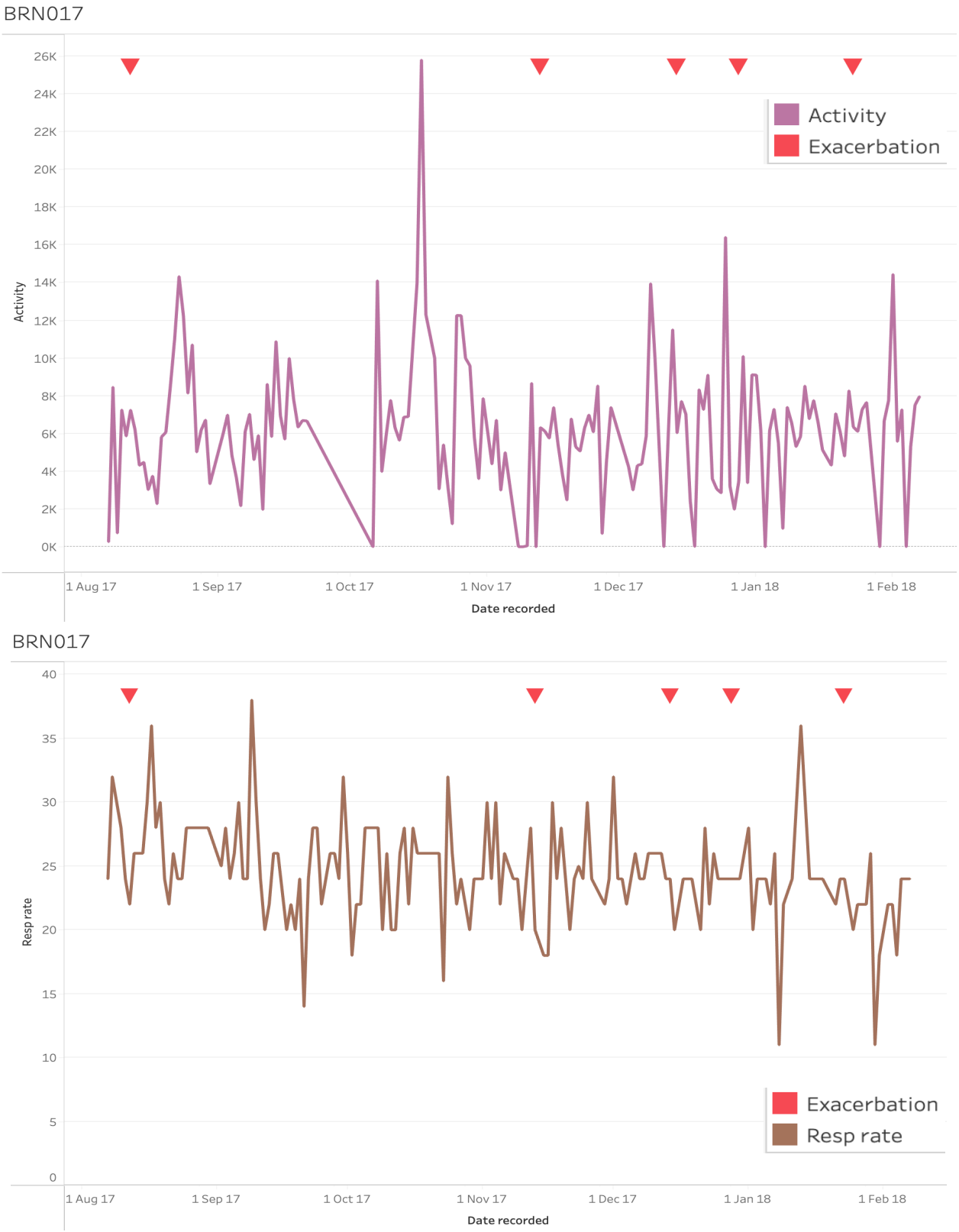


Figure 0-12 Activity in steps per day (top) and respiratory rate in breaths per minute (bottom) for BRN017 for her 6-month study period.

The red triangles depict the start date of a pulmonary exacerbation.

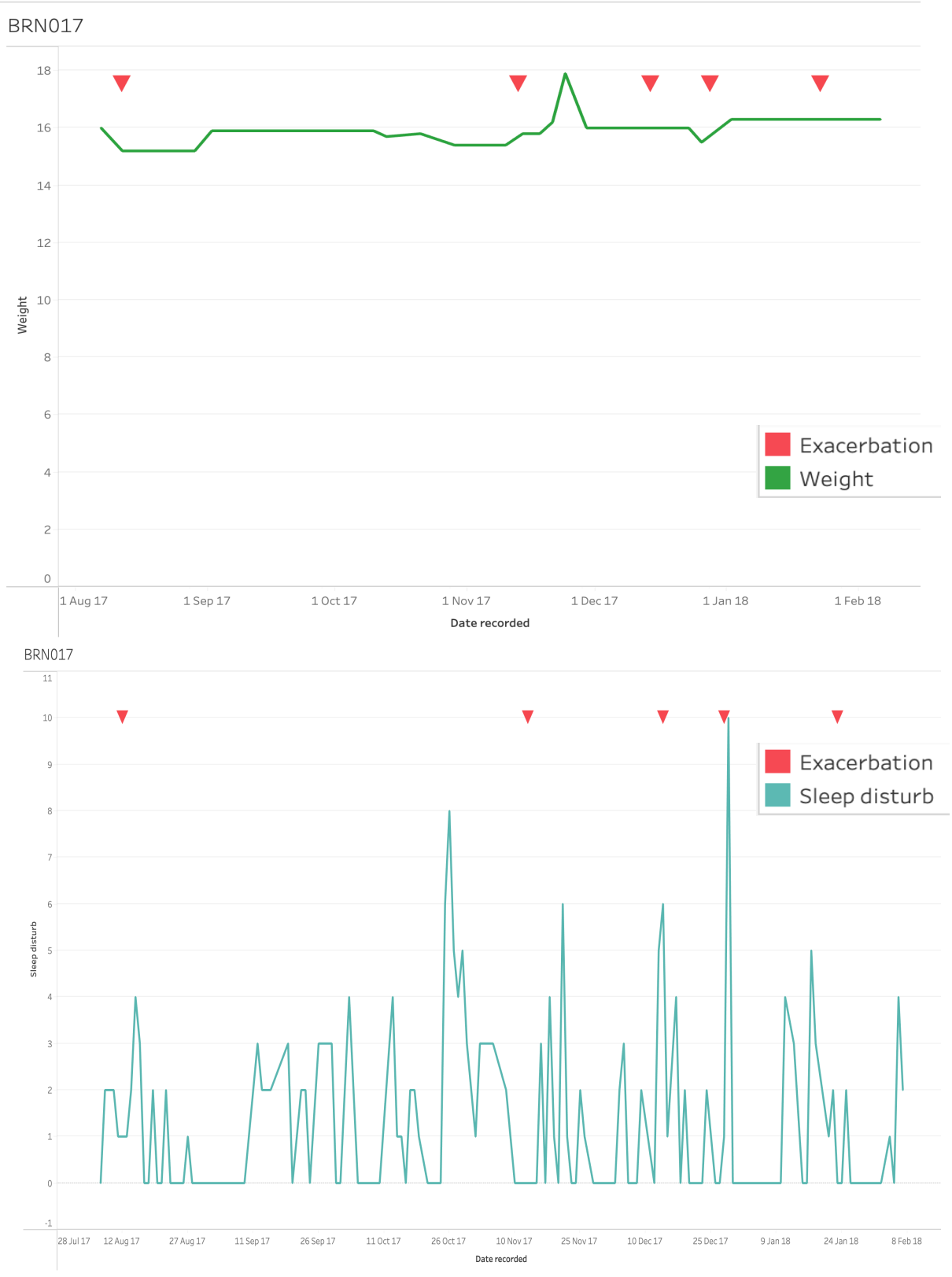


Figure 0-13 Weight in kilograms (top) and the number of sleep disturbances reported per night (bottom) for BRN017 for her 6-month study period. The red triangles depict the start date of a pulmonary exacerbation.

The last participant graphs shown below are from BRN013, a 14-year-old female who had 3 pulmonary exacerbations, treated with oral antibiotics, during the study period. During the 6-month period there was significant variation in most measures not clearly connected to the periods of pulmonary exacerbations (Figure 0-14, Figure 0-15, Figure 0-16, Figure 0-17, Figure 0-18). Her lung function showed a mean (SD) FEV_1 % predicted of 91.3% (6.3%). Her lowest recorded lung function was a FEV_1 % predicted 73.6% and that was recorded during a pulmonary exacerbation period in October/November. Towards the end of the 6-months it should also be noted that there is a loss of variability in respiratory rate, suggesting self-reporting of respiratory rate may not be reliable.



Figure 0-14 The results of the 7 wellness questions answered by BRN013 during her 6-month CLIMB-CF study period. Documented on the y axis are the wellness options she had the option of choosing from. The red triangles depict the start date of a pulmonary exacerbation. Improvements in score are associated with readings higher up the y axis.

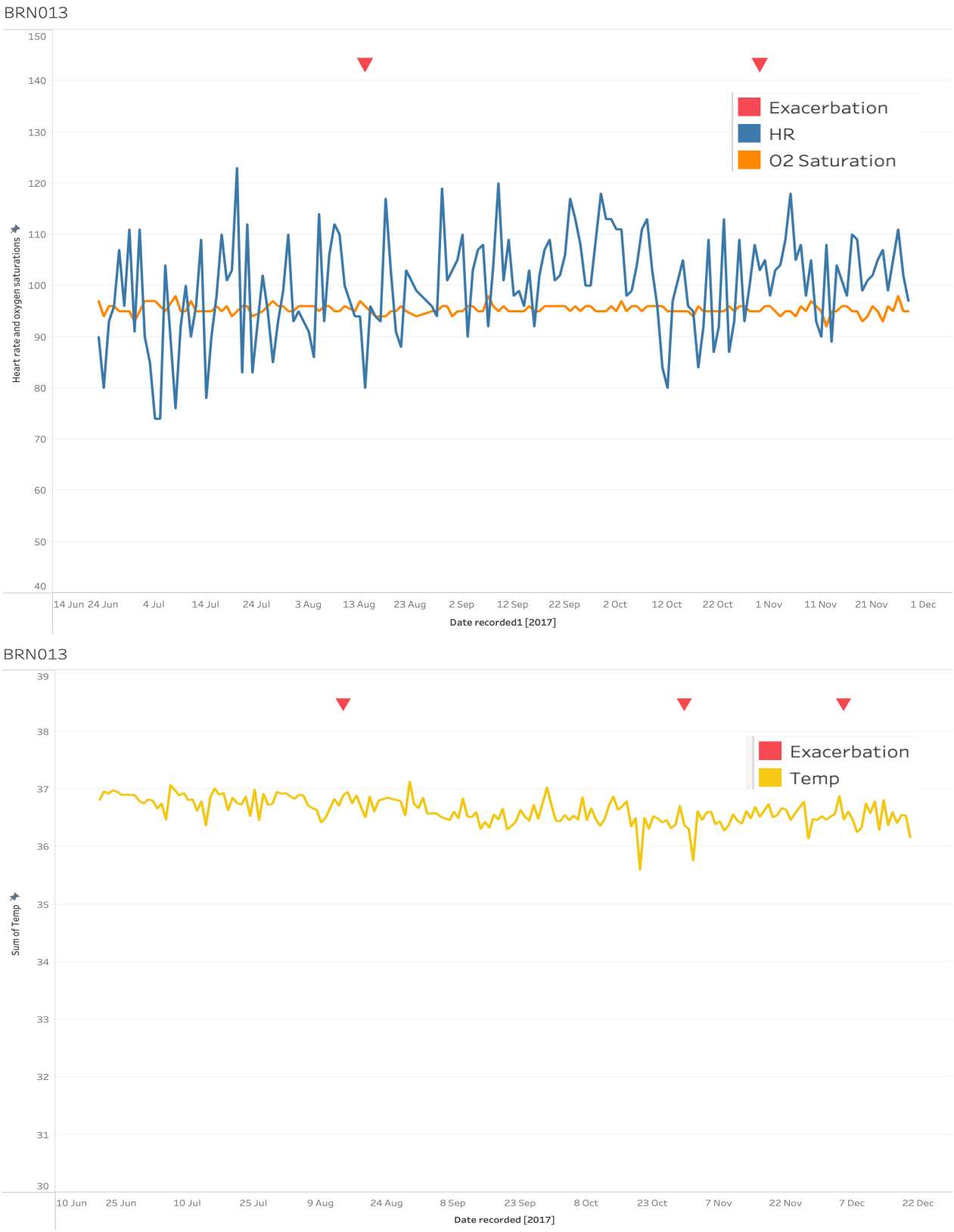


Figure 0-15 Heart rate, oxygen saturations (top graph) and temperature readings (bottom graph) for BRN013 during her 6-month study period. The red triangles depict the start date of a pulmonary exacerbation.

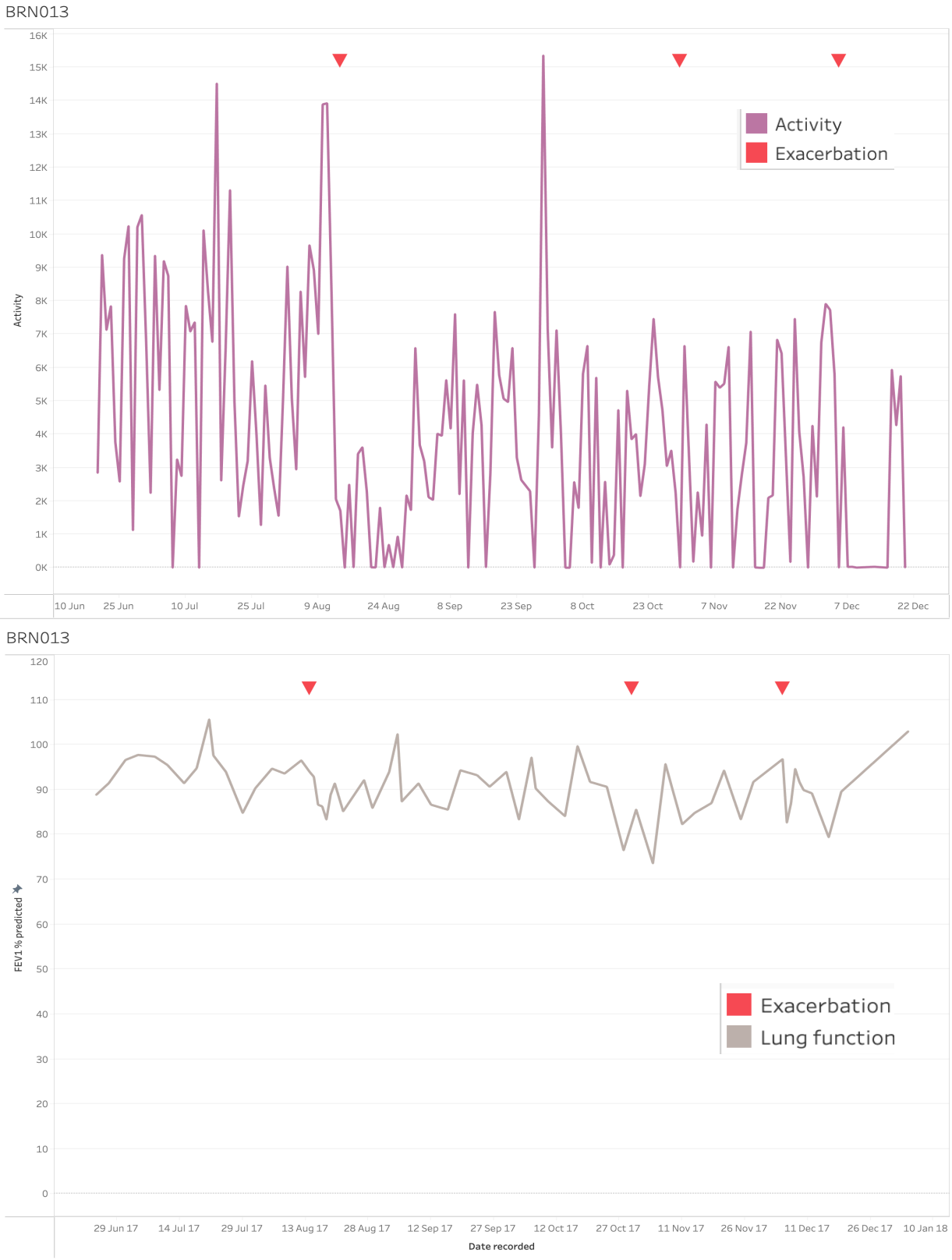


Figure 0-16 Activity in steps per day (top) and lung function as FEV_1 % predicted (bottom) for BRN013 for her 6-month study period. The red triangles depict the start date of a pulmonary exacerbation.

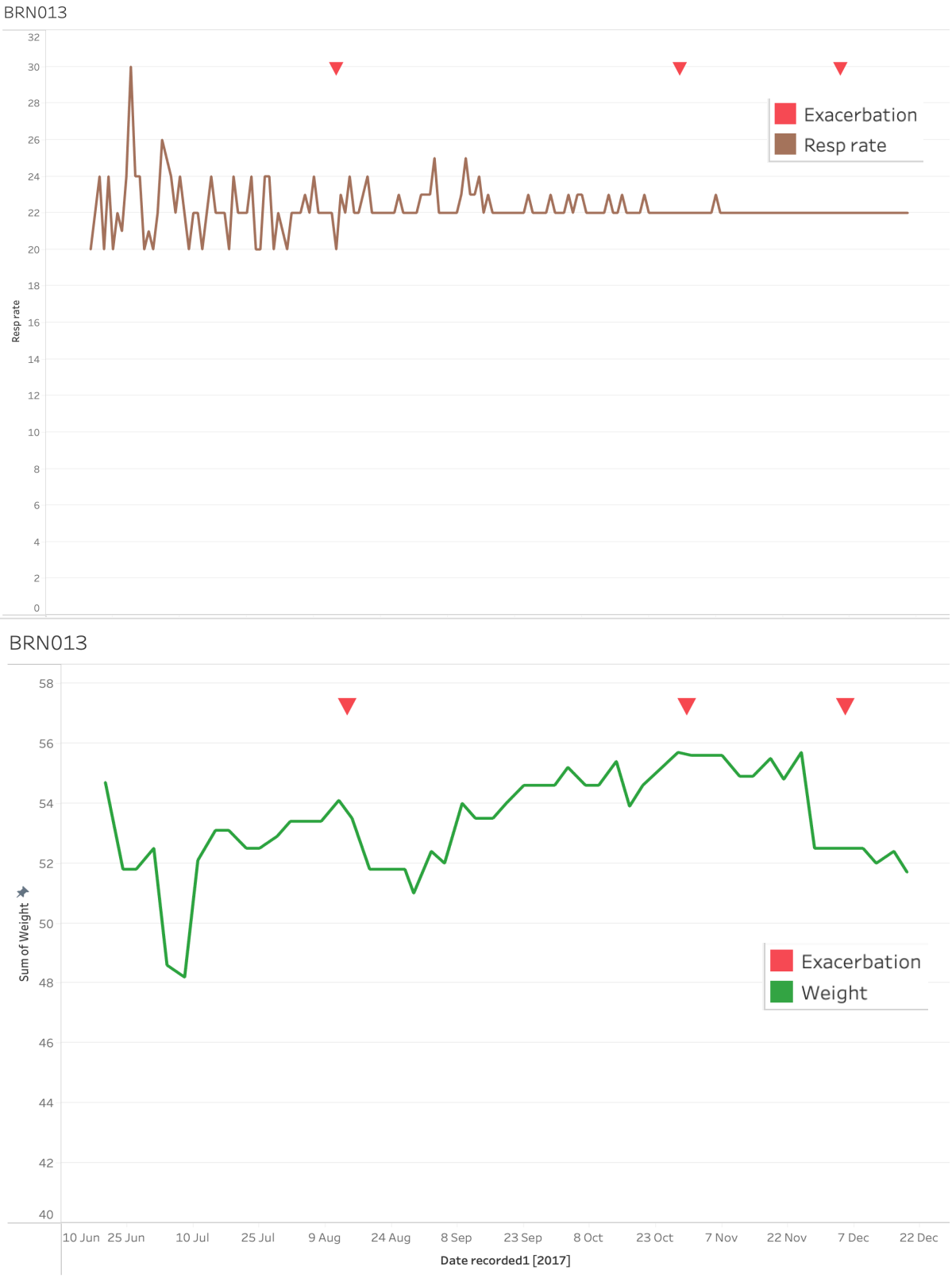


Figure 0-17 Respiratory rate in breaths per minute (top) and weight in kilograms (bottom) for BRN013 for her 6-month study period.

The red triangles depict the start date of a pulmonary exacerbation.

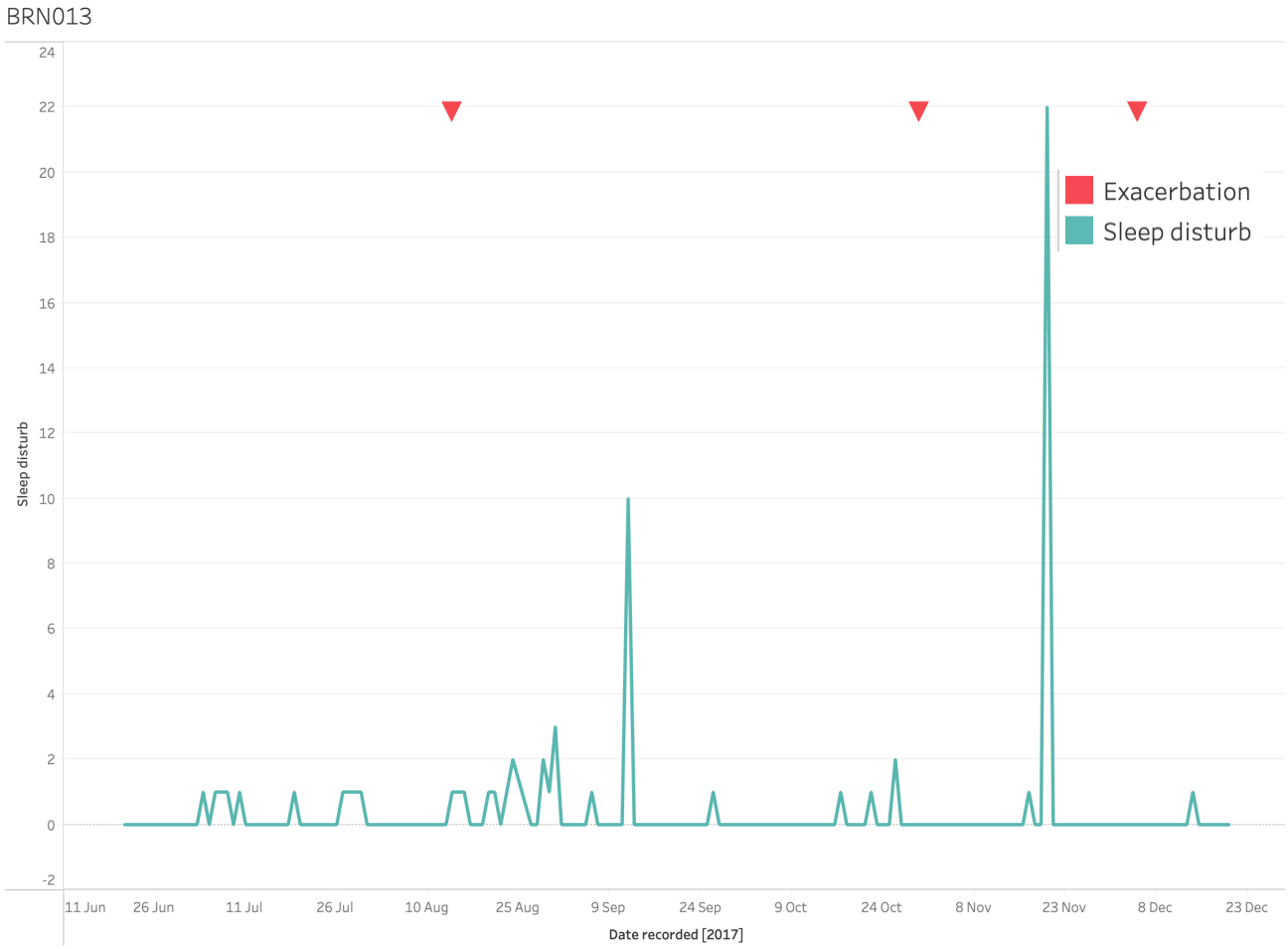


Figure 0-18 *The number of sleep disturbances reported per night for BRN013 for her 6-month study period. The red triangles depict the start date of a pulmonary exacerbation.*

Objective measures during periods of pulmonary exacerbations

Of the 14 participants who had at least one pulmonary exacerbation within the 6 months, 13 participants provided objective home monitoring data for analysis during periods of stability and pulmonary exacerbations. One participant was excluded as their exacerbation was documented at the end of study visit and had minimal associated readings. When comparing the whole groups data received during periods of stability with periods of pulmonary exacerbation, significant difference was seen in the median FEV_1 % predicted recorded. The difference between heart rate in the 2 groups also approached statistical significance. Similarly, when exploring CoV between the stable and

exacerbating groups this was approaching significance for FEV_1 % predicted and was significant for heart rate.

When exploring measures by individual, no measure showed a significant change in all participants between periods of stability and pulmonary exacerbations. However, 7 of the 13 participants were old enough to provide spirometry data, of those 7, 5 (71%) had a significant difference between their stable and pulmonary exacerbation spirometry results (Table 0-2, Table 0-3).

*Table 0-1 Medians and interquartile ranges for objective readings for the whole group during periods of stability and periods of pulmonary exacerbation and the results of the comparison analysis. Statistically significant p values are in red and highlighted with a *. Abbreviations IQR- interquartile range, CoV- coefficient of variation.*

	Stable Median (IQR)	**Pulmonary exacerbation Median (IQR)**	**p value**	**Stable CoV**	**Pulmonary exacerbation CoV**	**P value**
Activity steps per day	8057 (6262-11397)	7004 (5333-11713)	0.21	49.00	47.76	0.96
Heart Rate beats per minute	98 (95-108.3)	100 (94.8-112.5)	0.054	13.20	10.40	0.04*
Oxygen saturations percentage	98 (95.5-98)	98 (95-98)	0.5	1.800	1.100	0.57
Temperature degrees Celsius	36.5 (36.3-36.6)	36.5 (36.3-36.7)	>0.99	1.100	1.000	0.26
Weight Kilograms	30.7 (19.2-37.5)	29.6 (18.9-38.1)	0.75	3.300	2.600	0.55
FEV_1 % predicted	93.9 (77.1-99.9)	85.7 (75.5-91.3)	0.03*	8.200	9.400	0.07

*Table 0-2 Medians and interquartile ranges for objective readings per individual during periods of stability and periods of pulmonary exacerbation and the results of the comparison analysis. Statistically significant p values are in red and highlighted with a *. Abbreviations IQR- interquartile range, PEx – Pulmonary exacerbation, HR – Heart rate, 02- Oxygen saturations.*

	Activity Median (IQR)	Activity Stable vs PEx (p value)	HR Median (IQR)	HR Stable vs PEx (p value)	O2 Median (IQR)	O2 Stable vs PEx (p value)	Temperature Median (IQR)	Temperature Stable vs PEx (p value)	Weight Median (IQR)	Weight Stable vs PEx (p value)	FEV_1 % predicted Median (IQR)	FEV_1 % Predicted Stable vs Pex (p value)
NEW011 Stable	12794 (8854-16277)		95 (87-102)		98 (98-99)		36.42 (36.17-36.68)		31.8 (30.6-32.9)		95.9 (90.8-99.6)	
NEW011 PEx	14576 (10510-19901)	0.25	95.5 (86-102)	0.78	98 (97-99)	0.01*	36.58 (36.35-36.78)	0.06	31.9 (31.7-32.5)	0.74	91.4 (87.3-97.7)	0.12
RBH023 Stable	6662 (2361-8668)		97 (92-104)		96 (95-97)		36.51 (36.43-36.66)		34.2 (33.1-35.5)			
RBH023 PEx	5044(54-8093)	0.24	97 (89-105)	0.82	95 (94-98)	0.22	36.76 (36.69-36.83)	<0.0001*	34.7 (34.7-35.4)	0.27		
RBH008 Stable	6462 (4914-9290)		86 (81-94)		98 (97-98)		36.1 (35.89-36.31)		62.1 (61.5-62.6)		77.1 (75.4-79.1)	
RBH008 PEx	7004 (5378-10734)	0.16	88 (79-94)	0.94	97 (97-98)	0.17	36.23 (35.99-36.38)	0.06	63.1 (62.5-63.3)	0.001*	75.5 (73.9-77.3)	0.02*
LON004 Stable	6204 (4052-9298)		120 (114-126)		98 (98-99)		36.53 (36.33-36.94)		14.2 (13.9-14.5)			
LON004 PEx	5622 (609-6656)	0.06	119.5 (113-133)	0.59	98 (97-99)	0.36	36.36 (36.19-36.47)	0.01*	14.35 (14.2-14.5)	0.12		
IWK004 Stable	9260 (5963-11414)		95 (87-105)		98 (98-99)		36.87 (36.79-36.96)		31.35 (30.9-31.8)		81.7 (77.7-85.5)	
IWK004 PEx	7094 (4347-10508)	0.05	94 (87-100)	0.42	99 (98-99)	0.33	36.85 (36.8-36.93)	0.77	30.6 (29.7-31.3)	<0.0001*	82.1 (67.9-88.7)	0.84
BRN014 Stable	4651 (2237-6786)		103 (99-110)		94 (94-95)		36.65 (36.48-36.83)		40.9 (39.3-42.6)		75.3 (69.3-80.8)	
BRN014 PEx	4540 (2991-6267)	0.98	103.5 (95-110)	0.76	94 (94-94)	0.01*	36.66 (36.46-36.78)	0.45	41.5 (33.5-41.9)	0.26	67.9 (56.2-70.6)	0.007*
BRN013 Stable	4009 (2170-6670)		101 (93-109)		95 (95-96)		36.67 (36.49-36.85)		53.5 (52.5-54.6)		93.9 (87.4-97.5)	
BRN013 PEx	2644 (27-5734)	0.06	100 (93-108)	0.85	95 (95-96)	0.09	36.54 (36.42-36.7)	0.001*	52.5 (51.9-55.3)	0.73	89.5 (85.2-92.8)	0.003*

*Table 0-3 A table showing medians and interquartile ranges for objective readings per individual during periods of stability and periods of pulmonary exacerbation and the results of the comparison analysis. Statistically significant p values are in red and highlighted with a *. Abbreviations IQR- interquartile range, PEx – Pulmonary exacerbation, HR – Heart rate, 02- Oxygen saturations.*

	Activity Median (IQR)	Activity Stable vs PEx (p value)	HR Median (IQR)	HR Stable vs PEx (p value)	O2 Median (IQR)	O2 Stable vs PEx (p value)	Temperature Median (IQR)	Temperature Stable vs PEx (p value)	Weight Median (IQR)	Weight Stable vs PEx (p value)	FEV_1 % predicted Median (IQR)	FEV_1 % Predicted Stable vs Pex (p value)
ALD007 Stable	10000 (1000-13028)		85 (78-92)		98 (98-98)		36.29 (35.97-36.66)		30.7 (29.8-31.6)		99.9 (98-102.4)	
ALD007 PEx	11230 (8584-14195)	0.43	88 (79-93)	0.51	98 (97-98)	0.75	36.44 (36.09-36.76)	0.27	29.6 (29.6-30.9)	0.14	96.8 (95.8-98.3)	0.03*
ALD003 Stable	8486 (6642-10320)		97 (89-104)		98 (98-99)		36.27 (35.75-36.66)		25.1 (24.9-25.5)		100.1 (93.9-106.1)	
ALD003 PEx	7901 (5787-10818)	0.53	102 (96-111)	0.03*	98 (96-98)	0.001*	35.67 (35.24-35.85)	0.0002*	25 (24.5-25.6)	0.39	85.7 (80.1-101.6)	0.04*
RBH013 Stable	8057 (4936-11061)		116 (108-122)		98 (98-99)		36.3 (35.99-36.49)		18.35 (18.2-18.6)			
RBH013 PEx	6784 (5316-8688)	0.04*	118 (112-125)	0.06	98 (98-99)	0.04*	36.3 (35.91-36.6)	0.89	18.4 (18.3-18.9)	0.32		
LON007 Stable	12982 (10331-15347)		98 (92-105)		98 (98-98)		36.5 (36.33-36.63)		19.96 (19.7-20.2)			
LON007 PEx	13263 (10983-15026)	0.9	98 (92-104)	0.93	98 (97-99)	0.23	36.5 (36.34-36.7)	0.83	19.5 (19.3-20.3)	0.28		
IWK006 Stable	13415 (9318-15950)		111 (105-117)		97 (97-98)		36.8 (36.5-37)		25.2 (24.5-26.4)			
IWK006 PEx	12196 (9298-14306)	0.1	117 (107-126)	0.02*	97 (96-98)	0.29	36.8 (36.7-37.25)	0.12	24.9 (24.4-25.4)	0.13		
BRN017 Stable	6320 (4391-7836)		105.5 (98-112)		95 (94-96)		36.4 (36.21-36.66)		15.9 (15.7-15.9)			
BRN017 PEx	6098 (3680-7588)	0.42	108 (100-113)	0.32	95 (94-97)	0.99	36.37 (36.07-36.53)	0.19	16 (15.3-16.3)	0.25		

1.32 **Discussion**

The results in this chapter show that it is difficult to predict an exacerbation without the addition of machine learning or sophisticated mathematical analysis of all longitudinal measures as there is significant periods of variation noted during stability as well as during known pulmonary exacerbations.

While most data in this chapter are only from a small selection of participants who provided ≥ 80% of the requested data due to the consideration of future machine learning work (409-413), which makes reaching meaningful conclusions difficult some interesting initial patterns have emerged. In participants who were stable throughout the 6-month study there was visible variation in their results. As this is a retrospective analysis it is not clear if any action was taken during those periods of worsening symptoms and decreasing lung function. It could be postulated that the participant and their family felt this variation was within their normal clinical variation, or that it was discussed with their clinical team and again the decision was made that the variation was not secondary to a pulmonary exacerbation and did not require treatment. The clinical teams within this study did not have access to a participant's data in real time unless the participant chose to show them, it is possible that if the clinical team had been alerted to the changes in recorded measures in real time by the home monitoring app those episodes may have prompted treatment.

Analysis of the objective measures obtained during periods of pulmonary exacerbations of the whole group showed a statistically significant change in FEV_1 % predicted with the lowest FEV_1 % predicted

tending to be seen around the start date of an exacerbation for some participants (Figure 0-16) although again these data are limited by low numbers. This is similar to data from van Horck et al, who showed that FEV_1 % predicted tended to drop just prior to the start of pulmonary exacerbation treatment and that symptom score changes were an earlier predictor in their model showing a possible signal up to a month prior to the exacerbation start date, advocating for the potential that earlier changes in other measures may be useful prior to a decrease in FEV_1 % predicted (346). The ongoing machine learning work will look at the timing of FEV_1 decline and pulmonary exacerbations over the longitudinal data in more detail. It should also be noted that the difference in median FEV_1 % predicted during stability compared with the FEV_1 % predicted obtained during a pulmonary exacerbation was 8.2%, less than the 10% change accepted by some pulmonary exacerbation criteria, therefore would health care professionals deem this change clinically significant.

Individually while changes could be seen in some measures when they received treatment, these did not appear to be significantly outside the limits of change observed during periods of stability for most measures. This is in keeping with data shown by other authors that the views on the signs and symptoms experienced by people with CF and their regular treating clinicians do not always agree with arbitrary criteria, such as Fuchs, used to define a pulmonary exacerbation (156). These analyses suggest that moving forward it is unlikely to be one measure that can be used, rather it would require a collection of several measures in parallel and that it may need to be individualised (comparing data obtained from a person during their periods of stability and comparing it with their pulmonary exacerbation periods). This data could be inputted into a machine learning algorithm in real time. Predictive exacerbation modelling for asthma and adult CF is currently ongoing (344, 414).

One of the strengths of this study is that it is the first paediatric home monitoring study that includes additional wellness questions and objective measures such as heart rate, oxygen saturations and weight. This contrasts with van Horck *et al* who only asked three questions: cough, sputum, and dyspnoea on a scale of 0-3 (346). While, as of yet, it is not known which measures in paediatric CF may be predictive there is evidence from adult CF studies that a general wellness question, heart rate and oxygen saturations may strengthen a predictive model for pulmonary exacerbations (344).

One of the weaknesses of this study is the pragmatic decision made regarding the definition of a pulmonary exacerbation. As this was a feasibility study no criteria were given to sites regarding the diagnosis of a pulmonary exacerbation, this was decided clinically by health care professionals at each site. There is also the potential that the health care professional making the treatment decision may have also been in involved in CLIMB-CF which may have impacted their choice. As there is no standardized definition or treatment choice for an exacerbation there may have been variations between sites for which I am unable to correct. The start date for an exacerbation was documented as the start of antibiotics, however this does not allow for preceding symptoms prior to the prescription of antibiotics versus a possible noted drop in FEV_1 at a clinic appointment. This is also the date the antibiotic is prescribed rather than the definite start date of the antibiotics received by the participant. This definition has been used previously by other authors (128, 415) and was felt to be the most appropriate for this study. Analysis around the exacerbation was also expanded to include the week prior to the pulmonary exacerbation start date in an attempt to capture changes prior to the defined start date of the pulmonary exacerbation. However, for further work utilising our home monitoring platform a definition for a pulmonary exacerbation should be standard for all sites involved. In future studies the treatment choice will also need to be considered. In the eICE study it

was found that while participants in the early intervention (home monitoring) arm had more acute reviews by their CF centre, they also were more likely to receive oral antibiotics and they were unable to demonstrate a slower decline in FEV_1 percent predicted, potentially be down to treatment choice (341, 342).

Another limitation is that despite spirometry being the most completed measure requested during the study, the number of spirometry readings provided did not increase around periods of increased respiratory symptoms as had been requested. This could be due to the fact the participant was unable to complete spirometry due to their symptoms (as documented by one participant in their 'What's up?' diary) or that participants did not want to see what their lung function may have dropped to or that participants simply forgot as there was no specific alert on the app to remind them or to request the measure more frequently based on a change in their other parameters. This could be addressed in the future by routinely setting reminders within any future study apps and ultimately an alert requesting a spirometry reading due to changes recorded in other measures. This alert could be sent directly to the patient or could be sent to the health care team prompting a discussion with the patient and a decision regarding the need for treatment.

The retrospective nature of the study analysis means that unfortunately it is unknown what sign or symptom/s triggered the course of antibiotics for a pulmonary exacerbation. In future studies it would be useful to set criteria to define a pulmonary exacerbation but also to capture the reasoning behind any pulmonary exacerbations that do not meet the criteria but ultimately receive treatment.

Unfortunately, limiting analysis to only participants who completed ≥ 80% did reduce the number of participants included in the analysis. It should be noted though that after the initial stage of machine learning, participants with a less complete data set can be added to the algorithm (344). The data obtained from CLIMB-CF are currently being used in ongoing machine learning work with the team involved in the SmartCareCF analysis at the Cambridge Centre for AI in Medicine and the Machine Intelligence Group at Microsoft Research, to try and identify patterns or signals in the change of the data leading up to possible exacerbations to identify an algorithm that could be used clinically in the future. The initial stages of this work involve comparing the paediatric data with the algorithm from the SmartCareCF study to explore potential differences and similarities in the data set and then running separate analysis on the paediatric data with the additional data points collected in our study such as the additional wellness questions around appetite, breathlessness, sputum volume and tiredness and the additional objective measure of temperature.

This chapter explored the hypothesis that home monitoring could be used to predict pulmonary exacerbations by assessing the variability of measures during stability and periods of pulmonary exacerbation. The results of this chapter show that further work is needed within this area before home monitoring can be shown to predict pulmonary exacerbations. The next chapter presents the accuracy and variability of handheld spirometers, further addressing the question regarding feasibility of home monitoring.

Chapter 6 –Accuracy of handheld spirometers and remote spirometry readings

1.33 Introduction

Handheld spirometers have been commercially available for several years and have been used in both healthy adults and adults with a range of lung diseases. However, there is ongoing discussion regarding the accuracy of the handheld spirometers, the need for calibration of handheld spirometers, whether the data received via a handheld portable spirometer are equivalent to data obtained in a clinical setting and whether the use of a handheld device needs to be supervised by a trained professional.

There are three main different types of technology utilised in home spirometers: differential pressure pneumotachographs, which measure pressure changes across a flow sensor; ultrasonic flow meters, which include two ultrasonic transducers either side of the exhaled jet of air that emit and receive sound in alternative directions and integrated transit times into flow volume loops; and finally, turbine flow meters (416).

Unless specified below, described studies utilise a device with a turbine flow meter. Turbine flow meters work by having a swirl plate with a low inertial vane behind. The swirl plates deflect the flow of air past the vane, converting air flow from linear to helical. This in turn powers the vane and the frequency with which the moving vane then interrupts a pair of infrared beams is converted to a flow measurement and the number of pulses is proportional to volume (416).

The majority of these studies compare one handheld spirometer with a conventional hospital spirometer, usually under direct supervision with a trained professional.

Published data from adults

200 adult participants (150 with a variety of respiratory conditions and 50 healthy volunteers) performed paired spirometry readings on the Air Next handheld spirometer and the calibrated clinic spirometer (MIR Spirolab) (417). The order with which spirometry was performed was randomised and traces were assessed for quality according to ATS/ERS guidelines. The authors reported high levels of correlation between the handheld and clinic spirometer on all spirometry parameters (FEV_1 person correlation 0.976, intraclass correlation coefficients 0.976). They concluded the Air Next was reliable when used in a supervised manner. It should be noted that while visual Bland-Altman plots are provided, the actual values recorded by the two devices and the bias and limits of agreement are not reported in this study. Therefore, care needs to be taken accepting the levels of correlation presented as an over read by one device of double the recorded value of the other device would provide a perfect correlation but could not be used interchangeably clinically.

The use of home spirometry to monitor patients for pulmonary complications after an allogenic haematopoietic cell transplant has been explored. 437 participants were provided with the KoKo Peak spirometer and the nearest home readings to the clinic reading (using a Sensormedics device) were compared. The group found a small but negative bias for home spirometry readings at baseline, 80 days post-transplant (FEV_1 -0.13L 95%, CI -0.19- -0.8L) and 1-year post-transplant (FEV_1 -0.1L 95% CI -0.19—0.2L), with stronger correlation between readings the closer to each other they were. These

results led the authors to conclude home spirometry was a valid way to monitor these patients over time (418).

Barr and colleagues compared the accuracy of the EasyOne ultrasonic handheld spirometer to conventional clinic spirometry (using a volume-sensing, dry rolling seal spirometer) in 24 spirometry naïve adult participants (3 with an underlying diagnosis of asthma, 21 healthy) (419). Participants performed supervised spirometry twice on the handheld device then one final time supervised on the clinic spirometer at the same visit. Results were assessed for ATS acceptability and reproducibility criteria. They found significantly lower spirometry values in all readings except peak flow using the handheld spirometer. The handheld spirometer met criteria for reproducibility for FEV_1 but not FVC. There is the potential of a learning effect in these results as these participants were spirometry naïve and performed the clinical spirometry last, however it suggests further training may be beneficial before a spirometry naïve patient performs remote spirometry.

200 participants with a wide selection of respiratory conditions carried out paired supervised spirometry readings on the handheld Air-Smart spirometer or the clinic spirometer (Jaeger Master screen) (420) in random order. Bland Altman analysis revealed a mean bias of almost 0ml (95% limits of agreement -35ml to +35ml) for FEV_1. However, they did find a statistically significant bias when analysing FVC (-0.128L; $p<0.001$). The authors concluded that while this bias was statistically significant, it was not sufficiently large to be clinically relevant and therefore the Air-Smart spirometer was comparable to the conventional clinic spirometer. Similar results were obtained by Ramos et al who also concluded the Air-Smart was precise in an adult cohort and could be used for diagnosis and subsequent screening of respiratory conditions (421).

In 2016, one study reviewed adult spirometry results from 17 primary care offices in the USA using handheld spirometry units and found only 60% of the submitted readings met ATS/ERS criteria despite patients being supervised when carrying out spirometry (422) . They postulated that that was because most of the health care professionals had not received formal spirometry training and that a potential way to avoid such a high failure rate would be to upload the flow volume loops to a secondary or tertiary centre for review.

Recently, more papers have explored the accuracy of unsupervised home spirometry in adolescents and adults. A recent publication from the eICE study group analysed the data received from unsupervised home spirometry (AM2+ ® Lung function Monitor) readings from their participants aged ≥ 14 years of age and compared them to clinic readings obtained within a 7-day window (423). They found that home FEV_1 readings were 2 percentage points lower (95% CI 0.3,3.5) than the supervised clinic FEV_1 measurements. They also noted that longitudinal home spirometry remained lower than clinic spirometry over the yearlong study period, not showing a learning effect. However, it should be noted that the cohort providing 5 readings, that had matched clinic readings, over the yearlong study comprised only 44 participants, leading the authors to note that a larger longitudinal sample size may be needed for future longitudinal modelling studies.

Paediatric studies

76 children (aged 6 to 17) carried out supervised spirometry on a conventional clinic spirometer (Vmax Encore System) and Micro Loop handheld spirometer (424). The order of testing was randomised, and readings were compared to ATS/ERS criteria. Data on the handheld spirometer for 3 participants were rejected due to ATS/ERS criteria (1 participant also failed to satisfy those criteria

on the clinic spirometer). Bias in FEV_1 was reported as -65ml (limits of agreement +189 to -319mls, $p<0.001$) and FEV_1 % predicted was -2.4% (limits of agreement +9 to -13.9%, $p<0.001$). 15% of people tested had a ≥ 10% lower FEV_1 % predicted on the handheld device. They found the order of testing did not impact the results, with no fatigue effect noted. Based on these results they concluded that the devices could not be used interchangeably.

In asthmatic children, supervised spirometry using the EasyOne portable spirometer, an ultrasonic spirometer, compared with supervised clinic spirometry (a dry rolling seal spirometer) showed a mean (95% confidence interval) 0.02L (-0.08-0.15L) underread by the portable spirometer (425). In the same study they also compared the physicians' view of the flow volume loops with the inbuilt quality control software of the EasyOne portable spirometer and found that 25% of curves accepted by the internal software were rejected by the physicians. This was almost always due to problems at the end of the test, such as a cough, which may not have influenced FEV_1 readings.

Shakkottai and colleagues compared unsupervised home spirometry with corresponding clinic spirometry readings in 30 children with CF over the yearlong study period (348). They compared readings at 3, 6, 9 and 12 months and reported a high intra-class correlation (0.8). It is not clear how close the home spirometry reading was to the supervised clinic spirometry.

The success of supervised remote spirometry has been explored in children (426). Twenty-five children aged between 7 and 17 years participated in a pilot of remote, supervised spirometry using a SpiroUSB spirometer. Three participants were unable to take part as they did not have access to the technology required to participate. One participant had failed sessions due to unexplained

technological issues. 93% of attempted sessions met ATS/ERS criteria, leading the authors to conclude that remote supervised spirometry was feasible. No comparison of the results obtained remotely to the results obtained in clinic were made.

A combined study of young people with CF (n=23) and asthma (n=66) comparing same day clinic spirometry (MasterscreenTM Pulmonary Function Testing unit) with unsupervised home spirometry (Jaegar home monitor) found significantly lower home spirometry readings compared to clinic readings for both the young people with CF and with asthma (CF-mean difference 0.18L, 95% CI 0.08-0.27, asthma – 0.12L, 95% CI 0.05-0.19L) with no significant learning effect seen in either cohort (427). In the CF cohort they found that 50% had a difference of ≥ 0.15L, which was above the authors predetermined acceptability criteria based on ATS/ERS guidelines. In both the CF cohort and the asthma cohort the mean difference between the home and clinic readings increased with age.

This contrasted with results published by Kruizinga and colleagues, who reported technical validity of the Air Next device (Nuvoair) in children with asthma (n=50) and CF (n=7) and found a FEV_1 mean bias of 40ml (95% limits of agreement were -270ml and +352mls) (428). Participants continued to measure their lung function unsupervised at home and of 1821 home spirometry readings, 45% of them were considered acceptable and reproducible according to ATS/ERS criteria (428). The authors also explored device variability using a fixed volume calibration syringe (2994ml). They tested 20 devices 20 times. They found an intra-device CoV of 0.9% and an inter-device CoV of 2.8%, with 4% of the measurements failing to meet the 3% accuracy threshold in the ATS/ERS standards.

More recently, comparison of supervised home spirometry vs unsupervised spirometry using a Air Next device (NuvoAir) home spirometer in children found that when supervised, high-quality measurements were achieved in almost 90% of cases, compared to significantly fewer (74%) when unsupervised (429). 13 patients from the unsupervised home spirometry group (n=31) required further assistance from the clinical team for technique reasons. The data in this study were not compared with supervised clinic spirometry.

It should also be noted that the intrinsic variability of within spirometry values may vary between diseases and depend on the amount of airway liability in a participant (430). The spirometry manoeuvres themselves may change the airway properties of a participant e.g., bronchoconstriction in asthma or shifting mucus in CF and these factors may be relevant in studies that require multiple attempts on the same day. Some of the above studies have attempted to account for this by randomising participants to which spirometry method they perform first.

Calibration concerns

Calibration of handheld spirometers has also been an area of concern as many do not provide calibration information with the product information provided by the company. It has been stated that turbine flow spirometers are not affected by humidity or temperature so are stable and do not require regular calibration (416). There has been work exploring the long-term stability of turbine flow spirometers. Dirksen and colleagues checked the accuracy of 30 turbine flow spirometers monthly over a 2-year period in an adult study of patients with emphysema using 1L and 3L calibration syringes. They found that none of the handheld spirometers exhibited significant drift with the coefficient of variation of the calibration signal of 1-2%. One spirometer broke during that

period requiring replacement. They also found readings at the 3L volume were more accurate than readings at the 1L volume (431). Similar results have been shown in ultrasonic flow devices (432).

This chapter presents data exploring the accuracy of handheld turbine spirometers and the similarity of unsupervised home spirometry readings and supervised clinic readings, as well as variability of unsupervised home spirometry readings over time during periods of stability. The data within this chapter will be used to help address the hypothesis that home monitoring is feasible by aiming to assess the quality of the data received from home spirometry.

1.34 Methods

1.34.1 Unsupervised home spirometry readings compared to supervised clinic readings

Data from children aged ≥ 6 years of age were included in this analysis since guidelines for spirometry in children aged <6 recommend supervision by trained professionals (430). Paired readings were included if there was a supervised clinic spirometry reading on the same (or +/- 1) day as an unsupervised home spirometry reading. Each participant's first readings in the study that met these criteria was used in this analysis. Participants who had multiple (3+) readings during the study period that met these criteria were included in secondary analysis exploring temporal trends for evidence patterns suggesting either learning or fatigue. For this analysis their first, second and last paired readings were included. Throughout CLIMB-CF the handheld spirometer used by participants was the Vitalograph lung function monitor BT Smart.

Vitalograph software developers kit (Vitalograph, Buckingham UK) was purchased to enable download of data from the handheld Spirometers and visualise the flow volume loops.

1.34.2 **Variation in unsupervised home spirometry readings during period of stability**

As above, analysis included all participants who were aged ≥ 6 years of age and provided unsupervised home spirometry readings during the study period. To explore variation during periods of stability, all readings within the 4 weeks before and after the documented pulmonary exacerbation were excluded.

1.34.3 **Testing of handheld spirometers from three manufacturers using fixed volume calibration syringes.**

For this analysis two volume syringes were used; the 1 litre (L) fixed volume syringe (CareFusion calibration pump, Germany) and a 1 litre to 3 litre variable volume syringe which was set to 3L for the duration of the testing (Series 5530, Hans Rudolph inc, USA). Volumes of both syringes were recorded in triplicate on a calibrated Jaeger Vyntus Pneumo Spirometer (Vyaire Medical, Illinois, USA) which was located in the Lung Function Department at RBH. For each recording, all air was expelled from the syringe in one smooth motion. Once each of the triplicate tests for each syringe were recorded and the mean calculated, each syringe was used to test handheld spirometers from 3 different manufacturers. Four brand new, unused, handheld turbine spirometers were tested straight from the box. Devices were tested in triplicate at each syringe volume on 4 separate occasions and in a random order. The handheld spirometers and manufacturers were: Vitalograph lung function monitor BT Smart (the handheld spirometer used by participants in CLIMB-CF), Air Next (Nuvoair, Stockholm, Sweden) and MIR Spirobank Smart (MIR, Langlade, France).

1.34.4 **Statistics**

<u>Clinical spirometry</u>

All uploaded unsupervised home spirometry and documented supervised clinic spirometry readings were converted using Global Lung Initiative (GLI) normative data to obtain FEV_1 % predicted using the height documented for the participant in their closest corresponding clinic appointment.

Correlation coefficients were calculated for the supervised clinic spirometry and the unsupervised home handheld spirometry. Bland Altman plots were then generated to explore the agreement between the supervised clinic spirometry readings and the unsupervised home spirometry readings. The bias and standard deviation were calculated by subtracting the unsupervised handheld spirometry readings from the supervised clinic spirometry readings.

Testing of the devices

Means and standard deviation (SD) for each manufacturer were calculated by combining all replicates for the 4 devices per manufacturer.

1.35 **Results**

1.35.1 **Analysis of the home spirometry flow volume loops**

Unfortunately, despite numerous phone calls and emails with Vitalograph technology support I was unable to get the Vitalograph software developers kit to recognise the handheld Spirometers. I was therefore unable to assess the quality of each spirometry attempt independent of the internal validation within the spirometer.

1.35.2 **Comparison of home and clinic spirometry**

Of the 144 participants recruited to CLIMB-CF, 99 were provided with home spirometers and contributed at least one measurement. 67 participants had readings that met the inclusion criteria for analysis of home spirometry compared to clinic spirometry; their median (IQR) age was 10.7 years (7.6-13.9). In general, the home spirometers under-read: 51 (77.6%) participants' home readings were lower than their clinic readings. The mean (SD) bias for FEV_1 % predicted was 6.5% (± 8.2%) with wide limits of agreement -9.6% to +22.7%. The mean (SD) bias for FEV_1 in litres was 0.14L (± 0.2L) and again wide limits of agreement -0.27L – +0.54L (Figure 0-1,Figure 0-2).

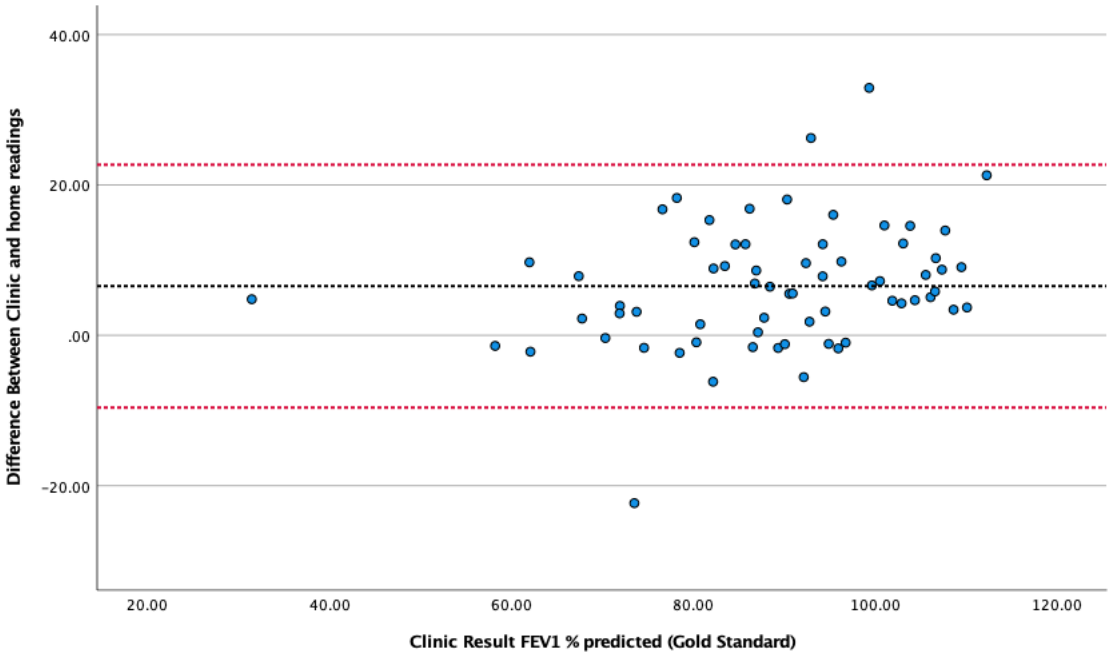


Figure 0-1 Bland -Altman plot for all participants aged 6 years and over with paired clinic (Gold standard) and home spirometry measurements in FEV_1 percent predicted. The red dotted lines indicate the limits of agreement, and the dotted black line is the mean difference (bias) Abbreviations: L-litres FEV_1- Forced expiratory volume over 1 second.

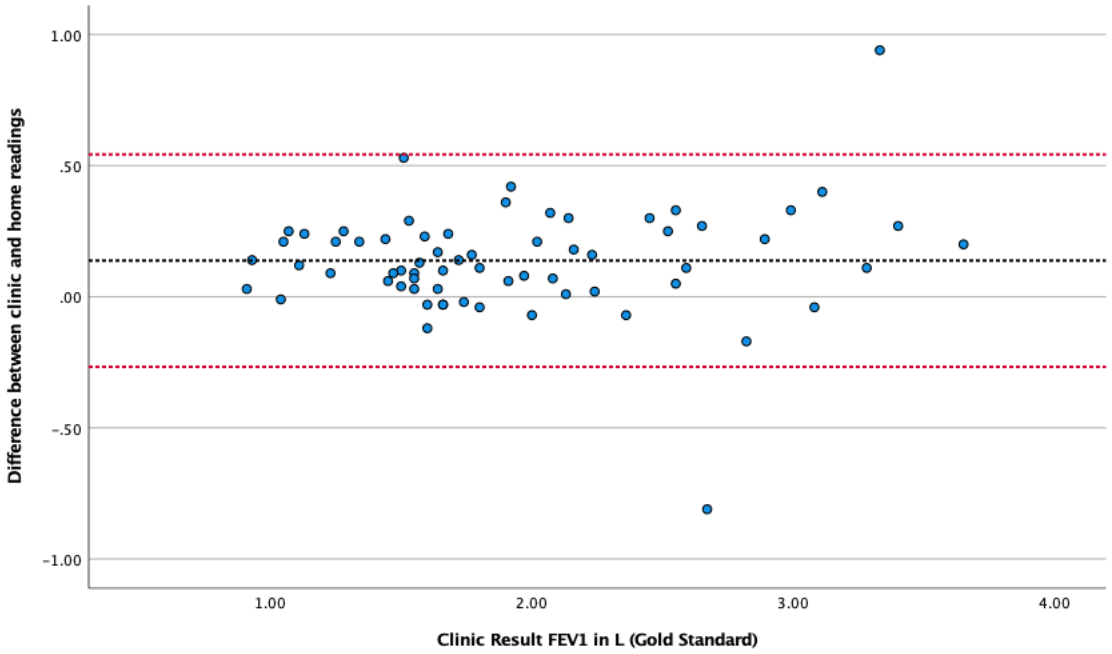


Figure 0-2 Bland -Altman plot for all participants aged 6 years and over with paired clinic (Gold standard) and home spirometry measurements in FEV_1 in litres. The red dotted lines indicate the limits of agreement, and the dotted black line is the mean difference (bias) Abbreviations: L-litres FEV_1- Forced expiratory volume over 1 second.

When further exploring differences in home and clinic FEV_1 in litres, there was no relationship with age and the discrepancy. However, the discrepancy in FEV_1 % predicted was significantly greater at the younger ages (Figure 0-3, Figure 0-4).

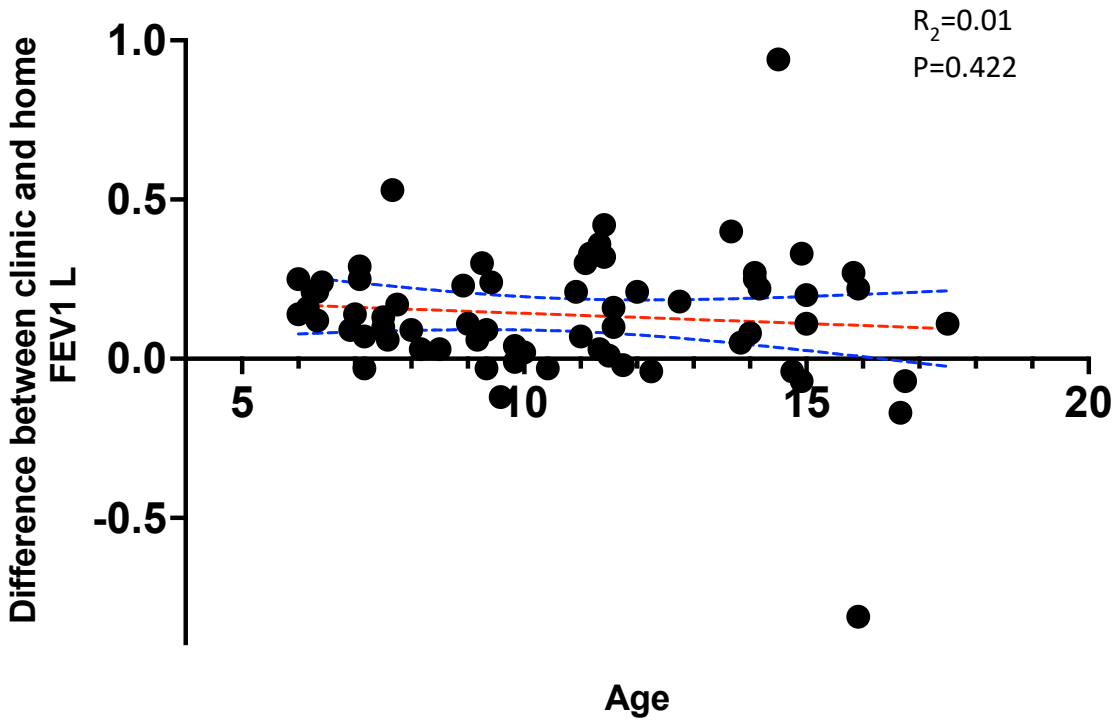


Figure 0-3 Difference between supervised clinic and unsupervised home spirometry readings of FEV_1 in litres shown by age of participant. (Blue lines represent the 95% confidence interval)

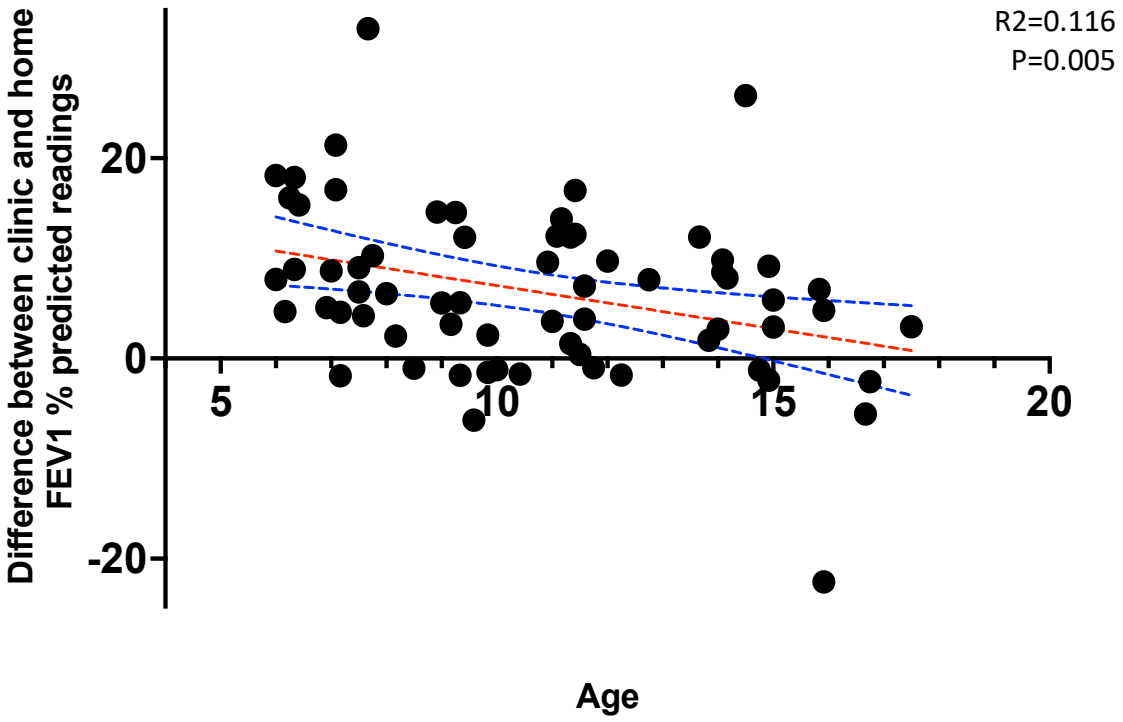


Figure 0-4 Difference between supervised clinic and unsupervised home spirometry readings of FEV_1 in percent predicted shown by age of participant. (Blue lines represent the 95% confidence interval)

I considered the possibility that the wide limits of agreement observed could have been due, in part, to the fact that measures from different days were compared. As an additional analysis, I therefore compared data from 29 participants who had unsupervised home spirometry readings on the same day as their supervised clinic spirometry with 15 participants who had home spirometry readings from the day before clinic and the 23 participants whose home spirometry readings were from the day after clinic. The mean difference and standard deviations were similar and not significantly different regardless of the day (Table 0-1).

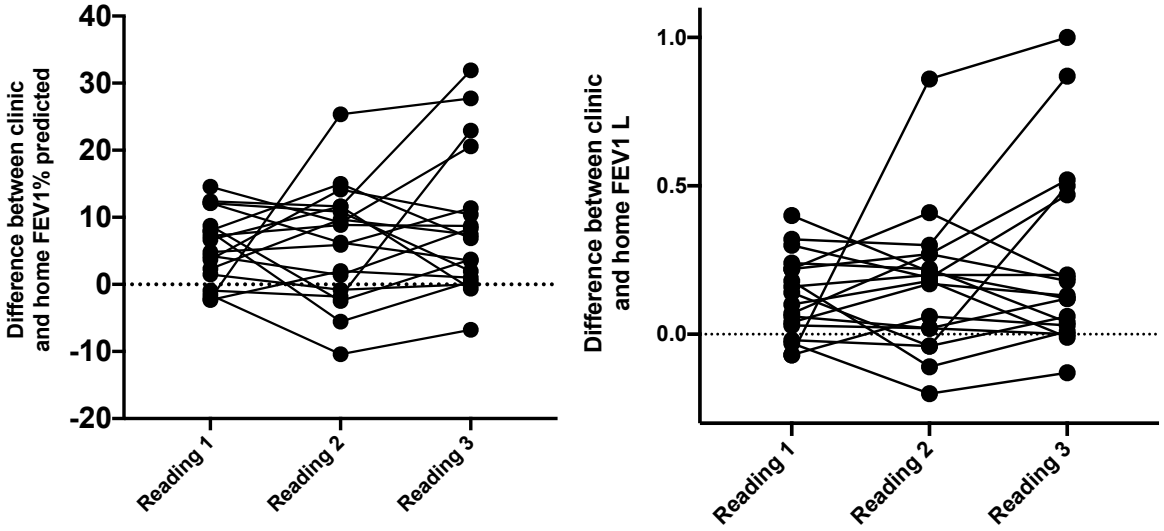
Table 0-1 Differences between home and clinic spirometry by day of home spirometry reading in relation to supervised clinic reading shown by FEV_1 percent predicted and litres. Abbreviations IQR- interquartile range, FEV_1- forced expiratory volume over 1 second, SD – standard deviation

	Difference in clinic vs home readings from day before clinic	**Difference in clinic vs home readings from day of clinic**	**Difference in clinic vs home readings from day after clinic**	**p value**
FEV_1 % predicted Mean (SD)	8.6% (9.8%)	5.4% (8.4%)	7% (6.7%)	0.64
FEV_1 in L Mean (SD)	0.17L (0.16L)	0.14L (0.26L)	0.12L (0.14L)	0.83

18 participants provided at least 3 pairs of readings during the study period that met the inclusion criteria. The median (IQR) age of this group was 11.3 years (7.6-13.87). Their 1st, 2nd and last readings were compared. There was no evidence of a learning effect of repeated measurements or worsening of the agreement as a group but there was individual variation (Table 0-2, Figure 0-5).

Table 0-2 Differences between home and clinic spirometry by days into the study shown by FEV_1 percent predicted and litres. Abbreviations IQR- interquartile range, FEV_1- forced expiratory volume over 1 second

	Days into the study Median (IQR)	**Difference in clinic vs home FEV_1 % predicted Median (IQR)**	**Difference in clinic vs home FEV_1 L Median (IQR)**
Reading 1	0.5 (0-39)	5.7% (0.9-9.5%)	0.12L (0-0.23L)
Reading 2	66.5 (39-100)	7.5% (-1.1-25.4%)	0.2L (0-0.27L)
Reading 3	123 (110-162)	7.1% (0.9-13.7%)	0.13L (0-0.5L)



Panel A Panel B

Figure 0-5 Differences between home and clinic spirometry readings plotted by individual for the 18 participants. Panel A shows FEV_1 percent predicted, and panel B shows FEV_1 in litres. Abbreviations FEV_1 Forced expiratory volume over 1 second. L – litres

1.35.3 **Variability of unsupervised home spirometry readings during periods of stability**

When variability of FEV_1 % predicted readings was looked at during periods of stability, 74 participants contributed data. Median (IQR) age was 10 years (7.8-12.7 years). Median (IQR) number of serial readings during periods of stability was 20 (8-35). The median (IQR) CoV of FEV_1 % predicted was 9.9% (5.8-14.2%).

While participants were provided with nose clips within the handheld spirometry kit there is no way to know if they were used. Similarly, while home spirometry was requested after physiotherapy it is unclear if this was adhered to.

1.35.4 **Accuracy of different manufacturer handheld spirometers**

To our knowledge at the time of the CLIMB-CF study set up the Vitalograph lung monitor BT was the only fully Bluetooth enabled handheld spirometer on the market. As demonstrated above I found that unsupervised home spirometry showed ~10% variation during periods of stability and wide limits of agreement when compared to supervised clinic spirometry. In view of this I wanted to explore the device's accuracy when tested using a fixed volume calibration syringe. The opportunity was also provided to test 2 further handheld spirometers that had subsequently become available to inform equipment choice in future studies.

The results of the 1L and 3L syringes when tested on the Jaeger Vyntus Pneumo Spirometer demonstrated a mean (SD) FEV_1 of 1.01 (0)L and 3.06 (0)L respectively. CoV for the 1L syringe was 0% and for the 3L syringe was 0.19%. Of the 3 devices, the MIR Spirobank Smart was found to have consistent and statistically significant mean (SD) under-reads of 60.6 (18.5) ml (p=0.01) and 101(21.8) ml (p=0.03) at 1L and 3L respectively. The Vitalograph lung monitor BT Smart also underread by a mean of 65.6 (21.1) ml at 1L (p=0.004) and 30 (50) ml at 3L (ns). The Air Next (Nuvoair) provided values which were not significantly different from calibration syringes at both volumes an underread of 10 (26.8) ml at 1L, and an overread of 20 (28.7) ml at 3L. Figure 0-6 shows the mean (SD) of the triplicate readings for all readings of an individual spirometer.

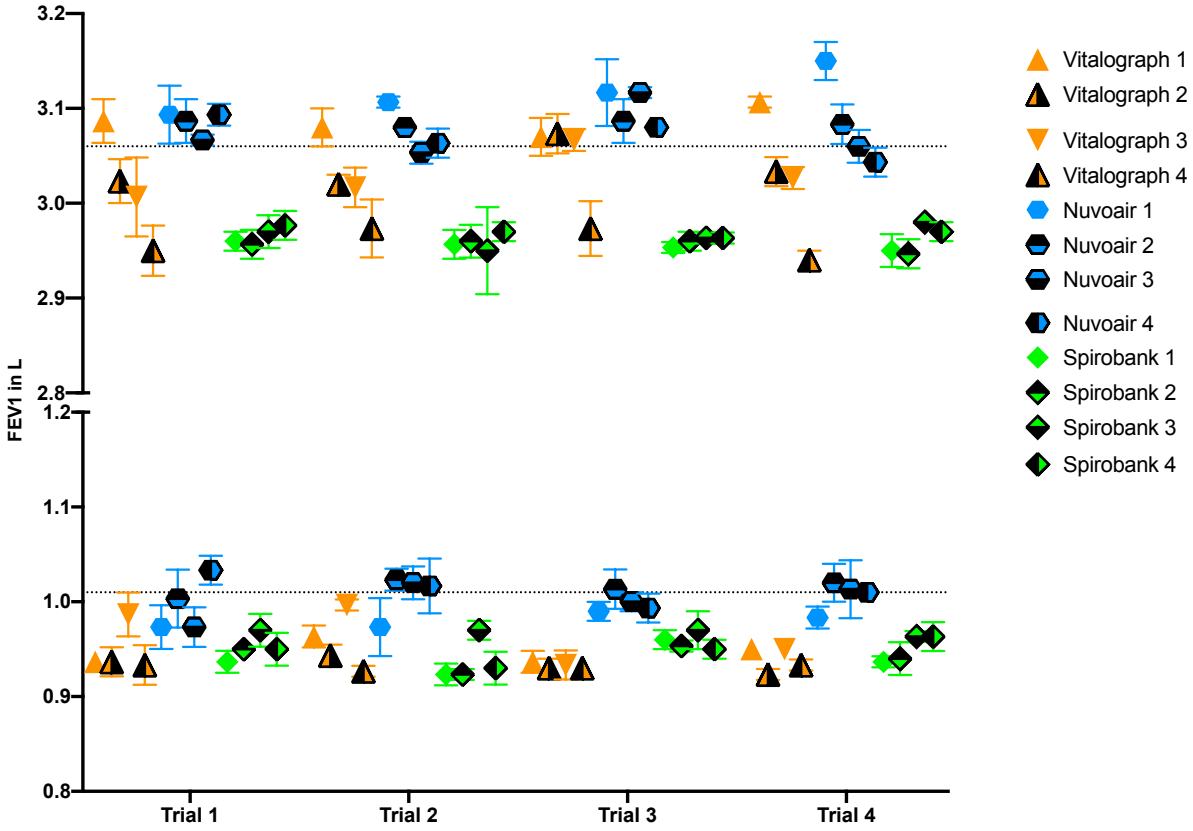


Figure 0-6 Mean (SD) of the triplicate readings obtained over 4 separate trials for each individual spirometer (labelled 1-4 and by manufacturer). The dotted lines represent the mean of the triplicate readings obtained on the Jaeger Vyntus Pneumo spirometer

The means, SD and CoV of all readings for each device at 1L and 3L are shown in Table 0-3 and Table 0-4. One spirometer (Vitalograph 3) had a CoV of over 3%.

Table 0-3 Mean (SD) with coefficient of variation by device using the 1L syringe. Abbreviations SD-standard deviation, L-litre

	Mean (SD)	Coefficient of Variation
1L Syringe	1 (0)	0.00%
Vitalograph 1	0.95 (0.01)	1.40%
Vitalograph 2	0.93 (0.01)	1.30%
Vitalograph 3	0.97 (0.03)	3.10%
Vitalograph 4	0.93 (0.01)	1.10%
Nuvoair 1	0.98 (0.02)	1.90%
Nuvoair 2	1 (0.02)	2.00%
Nuvoair 3	1 (0.03)	2.60%
Nuvoair 4	1 (0.02)	2.10%
Spirobank 1	0.94 (0.02)	1.70%
Spirobank 2	0.94 (0.02)	1.60%
Spirobank 3	0.97 (0.01)	1.30%
Spirobank 4	0.95 (0.02)	1.90%

Table 0-4 Mean (SD) with coefficient of variation by device using the 3L syringe. Abbreviations SD-standard deviation, L-litre

	Mean (SD)	Coefficient of Variation
3L Syringe	3.06 (0.01)	0.19%
Vitalograph 1	3.09 (0.02)	0.68%
Vitalograph 2	3.04 (0.03)	0.89%
Vitalograph 3	3.03 (0.03)	1.00%
Vitalograph 4	2.96 (0.03)	0.89%
Nuvoair 1	3.12 (0.03)	0.99%
Nuvoair 2	3.08 (0.02)	0.54%
Nuvoair 3	3.07 (0.03)	0.90%
Nuvoair 4	3.07 (0.02)	0.72%
Spirobank 1	2.96 (0.01)	0.40%
Spirobank 2	2.96 (0.01)	0.47%
Spirobank 3	2.97 (0.02)	0.81%
Spirobank 4	2.97 (0.01)	0.35%

1.36 **Discussion**

The results of CLIMB-CF have shown that the Vitalograph lung monitor BT, when used unsupervised home, has a tendency to underread compared to supervised clinic spirometry with over 77% of home readings recording lower than their matched supervised clinic reading. This underread can be as large as 23%. Some of this underread may be in part due to the device itself, as I have also demonstrated a significant underread in brand new devices using calibration syringes. The limits of agreement between the unsupervised home spirometry and the supervised clinic spirometry were wide and remained wide throughout the duration of the study suggesting moving forward these results cannot be used interchangeably. The results also show a variability of ~ 10% during periods of clinical stability

To date this is the largest paediatric CF study exploring unsupervised home spirometry and comparing it to supervised clinic spirometry. It is also the only study exploring variation of brand-new devices from multiple manufacturers.

The data from this study comparing supervised clinic spirometry with unsupervised home spirometry show wide limits of agreement, and while the readings were not taken at the same time, they would not satisfy the ATS/ERS standards for within test variability (104). This leads to the conclusion that the two measures cannot be used interchangeably and to do so may lead to incorrect clinical decision making, agreeing with the findings of Avdimiretz and colleagues (424). This contrasts with some other study findings (348, 420, 421). It is important to note that two of the studies that have concluded it is possible to use the handheld spirometer interchangeably with the conventional clinic spirometer do so based on results from adult studies which may not be applicable to children and young people

(420, 421). While Shakkottai and colleagues stated that unsupervised home spirometry in children with CF could be used interchangeably, their study size was sample (n=39) and only reported an intra-class correlation to assess reliability and do not present the limits of agreement found within their study (348).

Also in contrast to other study findings our data does not show an increasing difference between home and clinic spirometry readings with age (427), which may be due to the fact that our study cohort is larger. It should also be noted that while the raw FEV_1 difference in L was not significantly related to age the difference between the two devices in FEV_1 % predicted was greatest in the younger children involved in the study.

Similar to Paynter *et al* the differences between the unsupervised home readings and the supervised clinic readings did not decrease over time (423). This suggests that a lack of familiarity with the handheld device is not responsible. However, it should be noted both studies have small sample numbers limiting the analysis.

Previous supervised spirometry studies have shown 'normal' variation in FEV_1 % predicted values of 5.3-6.3% during periods of stability (107, 433, 434) and that even during a pulmonary exacerbation this variation does not differ significantly (435). The data from CLIMB-CF demonstrates a ~10% variation in FEV_1 % predicted during periods of stability, and while there is no clear definition of a pulmonary exacerbation a change of this magnitude would be considered clinically significant in the presence of other signs and symptoms (155). It has previously been suggested that unsupervised home spirometry can aid the prediction of pulmonary exacerbations in paediatric patients (346). The

variation in FEV_1 % predicted seen during periods of stability in CLIMB-CF would suggest that unsupervised trends may not be fully reliable and further work in this area is needed.

In terms of the accuracy, all the devices underread at 1L, regardless of manufacturer and this was statistically significant for 2 of the 3 devices. These 2 devices also under read at 3L, although this did not reach statistical significance. The underread at 1L may have a more particular importance in our younger paediatric population as their total lung volumes are lower. This underread could lead to an apparent clinical drop in lung function and therefore unnecessary treatment, especially if home spirometry was being used interchangeably with clinic spirometry. One of the device's CoV was also above the 3% recommendation (104). There is currently no way to accurately calibrate handheld spirometers and there is evidence they do not need ongoing calibration (431, 432). However, checking a device using a fixed volume syringe prior to it being provided to the patient may identify spirometers with a large CoV which should be returned to the manufacturer. Handheld spirometers CoV should also be routinely checked in clinic to ensure the CoV remains below 3%. As no manufacturer performed significantly better than another, I would conclude that a clinic should select a manufacturer or device and to not use devices interchangeably.

The above findings advocate caution in the introduction of and reliance on unsupervised remote spirometry. The advancement of the virtual platforms accompanying the various devices now allows for trained professional supervision and independent validation of flow volume loops. Despite this, even with supervision, the handheld spirometers tend to underread (by up to 23% in this study) suggesting that currently they are not interchangeable, however longitudinal sensitivity to change using one particular handheld spirometer remains unknown. We have shown significant variability

during periods of stability which needs further analysis. Concern would be that infrequent measures may not identify a person's 'stable' variability leading to inappropriate decisions around therapy. As discussed previously the optimal frequency of home monitoring to support clinical decisions is still being investigated; however more frequent spirometry measures may allow people to identify their variation during stability and aid pulmonary exacerbation algorithms. This needs to be balanced with the fact that, as discussed in Chapter 3, spirometry was one of the least popular of the home measures requested. Longitudinal home spirometry studies may allow for identification of individual stable variability, as well as potentially being able to identify the MCID needed outside of stability to identify a pulmonary exacerbation.

The COVID-19 pandemic required clinicians to quickly adapt how they provided care and for many CF centres this included the introduction of remote spirometry (429, 436). However, at the end of 2021 where many centres are now returning to seeing patients face to face the opportunity could be taken to compare the handheld spirometer with the clinic spirometer at every visit.

The results of this chapter suggest that while unsupervised home spirometry is feasible, as postulated in my hypothesis, further work is needed to explore the quality of the data obtained by unsupervised home spirometry moving forward. The next chapter will describe the exploratory biomarker analysis that I carried out within CLIMB-CF.

Chapter 7- Urine biomarkers of CF pulmonary exacerbation: CLIMB-CF data

1.37 Introduction

In 1990, Hulka defined biomarkers as 'cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells or fluids' (437). From then on, the search for the perfect biomarker has begun in all spheres of medicine. These include biological biomarkers to diagnose disease, to predict prognosis, to determine treatment (in particular, in the sphere of 'personalised medicine'), to monitor therapeutic response or to identify a cause for a disease.

There has been significant research into biomarkers in CF, in diagnosing an acute pulmonary exacerbation, monitoring response (and predicting failure) to acute exacerbation treatment and to predict future acute exacerbations. Several different biomarkers have been proposed, but currently none are widely used in clinical practice.

In an ideal world clinical teams would benefit from minimally invasive/non-invasive biomarkers with the ability to aid in the following.

- Diagnose a current acute exacerbation (currently clinician defined)
- Monitor response or otherwise to treatment of an acute exacerbation, including duration of treatment
- Predict at the outset which patient will not recover spirometry on conventional treatment
- Predict risk of future acute exacerbations

A small number of studies have explored whether it would be possible to detect a pulmonary exacerbation and monitor the response to antibiotics treatment in people with CF by measuring certain biomarkers in urine samples.

Two studies explored desmosine in urine of people with CF. Desmosine is a marker of elastin destruction and lung injury (438). In a pilot study investigating the use of radioimmunoassay (RIA) of desmosine as a diagnostic tool 16 patients with CF admitted with a pulmonary exacerbation (aged 4-28 years) provided urine samples daily throughout their hospitalisation and any further hospitalisations during the study period (438). Healthy controls also provided daily urine samples. Desmosine levels were corrected to urinary creatinine. Desmosine levels in all healthy controls showed a daily fluctuation of less than 20%, however this pattern was not replicated in the CF cohort, with some participants demonstrating minimal daily fluctuating and some participants showing daily changes of over 100%. They postulated this was secondary to increased active elastin catabolism in people with CF. While they found higher levels of desmosine in 10 of the 16 patients with CF compared to controls, they found no correlation between desmosine levels at the start and end of antibiotic treatment. Laguna *et al*, however, found a significant decrease in serial desmosine levels in 53 patients with CF admitted to the Children's Hospital in Denver for a pulmonary exacerbation (439). Desmosine was again analysed by RIA and corrected to participant's specific gravity results. Urine samples were taken within the first 72 hours of starting IV antibiotics, on day 3-9 and on day 7-12. For participants who were able to expectorate sputum samples were collected at the same time points and analysed for desmosine, IL-8 and NE. Paired blood samples were also taken for CRP and IL-8. They found a significant decrease in desmosine levels between the initial urine sample and the interim sample at day 3-9 but then no significant further decrease in desmosine levels between the

interim sample and the final sample. They did find that urine desmosine levels were positively correlated with plasma IL-8 but not with sputum desmosine, FEV_1 or other inflammatory markers explored in this cohort. Comparison of these two studies is difficult as different methods to normalise the urine desmosine levels (one study using creatinine and one study using specific gravity).

Pseudouridine (PSU) is an indicator of RNA and cellular protein breakdown and has been linked to the severity of lung disease in CF (440). Levels of PSU were analysed using high-performance liquid chromatography in 26 adults with CF experiencing a pulmonary exacerbation (mean age 23.8 years, all chronically infected with *P.aeruginosa*) and 25 age matched healthy controls. Blood was also obtained for measurements via ELISA of CRP, IL-6 and TNFα. Urine samples were provided at the start of antibiotic treatment, the end and 2 weeks later. PSU values were found to be higher in people with CF compared to healthy controls, but no difference was found between PSU values at the 3 time points tested in the people with CF (mean PSU at the start of treatment was 49.7 μmmol/mmol compared with 40.5 μmmol/mmol at the end of treatment). Circulating levels of the inflammatory markers were statistically higher at the start of the exacerbation than at the end, and interestingly both CRP and IL-6 levels were statistically significantly higher 2 weeks after antibiotic treatment than they were at the end of treatment (440).

The described markers have limited published data with small sample numbers, no longitudinal data, or contradictory published results. Further work for the ideal biomarker/biomarkers is needed. This chapter next explores the urine biomarker discovery work carried out attempting to address the hypothesis of whether home-collected samples could be used to predict pulmonary exacerbations

earlier than clinically detectable by measuring levels of selected biomarkers collected at home and assessing the variability during periods of stability and periods of pulmonary exacerbation.

1.38 Home sample collection and biomarker exploration decision

1.38.1 Selection of the urine biomarker

As discussed in Chapter 3, based on analysis of the pattern and quality of home sample collections, it was decided that urine provided a feasible non-invasive sample type to use to carry out exploratory biomarker work. During this time, we were also approached by Mologic (Bedfordshire, UK), a company working on rapid diagnostic technologies, regarding collaborating on exploratory urine biomarker work they were planning in paediatric CF. They had just completed a biomarker exploration study in COPD (441) and were carrying out a biomarker study in adult CF with Dr Nash (West Midlands Adult CF Centre) and based on the provisional results of those two studies had developed a panel of 26 biomarkers to investigate in paediatric CF. They were able to test a limited number of our total samples for all 26 markers.

High levels of MMP-9 have been found in the sputum of exacerbating children in CF (145) as well as being noted to correlate with CF disease severity (442). MMP-9 has also been detected in urine in other conditions including COPD (443-445), and has been shown to be detectable in urine samples frozen for up to 15 years (446). To our knowledge MMP-9 in urine had not yet been explored in CF. There was an MMP-9 assay easily available and on discussion with Mologic, it became apparent that MMP-9 was within their exploratory panel, therefore it was felt that if there was a signal, I would be able to compare the in-house assay with the results obtained by Mologic. The decision was subsequently made to explore MMP-9 in house.

1.39 **MMP-9 Biomarker methodology**

Samples collected and labelled at home were frozen by the participants and then transferred to the research site in a cool bag with ice blocks. All sites had access to a -80 degree Celsius freezer to store samples prior to transfer to Imperial College London. Samples were transferred frozen via courier using dry ice and then tracked into the study -80 freezer in Imperial College London.

Prior to analysis all samples were defrosted in a room temperature laboratory, agitated using Eppendorf MixMate (Stevenage, UK) and then urinalysis was undertaken to obtain a reading of specific gravity for each sample. In brief this involved turning on the Siemens Clinitek status (Siemens Healthcare diagnostics, NY, USA) and entering the sample number, then a new test would be selected. There was 30 seconds to complete the test. This involved dipping a Siemens Multistix 10SG briefly (maximum 1 second) into the urine so all areas on the Multistix were wet. The Multistix edges were placed briefly on a paper towel to clear off excess prior to being inserted in the specific channel on the Siemens Clinitek status. This channel would then be retracted back into Siemens Clinitek status and analysed. A result would be printed from the top of the machine and documented. If a strip was not correctly registered by the machine an error message would appear and the sample would be retested with a new Multistix strip.

Specific gravity was chosen to correct the urine samples received as it has been shown to be a more robust correction in children compared to creatinine due to potential inaccuracies in creatinine correction in children with their reduced muscle mass. It is easy to perform and obtain immediate results (447). The equation used for the correction was (447):

$$\text{Chemical Concentration}_{sgcorrected} = \frac{\text{Urinary chemical concentration}}{(\text{Specific gravity} - 1) \times 100}$$

All results documented below are MMP-$9_{sgcorrected}$.

Human MMP-9 ELISA methodology

Human MMP-9 was assayed using the DuoSet ELISA Development system kit (DY911, R&D systems, Oxford, UK). Methodology was as per the instructions provided with the human MMP-9 ELISAs.

Plate preparation

The mouse anti-human MMP-9 capture antibody was reconstituted in 1ml of phosphate-buffered saline (PBS) (#DY990, R&D systems, Oxford, UK). This was then diluted to the working concentration in PBS without carrier protein. 100 μl was then immediately applied to coat each well of the 96-well Flat bottom High Binding microplate (Corning, New York, USA). The plates were then sealed (plate sealers, #DY992, R&D systems, Oxford, UK) and left at room temperature overnight.

After the overnight incubation each well was aspirated and then washed with 400μl of wash buffer (0.05% Tween 20 in PBS, #WA126, R&D systems, Oxford, UK). This was repeated 3 times. After the third wash the plates were inverted and blotted using clean paper towels to ensure there was no remaining wash buffer.

Plates were then blocked using 300μl of Reagent diluent (1%BSA in PBS, #DY995, R&D systems, Oxford, UK) and left for an hour minimum to incubate at room temperature.

A wash step as documented above was completed post incubation

Assay preparation

Recombinant Human MMP-9 standards were reconstituted using 0.5ml of distilled water. A seven-point standard curve using 2-fold serial dilutions in Reagent diluent was prepared.

100µl of either standards prepared as above or undiluted urine sample was then added to each well on the 96 well plate, with 2 wells filled with Reagent Diluent to act as blanks. The plate was then covered again using a plate sealer and left to incubate for 2 hours at room temperature. The Detection Antibody was prepared by reconstituting Biotinylated Goat Anti-Human MMP-9 Detection Antibody in 1ml of Reagent diluent. It was then further diluted in reagent diluent and 2% heat inactivated normal goat serum (#DY005, R&D systems, Oxford, UK) as per the working concentration indicated on the Certificate of Analysis (COA). After incubation a wash step (as described above) was repeated. Post wash step 100µl of Detection Antibody was added to each well and the plate was again covered and incubated for 2 hours. A further wash step was then completed. Streptavidin-HRP A was diluted using Reagent Diluent to the working concentration specified on the vial and 100µl was added to each well. The plate was then sealed and incubated for 20 minutes at room temperature but away from direct light. The plate was then washed again as per the previous step. 100µl of Substrate Solution (#DY999, R&D systems, Oxford, UK) was then added to each well and incubated for 20 minutes at room temperature, avoiding direct light. After the final incubation step 50µl of Stop Solution (#DY994, R&D systems, Oxford, UK) was added to each well and the plate was gently tapped to ensure complete mixing.

The optical density of each well was then determined immediately by using FlUOstar Omega microplate reader (BMG Labtech, Ortenbery, Germany) set to 450 nm. Wavelength correction was applied at 540nm. Plates were read using Omega Software (version 5.11, BMG Labtech). Standard curves were created using four parameter logistic curve-fit with the MARS data analysis software (version 3.2, BMG Labtech) and analysed in GraphPad Prism 9.0.2. Samples were tested in triplicate

and the mean of the results were used. The lower limit of detectable MMP-9 was 39 pg/ml. Any value below the lower limit of detection was corrected to 39.0 pg/ml.

Home sample selection – stable participants

Samples were selected for analysis from participants who had no documented exacerbations during the 6-month total study period and who provided at least 3 or more samples during the 4-month sample collection period.

Home sample selection – exacerbating participants

Participants were included in this cohort if they had a documented exacerbation during the 4-month sample collection period and provided >1 sample during their periods of stability and during their exacerbation periods. Exacerbation samples were taken from the 14 days pre and post the documented exacerbation start date. For this analysis samples for pulmonary exacerbations that were treated with oral and/or IV antibiotics were included due to the low number of exacerbations treated with IV antibiotics in the study cohort.

Samples provided to Mologic for Multiplex ELISA analysis

Mologic were able to provide additional sampling for around 150 samples. In view of this I selected participants who had provided multiple consistent samples over a few weeks of the study, while ensuring the samples represented both sexes and a wide range of ages. I included participants who were stable and those who had a pulmonary exacerbation treated with IV or oral antibiotics. An aliquot (1 millilitre) of urine for each sample was sent to Mologic for analysis in duplicate via multiplex ELISAs. Mologic were not privy to the clinical data of the participants until after the ELISAs were complete. Data were transferred to me after averaging of the duplicates. The biomarkers included

on their panel were: Calprotectin, Lactoferrin, Cystain C, MMP Substrate, Desmosine, Cathepsin B, Retinol binding protein 4 (RBP4), Chitinase-3-like-protein-1, Clara cell secretory protein 16 (CC16), MMP-8, MMP-9, Tissue inhibitor matrix metalloproteinase 1 (TIMP-1), Fibrinogen, Ribonuclease 3 (RNAse 3), Human neutrophil elastase (HNE), CRP, Beta-2-microglobulin (B2M), creatinine, Neutrophil gelatinase-associated lipocalin (NGAL), N-formylmethionyl-leucyl-phenyalanine (fMLF), Alpha-1 antitrypsin (AIAT), Interleukin-6 (IL-6), Myeloperoxidase (MPO), Periostin, Secretory leukocyte peptidase inhibitor (SLPI), Tissue inhibitor matrix metalloproteinase (TIMP-2).

1.39.1 **Statistical analysis**

Unless specified, data has been shown on a log y axis. When more than one data set has been compared, Krauskal-Wallis test has been adopted. Correlations were calculated using nonparametric Spearman r.

Mologic data

Data received from Mologic has been graphed using Tableau Desktop Professional Edition 2021.2.1. Data were received for 26 biomarkers per person with varying concentrations. Therefore, for each participant and for each biomarker the maximum value for each biomarker during periods of stability was identified and allocated the value of 100%. Percentage conversions where then carried out for all other readings for that individual biomarker for that participant and graphed together as percentage change.

1.40 Results

1.40.1 MMP-9 data during periods of clinical stability

46 participants had been stable with no documented pulmonary exacerbations during the study period and provided ≥ 3 urine samples. Median age (IQR) of this group was 8.6 years (5.9-11.5), 58% were female and the median (IQR) number of samples received was 12 (7.8-16.3). Figure 0-1 shows the raw data results per participant over the duration of the study sample collection period and visually shows variability between participants even during periods of clinical stability. Figure 0-2 shows the median and IQR data for each stable participant throughout the study period.

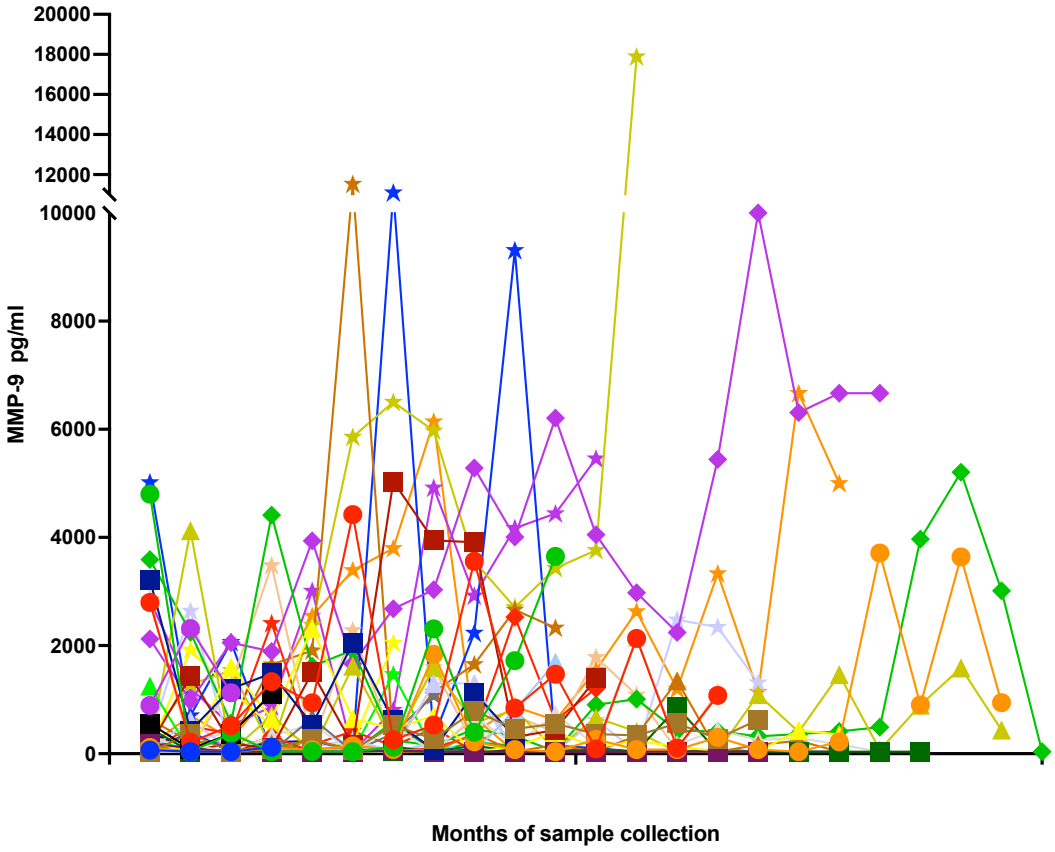


Figure 0-1 Stable participants MMP-9 raw data for each sample provided over a 4-month period. Each coloured line represents one participant. Each point is a received sample

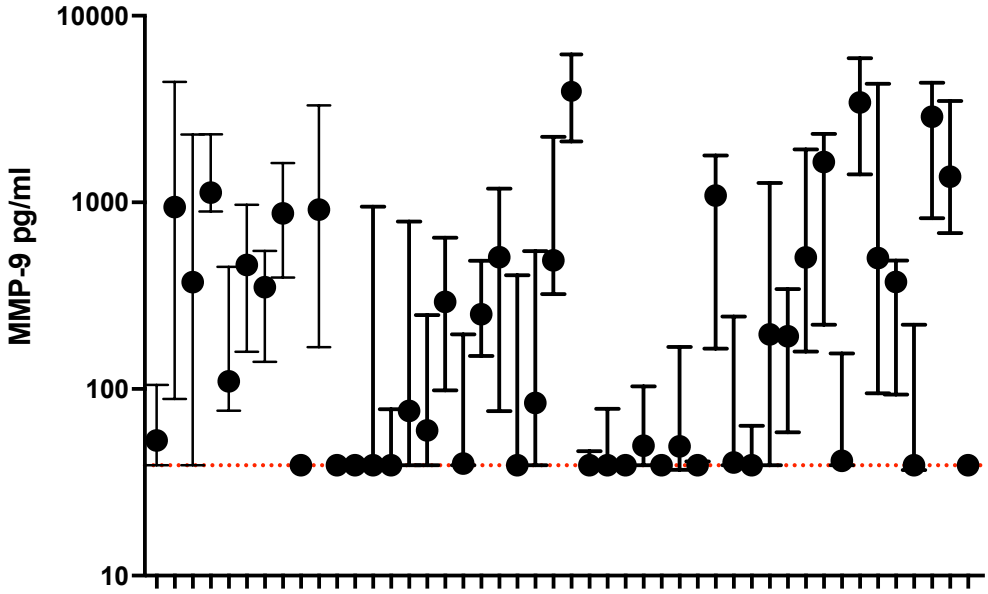


Figure 0-2 The median value and IQRs for all samples received per participant. The dotted red line represents the lower limit of detection of the ELISA. The y axis is on a logged scale. Abbreviations IQR - interquartile range

Median (IQR) for the whole group was 97.1 (39-507) pg/ml, with no correlation to age or FEV_1 % predicted (Figure 0-3, Figure 0-4).

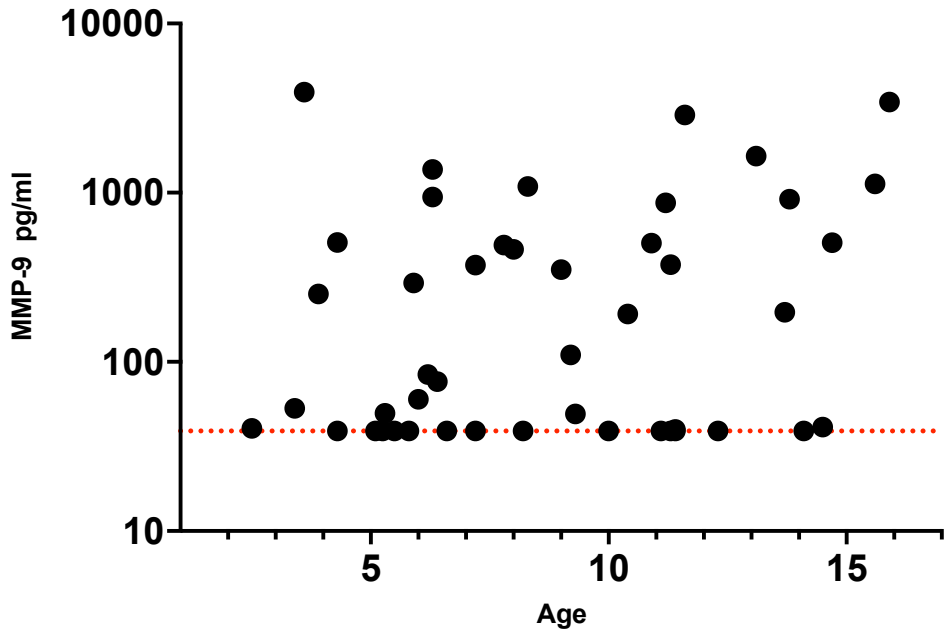


Figure 0-3 The correlation between MMP-9 during stability and age. Spearman r = 0.19. The red dotted line is the lower limit of detection for the ELISA and the y axis is logged.

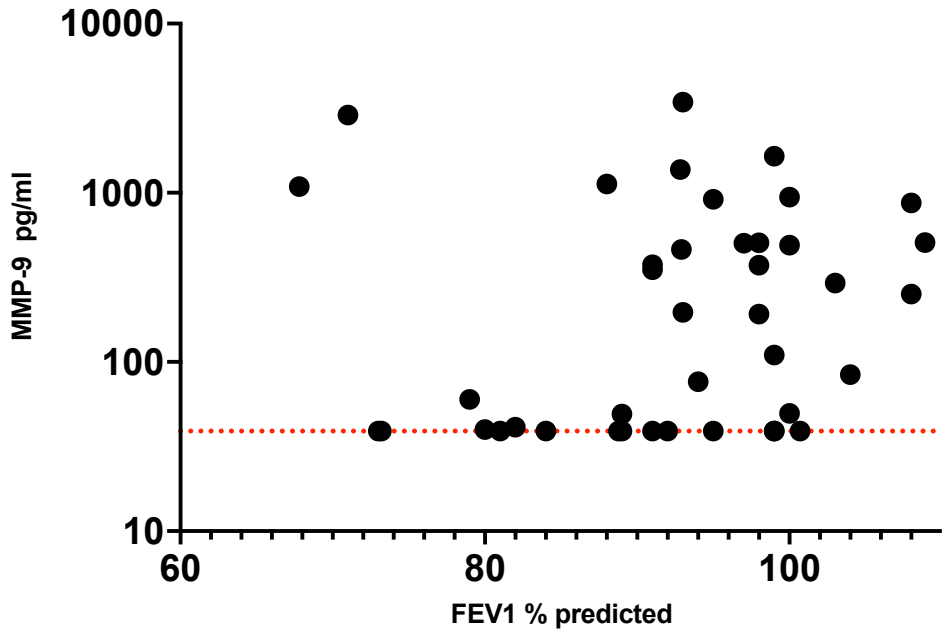


Figure 0-4 The correlation between MMP-9 during stability and FEV_1 % predicted. Spearman r = 0.2. The red dotted line is the lower limit of detection for the ELISA and the y axis is logged.

There was also no significant difference seen in those who were on treatment for chronic *P. aeruginosa* infection and those who were not (Median [IQR] MMP-9 93.2 pg/ml [46.7-957.7 pg/ml] for those on chronic *P. aeruginosa* treatment compared to 138 pg/ml [39-499.7 pg/ml] for those not on treatment.

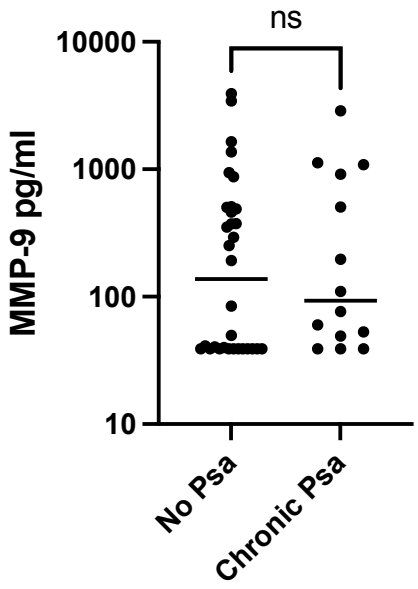


Figure 0-5 MMP-9 readings for participants on treatment for chronic P. aeruginosa infection compared to those not receiving treatment during the CLIMB-CF study.32 participants are included in the no Psa group and 14 participants are in the chronic Psa group. Abbreviations ns-non-significant, Psa - P. aeruginosa

The stable group was comprised of 27 females and 19 males and with a median (IQR) MMP-9 of 462 pg/ml (110-942.7 pg/ml) in the female group and a median (IQR) MMP-9 of 39 pg/ml (39-49.6 pg/ml) in the male group (p= <0.0001) (Figure 0-6).

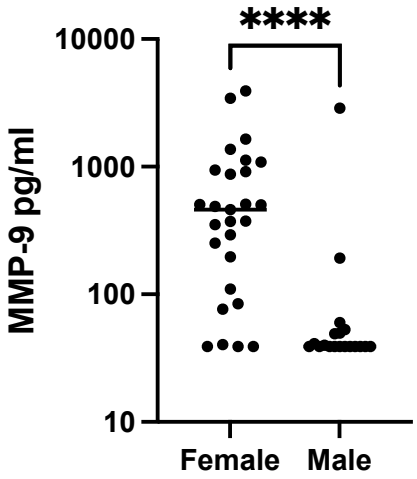


Figure 0-6 *MMP-9 readings for stable female and male participants during the CLIMB-CF study (****=p=<0.0001).*

In view of the above result, I further divided the female participants by age of menarche in case oestrogen could be a factor in the higher levels of MMP-9 seen in the females of this cohort. Based on the average age of menarche in the UK the age of 13 was used as a cut off (448). Of the 27 females included in this analysis 20 were less than 13 years of age and 7 were ≥ 13 years of age. MMP-9 levels did not significantly differ between age groups; however, those aged ≥ 13 years had a higher median (IQR) MMP-9 than the younger group (914.3 pg/ml (196.2-1646 pg/ml) compared to 374.1 pg/ml (90.7-781 pg/ml) respectively).

1.40.2 **MMP-9 during periods of stability and episodes of pulmonary exacerbation**

37 participants (median age [IQR] 7.5 [5.1-9.9] years, 54% female) had exacerbations during the study period and provided > 1 urine sample during both their periods of stability (median number of samples per participant [IQR] 9 [5-13]) and their periods of pulmonary exacerbation (median number of samples per participant [IQR] 4 [3-7.5]). Median (IQR) MMP-9 during stability for the whole group was 106.6 (39-380.3) pg/ml and during periods of pulmonary exacerbation was 175.4 (39-516.4) pg/ml (ns). (Figure 0-7, Figure 0-9).

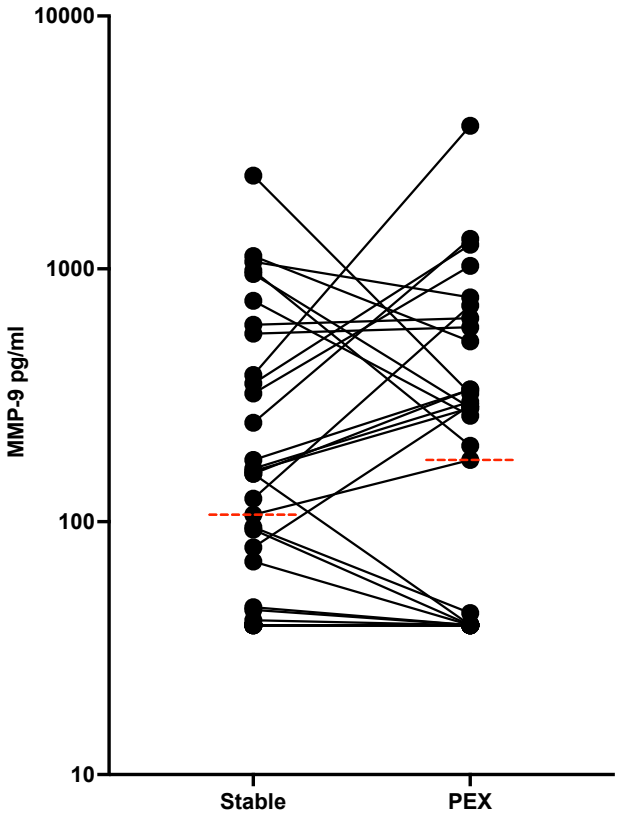


Figure 0-7 Participants median MMP-9 reading during stability and during pulmonary exacerbation. The red dotted lines indicate the median MMP-9 reading for the entire group. The y axis is logged. Abbreviations PEX-pulmonary exacerbation.

There were 20 females and 17 males included in the above analysis. When divided by sex there was no significant difference between MMP-9 readings during stability or during a pulmonary exacerbation for either group. However, there were significant differences between the stability readings and pulmonary exacerbation readings recorded for females and males. Median (IQR) MMP-9 for the female group during stability was 210.9 (110.8-710.8) pg/ml compared to 39 (39-82.4) pg/ml in males (p=0.01). Median (IQR) MMP-9 for the female group during an exacerbation was 309.8 (181.5-696.5) pg/ml compared to 39(39-41.3) pg/ml in the male group (p=0.001) (Figure 0-8).

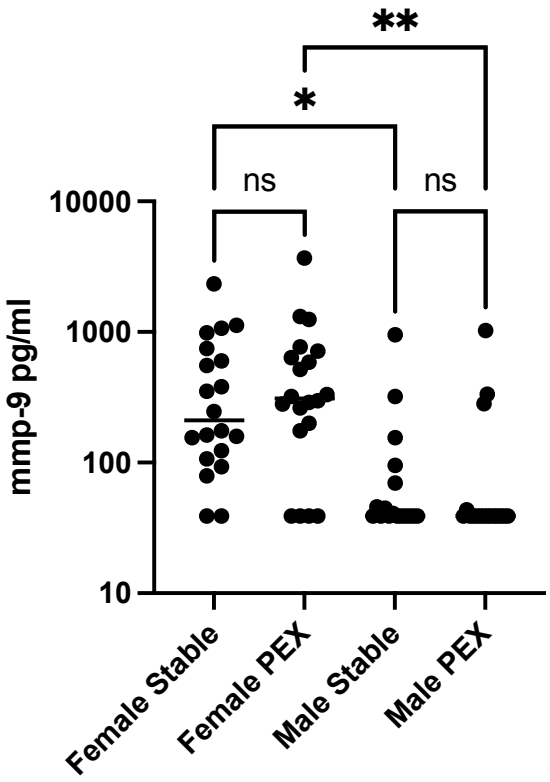
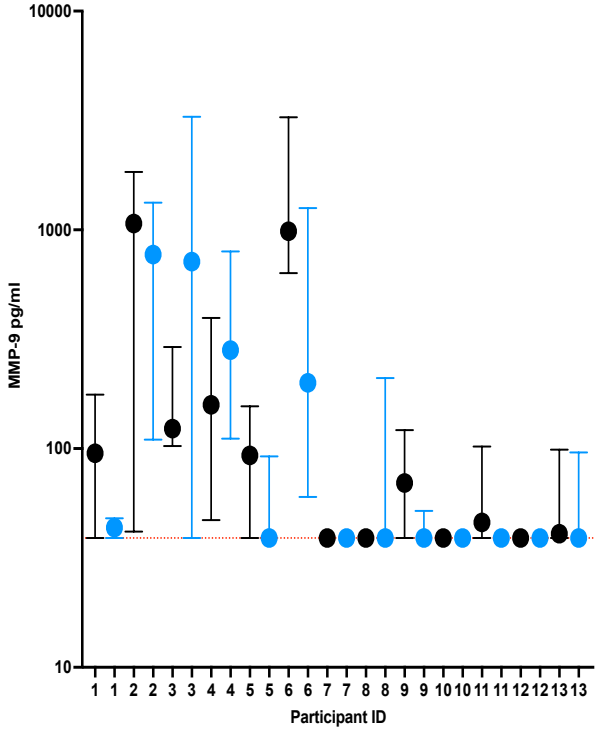
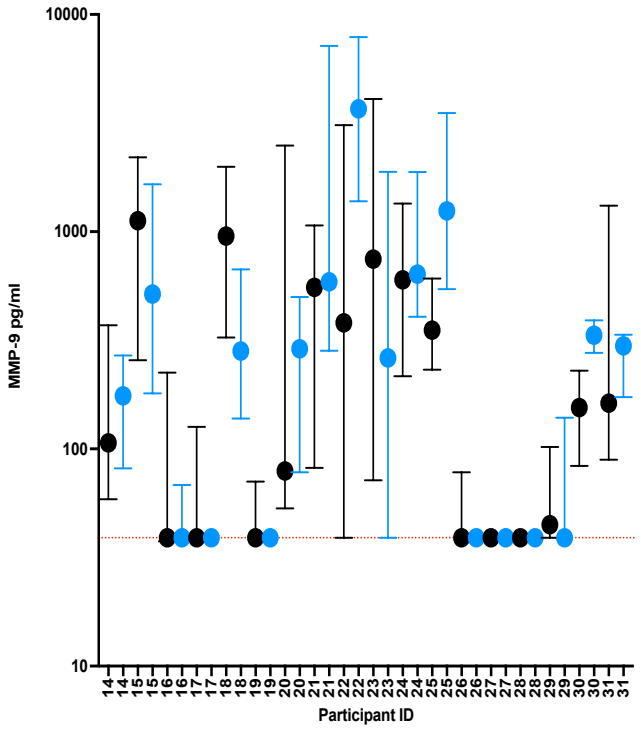


Figure 0-8 Participants median MMP-9 reading during stability and during pulmonary exacerbation divided by females and males. The y axis is logged. Abbreviations PEX-pulmonary exacerbation (=p ≤ 0.05, **=p≤0.001)*

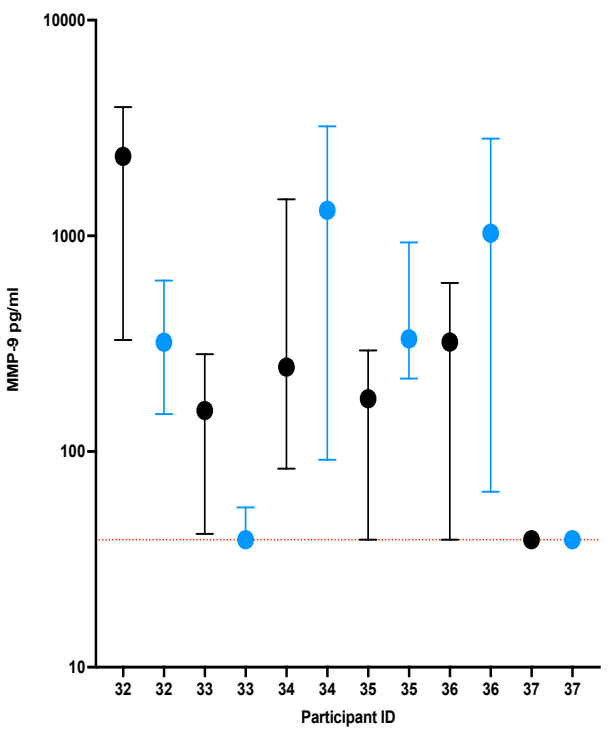
.



Panel a



Panel b



Panel c

Figure 0-9 Median and IQR results for MMP-9 per participant during periods of stability vs pulmonary exacerbations. Black dots are periods of stability. Blue dots are periods of pulmonary exacerbation.

Panel a shows participants aged 2-5 years. Panel b shows participants aged 6-11 years and panel c shows participants aged ≥ 12 years. Abbreviations IQR – interquartile range

1.40.3 **Results from Multiplex ELISAs**

Samples from 13 participants were sent to Mologic for analysis. Median (IQR) age 9.3 years (4.6-14.5), 61% female and between 10 and 13 samples per person. 3 participants were stable during the sample collection period, 6 had episodes of pulmonary exacerbation treated with oral antibiotics and 5 participants had episodes of pulmonary exacerbation treated with IV antibiotics (some received courses of oral antibiotics during the same period). The Mologic panel provided results for 26 biomarkers. For ease of presentation, as each biomarker had a different range, the results have been converted to a percentage based on a participant's maximum stable value for each biomarker during the sampling period. Therefore, any pulmonary exacerbation reading greater than the maximum stable reading of will appear on the graph as above 100% on the y axis. The figures below are split into the stable participants (Figure 0-10), participants who received oral antibiotics (Figure 0-11) and those who received a course of IV antibiotics (Figure 0-12). Even during stability there is variation in biomarkers. Around periods of pulmonary exacerbation, spikes can be seen in biomarkers for all 10 participants, but it is not consistently the same biomarker/s (either within participants if they have more than one antibiotic course or between participants) and some appear to increase after the treatment course has started. 21 of the 26 metabolites increased at least once around an exacerbation with participants appearing to have a rise in between 1 and 11 biomarkers over the sampling period, of which desmosine appeared increased in 7 participant exacerbations. MMP-9 was increased in only 2 participant exacerbations and MMP substrate was increased in 5 participant exacerbations.

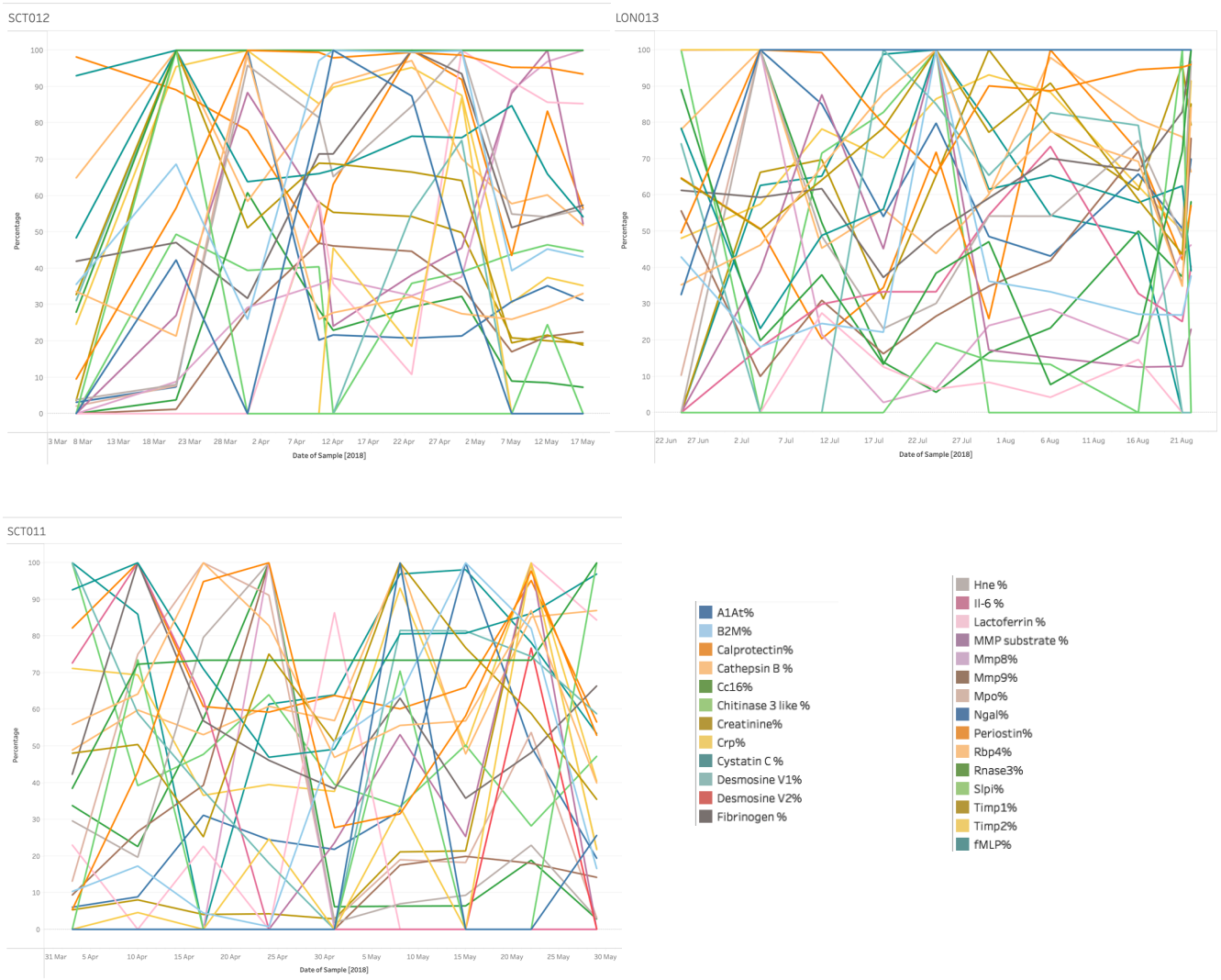


Figure 0-10 Mologic biomarker panels for 3 stable participants. Each graph is labelled with a participant ID and each coloured line represents a different biomarker. The y axis is percentage. Each biomarker is corrected so 100% indicates the highest recorded reading for that marker during periods of stability.

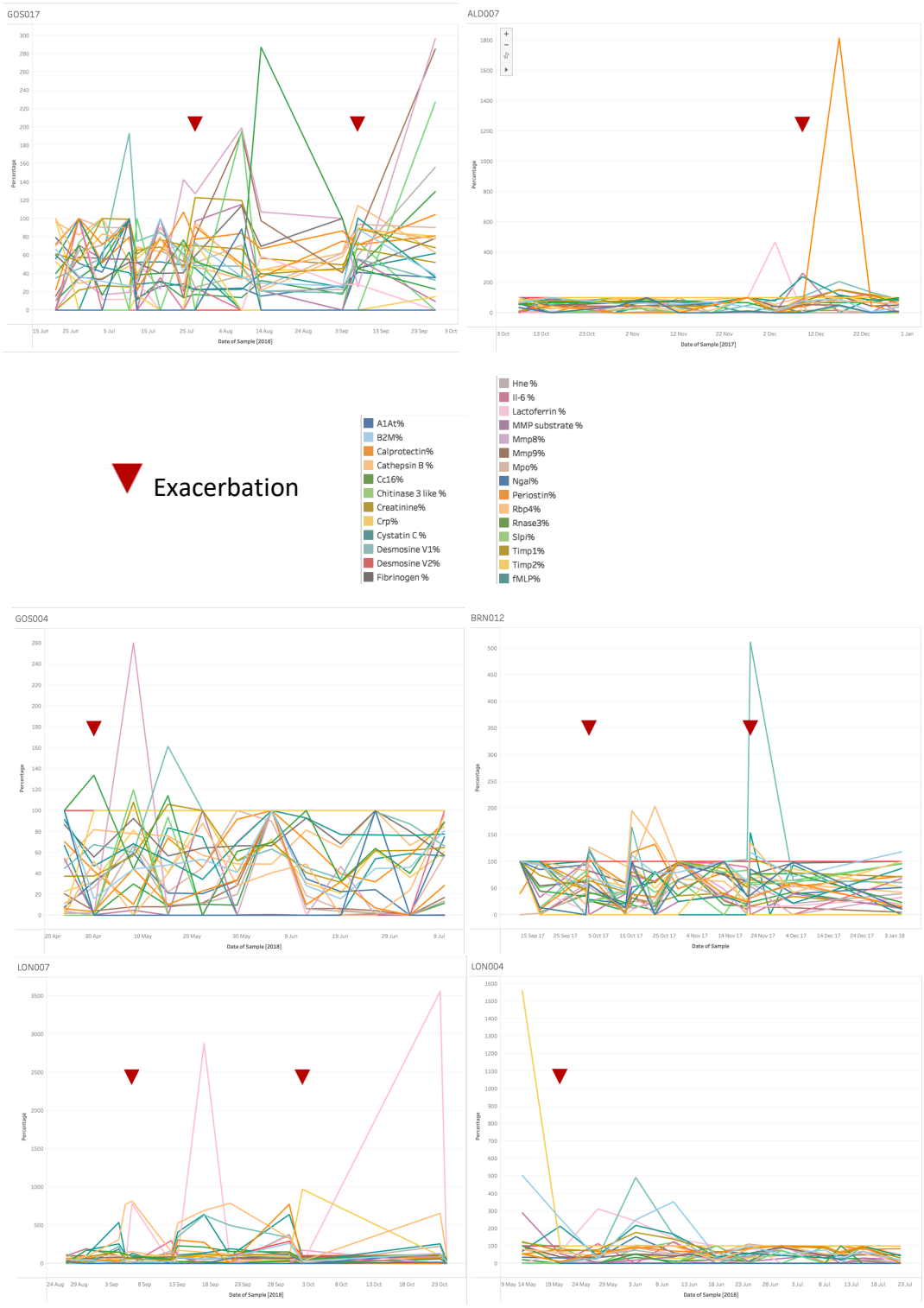


Figure 0-11 Mologic biomarker panels for 6 exacerbating participants who received oral antibiotics. Each graph is labelled with a participant ID and each coloured line represents a different biomarker. The y axis is percentage. Each biomarker is corrected so 100% indicates the highest recorded reading during the period of stability. The red arrow indicates the start date of the exacerbation/antibiotic course.



Figure 0-12 Mologic biomarker panels for 5 exacerbating participants who received IV antibiotics (+/- oral antibiotics). Each graph is labelled with a participant ID and each coloured line represents a different biomarker. The y axis is percentage. Each biomarker is corrected so 100% indicates the highest recorded reading during the period of stability. The red arrow indicates the start date of the exacerbation/antibiotic course. If there are 2 rows of red arrows, the higher arrows are when the participant received IV antibiotics and the lower arrows are courses of oral antibiotics.

1.41 **Discussion**

In this chapter I have presented the results of the exploratory urine biomarker analysis done in house and performed by our collaborators Mologic. My results show that MMP-9 in urine is not a valid marker in insolation for a pulmonary exacerbation in a paediatric cohort of patients. Even during periods of stability there is significant variation in the levels of urinary MMP-9. Detectable MMP-9 levels do not correlate with age or lung function or chronic infection with *P. aeruginosa* but there does seem to be a sex difference that may warrant further investigation.

The results from a small subset of patients who had urine samples sent to Mologic for further analysis again show significant variation during periods of stability. They also show that while there is variation in markers around a period of exacerbation there does not appear to be consistency in which biomarker changes even within person for participants who had more than one pulmonary exacerbation during the study period.

The higher levels of MMP-9 in the females of the cohort are interesting although should be considered with caution due to the relatively low participant numbers included in the analysis. Examination of the literature shows mixed results of the effect of sex on MMP-9 levels. In a study of urinary MMP-9 in healthy volunteers (n=45, ranging in age from 7 to 51 years) no difference was seen in MMP-9 levels when analysed by sex. Lower levels of urine MMP-9 were seen in adolescents (defined as 12-18) than in children aged <12 (449). In comparison to this, another study has shown higher levels of MMP-9 in females (MMP-9 298 ng/g) with type 1 diabetes mellitus compared to men (MMP-9 39 ng/g) in 121 participants (51% female, mean age 20.8 year $\pm$ 7.6) (450). Both studies postulated that the differences seen in MMP-9 within their studies could be connected to sex

steroids, in particular testosterone and oestrogen. The results from animal studies are not conclusive though with oestrogen and testosterone being shown to both up-regulate and down-regulate MMP-9 expression (451-454). When I further divided the females in this analysis by age of menarche no significant difference was seen in MMP-9 levels. There are some limitations to this analysis, the number of females aged ≥ 13 years were low, and the exact age of menarche was not documented within the study proforma hence the need for an arbitrary cut off. Historically delayed puberty was reported in females with CF (455), more recent data shows that the age of puberty and menarche in females with CF is normalising to the general population (456). Therefore, with the limitations documented above I feel the arbitrary cut off of ≥ 13 years is appropriate. These results need to be explored in a larger cohort of patients ideally with documentation of menarche and last menstrual period (if appropriate) given the conflicting results of the effect of sex steroids on MMP-9.

There are some weaknesses associated with the study: the definition of a pulmonary exacerbation was pragmatically clinician determined. The inclusion of multiple sites may have increased variation in the severity of clinical symptoms which prompted treatment. The start date was also arbitrarily set as the start date of the treatment course, symptoms however, are likely to have been present beforehand. In order to account for this samples from the 14 days pre and post the start date of treatment were included within the exacerbation data set in attempt to identify any earlier changes in biomarkers. This, however, may potentially dilute a signal in a biomarker should it only be present close to the start of the pulmonary exacerbation. As samples were not collected daily in CLIMB-CF, it is not possible to explore daily changes in biomarkers around the date of an exacerbation.

Another weakness of this study was that there were only a small number of pulmonary exacerbations treated with IV antibiotics. Information was not logged regarding the decision for oral antibiotics instead of IV antibiotics, but this may be representative of the fact that it is a paediatric cohort. Because of this the subgroup of participants who received IV antibiotics was too small to analyse separately.

A further weakness of the CLIMB-CF study is that while participants with CF provided samples during periods of stability, there was no healthy control comparison group. The median (IQR) MMP-9 level for the group during stability was 97.1 (39-507) pg/ml. This is higher than documented levels in healthy paediatric controls in other studies. Erol et al reported mean (SD) MMP-9 urine levels of 28.2 (± 16.8) in healthy controls (mean age 9.52 years) in their study using a Human MMP-9 ELISA kit (Abcam, USA) which had a lower limit of detection of 24.69 pg/ml (444). Slightly higher levels were found in the healthy controls with a mean (SD) age of 19.5 (10.3) weeks in a study Kleber and colleagues. The median (IQR) MMP-9 levels in their control group were 50 (27- 230) pg/ml using an MMP-9 Biotrak Activity Assays System from GE Healthcare. No lower limit of detection was documented in their publication (457). While these other 2 studies use different methodology and there is overlap between the ranges of the results published, they suggest that the level in stable children with CF may be higher than healthy control children; this warrants further investigation.

This chapter has shown that while urine collection was particularly acceptable to participants, I have been unable to identify a single biomarker or a clear panel of biomarkers in urine that helps identify periods of pulmonary exacerbation or correlates to disease severity. Further work is needed on identifying an appropriate biomarker to identify a pulmonary exacerbation, and when a biomarker

has been identified, the frequency of biomarker monitoring required. The association with sex and MMP-9 levels also warrants further investigation.

Chapter 8: Overall summary and Future work

CF is a lifelong genetic condition characterized by chronic inflammation and lung damage, detectable from an early age and the major determinant of survival (32). Pulmonary exacerbations are known to affect outcomes (131, 132, 134, 154) and yet there is no consensus on the definition of a pulmonary exacerbation or consensus on how pulmonary exacerbations should be detected in a timely fashion (125). Current standards of care advocate seeing a young person with CF around every 2 months (89). However, the introduction of CFTR modulators and the effects they are having on CF lung health must be considered when planning the provision of CF care in the future (196). One of the potential changes being seriously considered is the provision of remote monitoring and telemedicine (458).

CLIMB-CF has tested the hypothesis that:

- Home monitoring and sample collection will prove feasible and acceptable for patients and families whilst not adversely impacting on mood or quality of life.
- Home monitoring and non-invasive sample collection could be used to predict pulmonary exacerbations earlier than clinically detectable.

To test these hypotheses, I:

- Assessed the feasibility of home monitoring in children with CF, including the amount of requested data submitted as well as the quality of data received where possible, and the impact on quality of life and well-being both for them and their carers.

- Assessed variability during stability of the monitored parameters and changes around periods of pulmonary exacerbations (defined as leading to a change in treatment by an independent clinician) within the home-monitored group.
- Assessed the types of requested non-invasive home samples received.
- Explored the utility of non-invasive biomarkers.

My objectives within CLIMB-CF were:

- To design and lead an international, multicentre study of the feasibility of home monitoring, training, and coordinating of teams at partner sites and to recruit up to 20 RBH patients and 160 patients internationally. This included documenting the proportions of patients who completed each monitoring task, requested sample collection and acceptability of these interventions, and impacts on quality of life, with questionnaires at scheduled points during the 6 months to track change.
- To use data received to describe the variability in clinical measures during periods of stability and the variability in clinical measures around a period of pulmonary exacerbation.
- To measure levels of selected biomarkers in the non-invasive samples received from home.

CLIMB-CF was designed to add to our understanding about the feasibility of instigating remote monitoring in children and young people at home. It was a large multi-centre study run over 2 countries, recruiting participants for a 6-month period, and monitoring the feasibility of remote data collection, remote sample collection and the subsequent effect on mood and quality of life of the participants and their caregivers.

It adds to the small body of evidence on remote monitoring of people with CF.

1.42 **Strengths of CLIMB-CF**

CLIMB-CF is the largest paediatric remote monitoring study that has been undertaken to date. It was run over multiple sites in two countries with participant recruitment covering the whole target age range. This means the study population represents a wide age range of children and young people with CF, as well as a range of disease severities and other associated co-morbidities.

While the median percentage of completed data over the 6 months (40.1%) appears lower than other paediatric studies exploring remote monitoring, our data is from a larger cohort of patients and analysis did not exclude participants based on the amount of data returned, making it a more realistic representation of return rates of requested measures (338, 345, 346, 348). This is the first study in CF remote monitoring that presents usage broken down by month over the entire study period, which provides an insight into long term engagement and adherence. We observed that data collection increased in month 2, possibly due to participants becoming familiar with the equipment and after having had the 1-month call with their study team to discuss any issues that they may have been experiencing. Data entry declined after that point for the rest of the study, in particular in the older age group and the cohort who did not find the home monitoring helpful, and this should be considered in future interventions. There is also evidence in asthma that frequency of home monitoring readings decreases with time (301).

Another strength of this study is that I have presented the data of the whole cohort, including in the analysis participants who entered no or very minimal data. Other studies have excluded such participants from their analysis which may explain some of the discrepancies seen in our completion

rates (338, 345, 346). This, however, gives a more realistic representation of completion of remote monitoring in a real-world setting. In parallel to this, participants were all given the option of completing the acceptability questionnaires when they ended the study either at 6 months or when they chose to formally withdraw, and all data were included in the analysis giving a more realistic representation of acceptability.

As the cohort is large in CLIMB-CF, analysis has been able to be split by age bracket, identifying poor engagement with adolescents, one of the most at-risk groups (110, 391). With the move towards individualised care plans being considered, engagement of this high-risk group needs serious consideration (459). The introduction of incentives has been considered in adolescents in other disease groups. In type 1 diabetes mellitus financial incentives have been shown to encourage adolescents to record their blood sugar level, however this does not seem to improve their overall glycaemic control (460). There is an ongoing study exploring the use of incentives in asthma (461). While not specific for remote monitoring there is work ongoing exploring gamification in CF physiotherapy routines (354) which could be expanded to remote monitoring platforms in the future.

CLIMB-CF was the first paediatric home monitoring study that included additional wellness questions and objective measures such as heart rate, oxygen saturations and weight. This contrasts with van Horck *et al* who only asked three questions: cough, sputum, and dyspnoea on a scale of 0-3 (346). While, as of yet, it is not known which measures in paediatric CF may be predictive there is evidence from adult CF studies that a general wellness question, heart rate and oxygen saturations may strengthen a predictive model for pulmonary exacerbations (344).

CLIMB-CF explored the utility of two interfaces, which is unique to this study and the data clearly shows that when designing a remote monitoring solution, it needs to be easily accessible on a mobile phone to engage young people and families as engagement with the CLIMB-CF website was poor from all age groups. It is not clear why this was the case. It could be postulated that it was harder to access than an app on a phone screen home page. The participants in Arm 2 also did not have access to the Bluetooth equipment which may have had an impact. These results can be used to aid the design of future studies.

Another strength of the study is we recorded how many participants needed to contact their study team for technological support. Over 77% of participants required support at least once during the 6-month period, with over 22% requiring support more frequently than monthly and this needs to be considered with future study designs or implementation into clinical care and staffing costs to provide technological support should be considered in future cost-effectiveness analyses.

The strict inclusion criteria for the paired unsupervised home spirometry readings and the supervised clinic readings is another strength. Recent analysis of the eICE results allowed readings up to 7 days apart to be included (423), and another study of transplant patients used the closest home reading to the clinic spirometry with no predefined cut off (418, 423). It would be reasonable to assume that the further apart the readings the less likely they are to be comparable. To explore this, I looked at home data from the same day as the supervised clinic reading and compared it to the readings the day either side and found no significant difference. It should be noted, however, that the sequence of the readings was not taken into account in this analysis. As our participants continued to attend

their CF clinics regularly, I received updated heights which could be used to ensure their home spirometry readings were as accurate as possible.

I also tested multiple brand-new devices from three separate manufacturers. Few studies have looked at the accuracy of a device using a fixed volume syringe and no other study has published data on more than one (428).

The data adds to the argument that unsupervised home spirometry should not be used interchangeably with supervised clinic spirometry and that handheld spirometers tend to underread. This is the largest data set of purely children with CF exploring this issue and is one of the only data sets looking at variability during periods of stability, which at ~10% is higher than previously published data (107, 433, 434). Further research is needed in this area before unsupervised remote handheld spirometry is adopted fully into clinical practice.

CLIMB_CF has the benefit of being the first paediatric study to explore the impact of remote monitoring on mood and quality of life in people with CF and their care givers. Despite the caveats of it always being the same parent who completed the questionnaire and the limitations this imposes if a different parent attends clinic due to family commitments, we still received a good response rate to the questionnaires delivered (~80% for most measures). It also incorporated measures for both parents and participants to allow for assessment of the impact of home monitoring on the whole family. There is evidence in other diseases that home monitoring can either increase or decrease anxiety levels (333, 334). While not formally assessed using approved psychological tools, an adult CF study saw no increase in self-reported psychological concerns when compared to a control group

receiving standard care (340). While not all specific to CF, within CLIMB-CF only validated questionnaires were used to assess quality of life and mood; no negative impact of remote monitoring was noted on our cohort of patients as a whole, although screening did identify some parents who required referrals to psychological support services. The screening tools used are designed to focus on a short period of time preceding the completion of the questionnaire. In view of this and the fact the evidence for the effect of home monitoring on mood and quality of life is contradictory it is a strength that these measures were repeated regularly throughout the study. As these were completed within routine clinic appointments there was no significant additional burden to the participant and/or their family and the results allow for ratification of quality of life measures in future studies.

In terms of home collection of samples, a large percentage of participants engaged in home collection of non-invasive samples, in particular urine, proving that this could be feasible in the future. Fewer participants collected the DBS samples and the quality of the samples collected show that further work is needed in this area. It should be noted, however, that as the DBS sampling currently had no influence on clinical care, numbers of participants who were prepared to collect it may be lower and should a biomarker be identified adherence to this measure may increase.

A strength is the number of exacerbating participants that were included in the MMP-9 analysis (n=37) and that all participants had to provide more than one urine sample during both stability and pulmonary exacerbation periods. The majority of previous studies report on small sample sizes and/or did not analyse samples from multiple time points during stability or exacerbation. Despite MMP-9 being detectable in the urine and possibly due to the larger study cohort and sample numbers

there was no association with pulmonary exacerbations. These results do not match another paediatric study which did find an association between MMP-9 in the sputum and pulmonary exacerbations (145). Interestingly a study exploring chronic obstructive pulmonary disease exacerbations showed that while MMP-9 was not a good indicator for exacerbations in this cohort, sputum and urine MMP-9 levels were independent of each other (445). In view of this disconnect between sputum and urine MMP-9 levels and the previously published paediatric sputum data, a larger study exploring MMP-9 levels in sputum of young people with CF during exacerbations could be considered although the difficulties around sputum production in young people could make this challenging.

A high number of stability samples were received. The samples received were representative of the study cohort in terms of sex and age distribution. Only participants who had no documented pulmonary exacerbation at any point within the study period were included to try and ensure they were true stability samples. Despite this, unlike previous reports of MMP-9 levels in plasma, there was no association with FEV_1 (442).

1.43 **Limitations of CLIMB-CF**

One of the main limitations of this study is that as it was a feasibility study no clinical changes were made in response to the data collected. There is the potential that adherence to remote monitoring would increase if it was perceived to have an impact on outcomes or to allow for less frequent face to face clinic appointments, this could be particularly relevant to adolescents. Also, as it was a feasibility study there was no randomisation process to being consented to the home monitoring arm, participants were just approached at their routine clinic appointments. While a feasibility study

is an accepted step in a complex intervention process (462) this undoubtedly leads to some selection bias with a cohort of engaged families. Another factor that may have impacted selection bias is the fact that participants who attended fewer than half of their routine clinic appointments were excluded from this, potentially leading to selection of participants who are more adherent and despite this there were low levels of completion of the requested data. There was also no comparison control group continuing routine clinical care.

Throughout the six months home monitoring data collection showed that if a participant signed into the app, they would tend to complete all measures requested rather than picking and choosing which measures they completed e.g., just completing measures that did not require additional pieces of equipment. The exceptions to this appeared to be sleep disturbances and respiratory rate which were notably poorly collected. This could be connected to the potential difficulty in collecting and entering these data into the app. Further consideration should be given to app layouts moving forward regarding access to sub menus and all data entry categories.

Sleep disturbance was the least completed measure during the six months. There may be at least two possible reasons for this. The first is that the tile to enter sleep disturbances into the app was within the 'Measure up' sub menu, and while the top of the tile was visible when a participant entered the sub menu, it required the participant to scroll down to be able to select the tile and enter data. Participants and their families were shown this during the initial training session at the start of the study, however the visual reminder might not have been obvious on a daily basis in real life. The other reason may be the potential difficulty in quantifying the number of sleep disturbances during a night, in particular for younger children sleeping in their own bedrooms.

Respiratory rate was also a measure which was collected poorly during the study. Respiratory rate had to be manually counted and added on a daily basis. Parents were taught how to count the respiratory rate of the younger participants while they were calm having their heart rate and oxygen saturations recorded, and older participants were requested to ask a parent or family member to count their respiratory rate for them while they were completing other aspects of the data entry. The difficulty in accurately counting may have contributed to the lower percentage of completed entries during the study. It has been shown previously that even trained healthcare professionals have difficulty in counting a patient's respiratory rate and many devices that count a person's respiratory rate are unreliable (463, 464). Respiratory rates may also not be accurately recorded if the participant was aware they were being recorded, this is because a participant should be relaxed when respiratory rate is documented, and it is difficult to relax if the participant is conscious that they are being observed (465). This may have less of an impact on the younger participants who may not be aware they are being observed. Subgroup analysis by the Royal Alexandra Hospital is ongoing to explore whether it is possible to extrapolate respiratory rate from the Nonin 3150 device. This approach may be possible in future studies.

Another limitation is that although during the design process we had input from the CF Trust YA group, the app was not fully co-designed. It should be noted that while the CF YA group is mainly made up of adolescents with CF, this may ultimately have affected the engagement of this cohort. Future research should consider adopting a fully co-designed approach (466). Consideration should also be given to designing an interface that could be adapted and individualised by the participant,

as potentially future systems should not be a 'one-size-fits-all' but should allow for individual taste and motivations.

As the app was only available on the study provided android phones this did require participants to use a separate device to their normal smart phones which could have affected overall usage. Free text comments in the acceptability questionnaire requested an app that would be available on their personal devices. However, interestingly, the completion of data in arm 2 – the web page monitoring group was very low despite the fact that the web interface was such it could be accessed from any device that could connect to the internet, including the participant's personal smartphone. This could possibly be due to the fact the webpage requires a participant to remember to visit it, whereas an app would provide a visual reminder on the personal phone home screen. It could also be due to the aesthetic of the webpage not being engaging for young people as this element of the project was not co-designed with the CF Trust YA group. These results are similar to those of Roehrer and colleagues who piloted a myCF website for symptom monitoring. 14 participants were involved in a 6-week pilot, many of whom requested access to the site after the pilot had finished, however only 2 participants used it after the study end date. 20% of participants accessed the website via a mobile device and many expressed concerns regarding collecting data daily (467).

The equipment issues experienced throughout the study were definitely a major limitation and even led to a formal withdrawal of a minority of families due to frustration with the malfunctioning equipment. This was particularly noted around the activity monitor. The activity monitor was initially chosen as it was easy to integrate within the app without requiring participants to download and register with third party software. It was also being used in the adult SmartCareCF study at the time

with minimal issues. During testing it became apparent there were issues around the adaptability for paediatric usage and around being able to survive periods of play etc. Replacing the activity monitor with an alternative device was considered but could not implemented due to inability of another device to fully integrate into the app. The activity monitor was the only device that could store data and from which data could retrospectively be uploaded onto the app. It had the ability to store data for seven days at a time. The retrospective data entry for the activity monitoring might explain the slightly higher data completion percentage despite it being the piece of equipment that participants reported the most issues with. Frustration with the activity monitor led many participants to document their activity in the 'What's up?' section using alternative monitors. Participants and their parents documented in the free text sections of the acceptability questionnaire that they would like to be able to document more than just their daily step count. This implies that the frustrations expressed were directed at the specific activity monitor and there was a wish by participants to be able to document activity levels at home. This information should be used to consider the types of devices used for home monitoring moving forward and significant testing should be instigated before rolling out to prevent participants from withdrawing from home monitoring due to frustration.

Throughout the study, replacement pieces of equipment and replacement batteries were required. Costings for ongoing replacement of equipment needs to be considered in both future research studies as well as ongoing clinical care as many people with CF will not be able to absorb these costs themselves. While no significant difference was seen in the healthcare costs associated with the early intervention arm and standard care arm of the eICE study only the initial set up costs were considered (385). There was also no way of recording if a participant had tried to upload data from a piece of equipment, the piece of equipment failed to upload, and the participant decided not to enter

data manually. While the pattern of data usage implies that once a participant had started entering data, they tended to complete all requested data points, it is unclear whether this was influenced by the connectivity of the Bluetooth equipment or the order in which the participant decided to enter data. The app also did not record how long a participant was signed in for each day. Although the participants reported it only took around 10 minutes a day, it would be useful to explore exactly how much of an additional burden of time remote monitoring would represent.

The median amount of data collected in our study was lower than previously reported in a similar cohort of CF children (346) and, as discussed earlier in the chapter, this may be due to the fact CLIMB-CF had a larger cohort of children and included all children in the analysis regardless of how much data were collected over the time period. It could also be due to the fact data was requested more frequently than in other studies. Van Horck and colleagues only requested data three times a week in their study. Data were requested daily for most the measures in CLIMB-CF; however, completion rates were higher for measures requested twice a week. Overall completion for the study may have been better if all measures were requested twice a week, however as mentioned earlier the optimal amount of data collection required is not yet known. The addition of home sampling may have impacted on study fatigue. The request for daily data entry in CLIMB-CF and the addition of home sampling may have contributed to study fatigue. Participants and their parents reported they would like to collect data less frequently than daily if given the option. To date it is not known how often remote data needs to be collected in order to guide clinical decision making. There is the potential that data are required more frequently while developing machine learning algorithms and can then be rationalised in the future once the algorithms are established.

Alarms and reminders were not routinely set with in the CLIMB-CF app. Participants had the option to set daily alarms and more specific reminders, but these were not automatic and participants did not receive regular prompts from the study apart from the monthly phone call from the research team. We were able to analyse how many participants set reminders and only a small percentage utilised that function. There is the potential that not having alarms set automatically within the app impacted completion of the requested measures. A previous study has reported that participants would like to be able to control their own alarms/reminders based on their own schedule (384) but in retrospect having pre-programmed alarms in CLIMB-CF may have increased data entry. The use of self-set reminders in our cohort did not seem to affect completion of requested data, although the number of participants who utilised them were small. However, the use of reminders has been shown to aid asthma medication adherence and blood pressure home monitoring (468, 469). These studies used daily or twice daily reminders. Consideration should be given to alert fatigue in future designs (470). It should also be noted that studies in asthma exploring the use of reminders in inhaler adherence found in both the control group and the group receiving daily reminders adherence to medication fell during the first 12 weeks of the study. It then remained relatively consistent for the remaining duration of the study; this is similar to the pattern seen in our 2-5 year old age group (469). It should also be noted that while adherence to medication has been shown to be increased by reminders, it has not been shown to consistently improve quality of life or exacerbation rates in asthma (471).

Financial incentives rather than reminders have been explored in other disease groups. Interestingly in adolescents with Type 1 diabetes mellitus it has been shown that while a financial incentive does encourage adolescents to carry out checks of their blood glucose levels daily, it does not improve

overall glycaemic control (460). There are ongoing studies in asthma exploring this (461). Future work should consider the use of alarms and reminders and whether they should be pre-set and editable.

One of the weaknesses of this study is the pragmatic decision made regarding the definition of a pulmonary exacerbation. As this was a feasibility study no criteria were given to sites regarding the diagnosis of a pulmonary exacerbation, this was decided clinically by health care professionals at each site. There is also the potential that the health care professional making the treatment decision may have also been in involved in CLIMB-CF which may have impacted their choice. As there is no standardized definition or treatment choice for an exacerbation there may have been variations between sites for which I am unable to correct. The start date for an exacerbation was documented as the start of antibiotics, however this does not allow for preceding symptoms prior to the prescription of antibiotics versus a possible noted drop in FEV_1 at a clinic appointment. This is also the date the antibiotic is prescribed rather than the definite start date of the antibiotics received by the participant. This definition has been used previously by other authors (128, 415) and was felt to be the most appropriate for this study. Analysis of received data around the exacerbation was expanded to include the week prior to the pulmonary exacerbation start date in an attempt to capture changes prior to the defined start date of the pulmonary exacerbation. The retrospective nature of the study analysis means that unfortunately it is unknown what sign or symptom/s triggered the course of antibiotics for a pulmonary exacerbation. In terms of the biomarker analysis, samples from the 14 days pre and post the start date of exacerbation treatment were included to identify any earlier changes in biomarkers. This, however, may potentially dilute a signal in a biomarker should it only be present close to the start of the pulmonary exacerbation. As samples were not collected daily in CLIMB-CF, it is not possible to explore daily changes in biomarkers around

the date of an exacerbation. One of the limitations of the biomarker aspect of the CLIMB-CF study was that samples were requested weekly, there is therefore the potential that changes in biomarkers prior to an exacerbation have not been identified

Another weakness of this study was that there were only a small number of pulmonary exacerbations treated with IV antibiotics. Information was not logged regarding the decision for oral antibiotics instead of IV antibiotics, but this may be representative of the fact that it is a paediatric cohort. Because of this the subgroup of participants who received IV antibiotics was too small to analyse separately.

Consideration needs to be given to both the definition of a pulmonary exacerbation and treatment of the exacerbation in future studies exploring the use of remote monitoring as a detection method but also to capture the reasoning behind any pulmonary exacerbations that do not meet the criteria but ultimately receive treatment. In future studies the treatment choice will also need to be considered. In the eICE study it was found that while participants in the early intervention (home monitoring) arm had more acute reviews by their CF centre, they also were more likely to receive oral antibiotics and they were unable to demonstrate a slower decline in FEV_1 percent predicted, potentially be down to treatment choice (341, 342).

Unfortunately, limiting the analysis around pulmonary exacerbations in this thesis to only participants who completed ≥ 80% did reduce the number of participants included and this is a weakness of that section. The complex analysis of the changes in remote monitoring readings around periods of exacerbation when a participant has completed <80% of the requested data

were outside the scope of this thesis but it should be noted though that after the initial stage of the ongoing machine learning, the CLIMB-CF participants with a less complete data set can be added to the algorithm (344). The data obtained from CLIMB-CF are currently being used in machine learning work with the team involved in the SmartCareCF analysis at the Cambridge Centre for AI in Medicine and the Machine Intelligence Group at Microsoft Research, to try and identify patterns or signals in the change of the data leading up to possible exacerbations to identify an algorithm that could be used clinically in the future. The initial stages of this work involve comparing the paediatric data with the algorithm from the SmartCareCF study to explore potential differences and similarities in the data set and then running separate analysis on the paediatric data with the additional data points collected in our study such as the additional wellness questions around appetite, breathlessness, sputum volume and tiredness and the additional objective measure of temperature.

A weakness of the biomarker section of CLIMB-CF study is that while participants with CF provided samples during periods of stability, there was no healthy control comparison group. The median (IQR) MMP-9 level for the group during stability was 97.1 (39-507) pg/ml. This is higher than documented levels in healthy paediatric controls in other studies. Erol et al reported mean (SD) MMP-9 urine levels of 28.2 ($\pm$ 16.8) in healthy controls (mean age 9.52 years) in their study using a Human MMP-9 ELISA kit (Abcam, USA) which had a lower limit of detection of 24.69 pg/ml (444). Slightly higher levels were found in the healthy controls with a mean (SD) age of 19.5 (10.3) weeks in a study Kleber and colleagues. The median (IQR) MMP-9 levels in their control group were 50 (27- 230) pg/ml using an MMP-9 Biotrak Activity Assays System from GE Healthcare. No lower limit of detection was documented in their publication (457). While these other 2 studies use different methodology and

there is overlap between the ranges of the results published, they suggest that the level in stable children with CF may be higher than healthy control children: this warrants further investigation.

When exploring the quality of life and mood questionnaires response rates were generally high with some of the missed data points either due to a different parent attending clinic and therefore not being able to compare results or to incompletely filled in questionnaires during busy clinic visits. One potential way to mitigate against this in the future is to provide links to electronic versions of the questionnaire that can be completed remotely around the time of the planned appointment therefore the same parent can continue to complete the questionnaires regardless of it they are attending the clinic appointment or study visit and be easily alerted to any missing questions within the questionnaire.

Another limitation is that only the CFQ-R (and only one domain within it) is validated in CF. Despite only one domain having a recognised MCID, it has been shown that the CFQ-R can differentiate between whether someone with CF is sick or well, with significant differences between the two groups noted in all domains in both the child CFQ-R and parent CFQ-R (472). In the adolescent CFQ-R all domains apart from digestion showed a significant difference, with quality of life scores being lower when the adolescent with CF is unwell. Agreement between the child CFQ-R and the adult CFQ-R has also been shown for all matching domains, although this agreement is stronger for those domains that are observable such as respiratory, eating, or physical functioning. Interestingly children reported worse emotional functioning than their parents.

While the PHQ-8 and the GAD-7 are the recommended measures to use to screen for depression and anxiety in CF, they are not validated in CF. They are also non- specific measures, looking at a short snapshot of time, which can be influenced by other external factors. The PHQ-8 and GAD-7 explore only the preceding 2 weeks and can be affected by factors external to CF. However, it should also be considered that those factors can impact the ability to manage a child with a complex chronic condition (290). It should also be noted that the adolescents in CLIMB-CF did not complete a depression or anxiety measure. Screening for depression and anxiety in adolescents is recommended annually by the International Committee on Mental Health (277). The pragmatic decision was taken in this study not to include it as a measure for the adolescents to complete as there is no recognised MCID in adolescents with CF and at the enrolment visit they were receiving training on the use of the technology and at the visit ~ 2 months in they were trained on sample collection. Consideration should be given to an adolescent depression and anxiety screening measure in future studies and the frequency of completion required for that measure.

CLIMB-CF started in 2016, at which point, to our knowledge, the only available Bluetooth enabled handheld spirometer did not easily display flow volume loops. This means the study was reliant on the internal validation software and precluded any professional validation of the flow volume loops. The study database was also only set to store the highest 'approved' reading from the spirometer rather than all three trials carried out by the participant. Multiple attempts were made to access the flow volume loops using the subsequent software provided by Vitalograph but these proved unsuccessful. Reassuringly for our data, most professional rejections of flow volume loops validated by a handheld spirometers internal software were because of events at the end of expiration and should therefore not impact FEV_1 (425). The technology has advanced since 2016, with many

handheld spirometers on the market displaying the flow volume loops, and this should be considered when selecting a handheld spirometer for future research. Despite this, the initiation of home spirometry, which was accelerated during 2020 due to requirements of being able to remote monitor patients in their homes during the COVID-19 pandemic, has been challenging. One London CF centre has published data showing that some paediatric patients who have been known to have good technique in clinic have struggled to be able to reproduce adequate flow volume loops at home (436). Studies have shown that when supervised ≥ 90% of paediatric spirometry readings are able to satisfy ATS/ERS standards, although these readings have not been subsequently compared to supervised clinic spirometry (426, 429). One recent study has compared unsupervised handheld spirometry with supervised spirometry in adults with CF using the same device (either the Air Next or the Spirohome) and concluded readings were comparable. The mean difference observed between the paired readings was 0.7ml, however the limits of agreement were wide (±220ml) (473), this has not been replicated in a paediatric cohort.

Another limitation of our study is that, as the study was carried out over various study sites and in participants' homes, we could not standardise for the use of nose clips or the timing of spirometry with physiotherapy. Research has shown that whether nose clips are used or not does not introduce bias in the majority, though for a few individuals there were significant differences (≥190ml) (474). The fact we asked for participants to be consistent about timings and whether they did or did not wear a nose clip has hopefully mitigated for some of that bias in the longitudinal measurements; efforts to document compliance with this would be useful in future studies. Also due to the multi-site nature of CLIMB-CF, the hospital devices used by each clinic were not standardised.

1.44 Discussion of hypotheses, unanswered questions and future work

Based on the results of this thesis I consider that my hypothesis that 'home monitoring will prove feasible and acceptable for patients and their families whilst not adversely impacting mood or quality of life' can be partially accepted. Home monitoring is definitely feasible for some participants and does not adversely affect mood or quality of life, but I have also shown a highly variable completion rate which did worsen over time, implying home monitoring is not appropriate for everyone and should not be a 'one-size-fits-all' option. I have also shown that engagement with a web-based interface rather than an app is particularly poor and this information should aid design of future studies CLIMB-CF is a home monitoring feasibility study and was not focused on clinical outcomes which has limitations for the conclusions that can be drawn from these results as there is no immediate benefit to the participants. However, the rates of completed data received are like those seen in studies designed to respond to the home monitoring signals (341, 346). For the duration of CLIMB-CF the majority of the data was requested daily which is more frequent than in other studies and this could have contributed to study fatigue and drop off of data collection and would need to be considered in any future study. There is evidence that home monitoring could be incorporated into a pulmonary exacerbation 'early warning' system (344) however CLIMB-CF has shown that consideration would need to be given to which patients would be able to benefit from this system by providing the required data as the participants in CLIMB-CF were not randomised to home monitoring suggesting they were motivated participants and data return was still low. Consideration could be consider to a "trial"of home monitoring with an agreement between the clinical team and the patient and their family with clear discussions regarding the amount of data return needed and achievable. Ultimately, an individualised monitoring system and approach may be required.

Home monitoring is not an end in itself, it must deliver improved outcomes in order to be worthwhile. There is the potential that home monitoring could be used in the future to develop a hybrid clinic system with remote consultations being used interchangeably with face to face clinic appointments allowing patients to use the home monitoring technology at pre-defined times rather than using it regularly as would likely be required in pulmonary exacerbation identification. During the time of this PhD there was a global pandemic caused by the COVID-19 virus which prompted urgent and radical changes to how CF centres were able to deliver care. Hospitals across the world had to accommodate significant numbers of patients infected with COVID-19 forcing them to adapt many aspects of routine care. In the UK people with CF were advised to 'shield' in their own homes as it was uncertain the impact the virus would have on the CF lung (458). This resulted in centres urgently transferring face to face CF clinics to remote video-link clinics, with centres being able to adapt the MDT working to a virtual clinic space and publishing protocols for change (475, 476). Consideration was given as to how to remotely monitor patients at home during the pandemic with most CF centres in the UK providing handheld spirometers to their patients. This did present challenges, including difficulties with remote training and poor technical quality on tests submitted requiring further training sessions and clinic team contact (436, 476). The introduction of video-link clinics was not limited to CF, with paediatric difficult asthma services also having to explore alternative ways to deliver care; one London centre published data that home administration of biologics using a video-link for support was feasible (477). At the point of writing this thesis different areas of the world are further adapting how they continue to see patients 18 months into the pandemic, with many currently adopting a hybrid clinic set up, seeing some patients remotely and some in person dependent on patient need (478). Only 36.5% of participants in CLIMB-CF stated they would consider reducing the number of face to face clinic appointments they had by utilising home monitoring but acknowledgement must

be given to the fact that these views might have been changed by the subsequent COVID19 pandemic.

While the pandemic forced CF centres and patients to adapt in a dangerous and rapidly evolving situation there remain concerns around some of the home monitoring methods employed, in particular in paediatrics around spirometry. I would suggest unsupervised remote spirometry is currently not used and where possible paediatric spirometry should be supervised with flow volume loops assessed by a trained professional and paired clinic spirometry and handheld spirometry measurements should be obtained at any available opportunity. I would propose caution accepting sudden changes in remote spirometry with no associated clinical symptoms given the evidence presented of the under-read in handheld spirometry presented in this thesis until we have clearer longitudinal data using the same handheld spirometer.

A recent cross-sectional survey of 11 CF centres in the USA, surveying both adults with CF and parents of children with CF on their views on the change to telehealth care delivery during the COVID-19 pandemic found that most people were highly satisfied (479). Concerns were raised however regarding the ongoing delivery of measures such as sputum collection and spirometry. Of the parents of children with CF, 69% expressed an interest in having some clinics virtually and some in person. A recent Lancet Commission has been published exploring how to integrate digital transformation into healthcare systems permanently (480). I would suggest that if home monitoring can be shown to be non-inferior to in person clinic appointments, with the advent of CFTR modulators and the postulated improvement in lung health, hybrid clinics could become the CF clinic set up of the future.

Prior to home monitoring becoming standard I believe further work needs to be carried out exploring the design of future apps, including a full co-design process, how frequently data needs to be collected, the use of alarms and incentives and exactly which pieces of data need to be recorded. A summary of potential issues and possible solutions has been included in Table 0-1.

The hypothesis that 'home sample collection is feasible' can be accepted depending on sample type. I have shown home sample collection of minimally invasive samples such as urine and throat swabs are feasible, but that DBS are collected less frequently and are often of poor quality. In terms of the final hypothesis that 'home monitoring and non-invasive sample collection could be used to predict pulmonary exacerbations earlier than clinically detectable', I have not been able to confirm this. I have shown that MMP-9 levels in urine are not correlated to periods of pulmonary exacerbation and are highly variable within subject even during periods of stability. It therefore is not a viable biomarker in urine for future studies. The data collected from CLIMB-CF are currently being applied to machine learning pulmonary exacerbation algorithms adapted from the algorithms identified from the SmartCareCF adult cohort data (344) with collaborators at Microsoft Research (Cambridge, UK) and the Cambridge Centre for AI in Medicine and Department of Medicine (University of Cambridge, UK) in the hope that potential early warning systems for pulmonary exacerbations can be developed and then trialled in the future with the results from CLIMB-CF aiding future trial design. This further work exploring the home monitoring data during periods of stability and periods of pulmonary exacerbation using techniques such as machine learning is needed, as well as future work to try to identify a more relevant biomarker/panel of biomarkers and to then understand the frequency with which it/they needs to be measured to be able to accept or reject this hypothesis

One aspect of home monitoring that has not been discussed above and needs to be considered, not just in CF, is the ethics of digital health, as it is incorporated into health care. Parents of children with asthma were surveyed regarding their views on the use of artificial intelligence (AI) in medical decision making and management of their child's asthma. Of the 295 parents who responded 63% felt AI could aid physicians in diagnosing asthma but only 15% thought AI could replace physicians in diagnosing asthma. Only 4% agreed that AI could be relied on to make medical decisions when supported by the physician and no one supported the idea that AI could make medical decisions independent of the physician (481). Interestingly, in the same survey, 64% of the parents surveyed would not support an algorithmic decision system, even if it was proven to provide better asthma control than the doctor (481). This low level of trust for AI is not specific to patients, with doctors also expressing concern about not being able to explain a patient's AI results to them (482). The risks associated with the adoption of digital healthcare include the digital divide, and while this is particularly relevant in the developing world it also encompasses the developed world with up to 20% of EU citizens thought to not have access to/use the internet (483, 484). There is also the fundamental risk of both systemic and sample bias within an AI algorithm as a training set used in the algorithm may not be representative of the entire patient cohort. This is particularly true when exploring race and sex bias (485). The addition of digital health or AI to aid decision making may also lead to automation bias by clinicians. Humans have been known to disregard information that contradicts a result postulated by a computer (486). This may have significant consequences in health care and needs to be considered in any future pulmonary exacerbation algorithms.

The use of digital health technology and AI in children needs particular consideration. There is concern that the pressure of meeting objectives set by the digital health platform may present a risk

for the development of self-esteem and may affect a child's sense of competency (487). There has also been concern raised over the diffusion of responsibility. If an algorithm goes wrong who is responsible? Is it the developer or the healthcare provider? (488). The final consideration is environmental as it has been shown that the training of one AI algorithm can emit as much carbon dioxide as 5 cars produce in their lifetime (489). The WHO have published guidelines to assist health care professionals in managing the above risks (490) and I suggest that consideration should be given to how to mitigate these factors in further research studies and clinical practice.

The data collected in CLIMB-CF were anonymised, but data privacy and confidentiality need to be addressed in remote monitoring systems moving forward, especially if they become part of clinical care. Currently there is no universally agreed standards for health data privacy, but Choi and Walker suggest the following principles should be incorporated when developing a remote monitoring system (491):

1. Consent for data collection and an individual's right to review and access their information.
2. Specific consideration for what information will be shared; with whom; and for how long.
3. Transparency about how failures of privacy and confidentiality will be managed.

Patients should give individual and informed consent, and that should include discussions around what the data will be used for, who will be looking at the data and how often (491). This may be particularly relevant if acute changes in remote monitoring data could signify a medical emergency to ensure there is no misunderstanding regarding whether real-time medical reviews are occurring or if the patient would need to access medical help from an alternate route.

1.45 **Conclusion**

The conclusions from CLIMB-CF are:

- Median percentage of completed data over the 6 months was 40.1%, which is lower than some previously published studies but did not exclude participants who entered minimal data from the analysis and therefore more realistic, although the observational study design needs to be acknowledged.
- The amount of data collected was highly variable per participant and particularly low in adolescents (a high risk group), raising questions around ongoing utility if remote monitoring use is not targeted especially in this age group.
- Participants and their families who perceived home monitoring to be useful completed significantly more of the requested measures suggesting participant and family engagement is key for future studies.
- Engagement with the online web based only symptom diary (Arm 2) was particularly poor.
- Home monitoring was acceptable to the majority of young people with CF and their families and does not adversely affect quality of life or mood in the cohort.
- Some parents of children with CF have high levels of anxiety and depression at screening.
- Spirometry data generated adds evidence to the argument that when performed unsupervised in the home environment, there is substantial variability even during periods of apparent clinical stability suggesting unsupervised readings should not be used to make clinical decisions unless healthcare teams can review the raw data.

- Differences demonstrated in measurements obtained from handheld and clinic based devices indicate that they should not be used interchangeably, and trends or change should only be assessed on a single device.
- As handheld devices become more commonly used catalysed by the COVID-19 pandemic, opportunities should be taken to compare same day clinic and home measurements in individuals so that such differences can be documented as well as individual longitudinal readings.
- It is possible to collect samples non-invasively at home, although to date, exploratory work on urinary biomarkers, including MMP-9, for possible pulmonary exacerbations have been negative.
- Urinary MMP-9 levels appear higher in females with CF compared to males with CF.

Consideration needs to be given to new approaches moving forward. Since the start of CLIMB-CF remote technology has advanced significantly, potentially allowing for monitoring devices that will provide better efficiency for patients such as watches that will track activity, heart rate and oxygen saturations automatically, potentially improving acceptability. Data collected in real time could be applied to machine learning algorithms developed from this study data. These data could be integrated into a randomised control trial with clinical decisions being made in response to the remote monitoring data. In parallel further work is needed in both the definition of a pulmonary exacerbation and the markers that could be used to identify them.

Table 0-1 Considerations for future studies. Learning points from CLIMB-CF and suggestions. Reproduced and adapted from Edmondson et al (388)

Considerations for future studies	Learning points and suggestions
Design of study, in particular, measures to be collected	• Ongoing data analysis e.g., using machine learning to identify which parameters best recognise a pulmonary exacerbation early and allow prompt treatment.
Specifics of device performance	• Carry out 'in-house' testing of devices before launch. • Some devices more susceptible to damage in 'real life' contexts. • Consider pilot testing with the intended age group. Recognition that unsupervised device use may not give reliable results; further investigation required. Consider direct observation via video for e.g., home spirometry
Engaging the population on visual design	• Involve people with the condition in the design process. • Recognise and specifically engage hard to reach groups e.g., adolescents
Adopting a user interface journey that is engaging and practical	• Expect/ plan for a long process. • Testing is required at multiple phases, including regularly testing the 'patient journey' within the app that is being developed.
Financing development of an app that can be used over multiple interfaces	• Consider likely interfaces (e.g., android, Apple), impacts on functionality and budget

Access to equipment	Consider financial implications of home monitoring • Equipment (and replacements) • Staff costs • To be financed by clinic or patient? • Weighing affordability against device performance, accuracy etc • Batteries, chargers etc
Access to WiFi/data	• Consider patient access to reliable WiFi or additional mobile data and those in remote locations
Data protection and storage	• Consider data transmission and secure storage
Increased anxiety or concern with the additional burden at home	• Consider screening pre-enrolment to identify families that may have higher levels of anxiety; seek to maintain inclusivity whilst providing sufficient support
Ensuring it is beneficial for the participant	How to make a study beneficial for participants? • Reward systems? • The ability to miss clinic? • Real/ close-time responsiveness: e.g., detection and treatment of a deterioration • Does it deliver better outcomes?
Safeguarding concerns with home monitoring	• Less face-to-face contact may be a detriment for younger or more vulnerable patients.
Technological support	• Plan for provision and funding. • Awareness that resource intensive, especially during set-up

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Appendices

Appendix 1 – Systems requirement document

SmartCare Paediatric Study - Project Requirement Catalogue
Study Aims
1. To assess the feasibility of home monitoring of children with CF over a period of 6 months
2. To assess the feasibility of sample collection by families at home
3. To assess the impacts of the study on quality of life indicators
4. To assess adherence to home treatment
5. To establish methodology for sample processing to aid future biomarker discovery
Outcome measures
Primary outcome:
Completeness of requested clinical data collected by children and families

Secondary outcomes:
Ease of use and acceptability
Quality of Life assessed by child and parent questionnaires
Depression/ anxiety scores for child and parent(s)
Proportion of requested biological samples collected
Reasons provided for non-collection of data/ samples
Reasons for possible non-adherence

Exploratory Outcomes:
Variability of clinical data during periods of stability
Changes in clinical data during periods of exacerbation
Suitability of collected samples for biomarker processing and optimisation.
Population:
Cystic fibrosis
Eligibility:
Children aged 2-17 years with cystic fibrosis confirmed on standard criteria.

Requirement ID	FR01
Requirement Name	Record Pulse rate and Oxygen Saturation
Area / Domain	Data Collection
Source	Adult Study
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A patient or family member must be able to use the Nonin Pulse Oximeter and the Android app to measure pulse rate and oxygen saturation and have the data automatically transfer to the study database.
Associated Non-functional Requirements	One pulse rate and oxygen saturation % can be recorded once a day Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available Patients / family members will be able to use the device successfully with training given at initial briefing session Integration with the Android app will be required for the following model(s): 3230, 3150 (required for Pleth Trace – see FR09),
Acceptance Criteria	All required measures from the device are transferred to the Android app. Measures from the device recorded each day are recorded in the database and a full history can be viewed in the Android app.
Rationale / Benefits	The ability to transmit data from a medical monitoring device streamlines the process of keeping an ongoing record of daily health. Multiple data can be written to the database within a single process.
Expected Delivery	First Release
Additional Comments	Data received by the Android app is displayed to give the user the opportunity to verify accuracy prior to committing the data to the web database. In the event of a transmission error, it should be possible to the user to manually enter a measure onto the app to ensure data completion. The user will be prompted to record one complete set of measures each day.

Requirement ID	FR02
Requirement Name	Record Lung Function
Area / Domain	Data Collection
Source	Adult Study
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A patient or family member must be able to use the Vitalograph Lung Monitor and the Android app to measure FEV1% and have the data automatically transfer to the study database.
Associated Non-functional Requirements	One FEV1% value can be recorded once a day (maximum, see Appendix 5) No probability of data corruption during transfer Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available Patients / family members will be able to use the device successfully with training given at initial briefing session
Acceptance Criteria	All required measures from the device are transferred to the Android app. Measures from the device recorded each day are recorded in the database and a full history can be viewed in the Android app.
Rationale / Benefits	The ability to transmit data from a medical monitoring device streamlines the process of keeping an ongoing record of daily health. Multiple data can be written to the database within a single process.
Expected Delivery	First Release
Additional Comments	Data received by the Android app is displayed to give the user the opportunity to verify accuracy prior to committing the data to the web database. In the event of a transmission error, it should be possible to the user to manually enter a measure onto the app to ensure data completion. The user will be prompted to record one complete set of measures each day. In addition to the FEV1% that will be displayed to the Android user, the device will also write values for FEV1, FEV10 and PEF to the database for analysis.

Requirement ID	FR03
Requirement Name	Record Daily Activity
Area / Domain	Data Collection
Source	Adult Study
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A patient or family member must be able to use the Misfit Activity Monitor and the Android app to measure daily activity in steps and have the data automatically transfer to the study database.
Associated Non-functional Requirements	One total daily steps value can be recorded once a day (maximum, see Appendix 5) No probability of data corruption during transfer Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available Patients / family members will be able to use the device successfully with training given at initial briefing session
Acceptance Criteria	All required measures from the device are transferred to the Android app. Measures from the device recorded each day are recorded in the database and a full history can be viewed in the Android app.
Rationale / Benefits	The ability to transmit data from a wearable device streamlines the process of keeping an ongoing record of daily health. Multiple data can be written to the database within a single process.
Expected Delivery	First Release
Additional Comments	The user will be prompted to record one complete set of measures each day. As data from multiple days' activity can be retained on the device, the app will transfer all data stored since the last sync.

Requirement ID	FR04
Requirement Name	Record Weight
Area / Domain	Data Collection
Source	Adult Study
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST

Stakeholders	CFT, JD, PS, End-users
Description	A patient or family member must be able to use the Pyle Smart Scales and the Android app to measure weight in KG and have the data automatically transfer to the study database.
Associated Non-functional Requirements	One weight value can be recorded once a day (maximum, see Appendix 5) No probability of data corruption during transfer Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available Patients / family members will be able to use the device successfully with training given at initial briefing session
Acceptance Criteria	All required measures from the device are transferred to the Android app. Measures from the device recorded each day are recorded in the database and a full history can be viewed in the Android app.
Rationale / Benefits	The ability to transmit data from a device streamlines the process of keeping an ongoing record of daily health.
Expected Delivery	Second Release
Additional Comments	Data received by the Android app is displayed to give the user the opportunity to verify accuracy prior to committing the data to the web database. In the event of a transmission error, it should be possible to the user to manually enter a measure onto the app to ensure data completion. The user will be prompted to record weight at least once a week.

Requirement ID	FR05
Requirement Name	Record Temperature
Area / Domain	Data Collection
Source	Adult Study
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A patient or family member must be able to record internal temperature via the Pyle Bluetooth Thermometer integrating into the Android app.
Associated Non-functional Requirements	One temperature value can be recorded once a day (maximum, see Appendix 5) Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available Patients / family members will be able to use the device successfully with training given at initial briefing session
Acceptance Criteria	Measures from the device recorded each day are recorded in the database and can be viewed in the Android app.
Rationale / Benefits	The ability to transmit data from a device streamlines the process of keeping an ongoing record of daily health.
Expected Delivery	Second Release
Additional Comments	Temperature – Must be recorded numerically in ˚C. Data received by the Android app is displayed to give the user the opportunity to verify accuracy prior to committing the data to the web database. In the event of a transmission error, it should be possible to the user to manually enter a measure onto the app to ensure data completion.

Requirement ID	FR06
Requirement Name	Enter Symptom Record
Area / Domain	Data Collection
Source	Adult Study / JD
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A patient or family member must be able to manually record daily data based on their perception of key symptoms via the Android app and via the web app.
Associated Non-functional Requirements	The interface will be intuitive enough for users to be able to record health measures without any training

	Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available One response to each health question can be recorded once a day Measure values can be selected on the Android app by using a sliding scale The patient group that do not have the study devices will be able to log into the web app as a patient and record their measures as part of a dated symptom diary.
Acceptance Criteria	Measures from each health question recorded each day are recorded in the database and can be viewed in the Android app. Responses to health questions are based on a standard scale which is easy to understand. A non-device user will be able to record these measures through the web app on a regular basis and view charts and details of their responses over time.
Rationale / Benefits	Where data is recorded from devices without the possibility of integration, or a device from which to capture (opinion based measures), data entry should be made as simple as possible. Opinion-based data recorded on a standard scale (relevant to the question) will aid analysis.
Expected Delivery	First Release
Additional Comments	Wellness Cough Severity Sleep Quality Breathlessness / Tightness Appetite Tiredness Sputum Volume All the above to be measured on the following scale: Much better than usual 5, slightly better than usual 4, same as usual 3, slightly worse than usual 2, much worse than usual 1 Sputum colour - None, Clear / White, Yellow, Green, Brown

Requirement ID	FR07
Requirement Name	Record Sleep Disturbance
Area / Domain	Data Collection
Source	JD
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A patient or family member will be able to manually record the number of instances of sleep disturbance during the previous night to the Android app, and the web app.
Associated Non-functional Requirements	The interface will be intuitive enough for users to be able to record health measures without any training Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available One response to each health question can be recorded once a day The patient group that do not have the study devices will be able to log into the web app as a patient and record sleep disturbance as part of a dated symptom diary.
Acceptance Criteria	Measures from each health question recorded each day are recorded in the database and can be viewed in the Android app. The number of disturbances entered by the patient will be timestamped o the point of entry, but also include the date of the previous day to reflect the night being recorded. A non-device user will be able to record disturbance through the web app on a regular basis and view charts and details of their responses over time.
Rationale / Benefits	Data recorded will show any trends related to increases / decreases of sleep disturbance in the context of the other measures recorded.
Expected Delivery	Second Release
Additional Comments	

Requirement ID	FR08
Requirement Name	Enter Respiratory Rate
Area / Domain	Data Collection
Source	JD
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A family member must be able to manually record a manually counted respiratory rate via the Android app.

Associated Non-functional Requirements	The interface will be intuitive enough for users to be able to record respiratory rate having been given an initial training session Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available One measure can be recorded once a day
Acceptance Criteria	Measures of respiratory rate provided each day are recorded in the database and can be viewed in the Android app.
Rationale / Benefits	
Expected Delivery	First Release
Additional Comments	To be measured as n per minute Not required as part of the patient view of the web app

Requirement ID	FR09
Requirement Name	Record Pleth Trace
Area / Domain	Data Collection
Source	Adult Study / JD
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	A subset of patients will use an alternative Nonin Pulse Oximeter to record a two-minute Pleth Trace, which will be transmitted via Bluetooth to the Android app, and converted into a file which can be saved to the patient record for later analysis.
Associated Non-functional Requirements	Android app will need to be capable of storing files for upload to the database. No probability of data corruption during transfer Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available. Patients / family members will be able to use the device successfully with training given at initial briefing session.
Acceptance Criteria	File is transmitted in a format that can be accessed by analysts. Files are timestamped to enable the analysed data to be compared to other captured measures. Data is recorded each second over the two minute period.
Rationale / Benefits	More complex data can be captured which requires analysis to discern results
Expected Delivery	Final Release
Additional Comments	It must be possible when setting up a patient account to select which devices the patient is using (see FR18). The Android app must make any additional steps / interactions involved clear to the user.

Requirement ID	FR10
Requirement Name	Indicate Samples Taken
Area / Domain	Data Collection
Source	Adult Study / JD
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	Patients or family members will be able to record the date when a sample has been taken, and the type of sample taken on the Android app. This includes urine, sputum, nasal samples, blood and throat swab
Associated Non-functional Requirements	No probability of data corruption during transfer Data can be temporarily stored on the app for transmission to the web database when a Wi-Fi connection becomes available As multiple types of sample will be required, it will be possible to record more than one sample of different types each day. Entry of a sample record will not form part of the daily health measure requirement.
Acceptance Criteria	Patients are not prompted by the Android app to record a sample each day. More than one sample of different types can be recorded against the same date.

	It is possible to access a list of all sample types and dates recorded through both the Android and web app (for clinical research team).
Rationale / Benefits	This will help researchers to know where various samples have been taken and link this to the monitoring data being recorded.
Expected Delivery	First Release
Additional Comments	The different types of samples will be Sputum, urine, nasal samples, blood spot samples and throat swabs.

Requirement ID	FR11
Requirement Name	Record Supplementary Information
Area / Domain	Data Collection
Source	Adult Study / JD
User	Patient / Family Member /Clinical Research Team
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	Other information that might provide context to the medical measures being recorded can be inputted into the Android app or into the web app by patients, or by a clinical research team at out-patient appointments in their view of the web app.
Associated Non-functional Requirements	No probability of data corruption during transfer Data can be temporarily stored on the mobile app for transmission to the web database when a Wi-Fi connection becomes available Data can be entered by the patient via the Android app, or by the clinical research team / study administrator via the web app. The data recorded is included in any data exports from the web app. Patients can view a history of all recorded entries via the Android app.
Acceptance Criteria	Patients or family members and clinical research team can select from a pre-defined list of categories of events. Events will have attached timestamp metadata and include the category and any free text entry. These will be included in the data export. Patients and clinical research team can view the events as elements on the charts of other measures for context, and also see a list of all events recorded.
Rationale / Benefits	Additional context can be provided to health measures on an ad hoc basis to enrich analysis, for example, the start of a new treatment, courses of IVs, allergic reactions etc.
Expected Delivery	First Release
Additional Comments	To ensure consistency for analysis, both the Android and web entry must include broad categories to describe the information being captured, with the facility to add further detail as a free-text entry. Categories– patient categories and clinical categories (depending on user) – See Appendix 6. Metadata will confirm whether the information has been entered by the clinical research team or the patient (based on the logged in user).

Requirement ID	FR13
Requirement Name	View Historic Data
Area / Domain	View Data
Source	Adult Study / JD
User	Patient / Family Member
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS, End-users
Description	It must be possible for patients and family members to view data for each measure previously collected via the Android app, or the web app (dependent on their access method) via a graphical representation in order to show changes in their health measures over time.
Associated Non-functional Requirements	Data will be presented in a format that fits the timeframe and measures collected. Information will be easy to understand for the end user. Measures will be shown immediately upon transmission to the database.
Acceptance Criteria	Patients and family members will be able to record each measure each day, and view these results on a chart. All information captured will be displayed on the relevant chart.
Rationale / Benefits	The ability to view health data over time will provide study participants with an overview of their condition, and empower them to better understand periods of ill health.
Expected Delivery	First Release

Additional Comments	Users of the Android app can choose between a view of the most recent week, month, or all data. Users of the web app will be able to pan and zoom charts to view data as required.

Requirement ID	FR14
Requirement Name	Create User Account
Area / Domain	Patient Set Up
Source	Adult Study / JD
User	Study Administrator
Requirement Type	Functional
Priority	SHOULD
Stakeholders	CFT, JD, PS
Description	It will be possible for the study administrator to record key details to the patient user account in order to derive information about the data required and ensure that the patient / family members can be contacted.
Associated Non-functional Requirements	Must be accessible via NHS supported browsers (not IE 6) The user profiles that a study administrator can view will be restricted to those within their site The web app will be available during hospital core working hours
Acceptance Criteria	The system will generate a unique ID which will be used to identify each patient record. The gender and age of each patient will be included in the export for analysis. An email address associated with the user profile and the Android Smartphone can be utilised to set / reset a password.
Rationale / Benefits	Patient identifiable data (name) will be masked for the Researcher user type to ensure anonymization. Gender and age can be recorded to aid analysis. ID reference can be used to ensure that individual patients are not identifiable to the research team. Contact email will be used to set up a Google account with which to download the app and push updates, and communicate any study specific information.
Expected Delivery	Second Release
Additional Comments	It will be possible for the Site Administrator to define which methods of recording measures each patient will be using, which will affect which functions are available to the patient in the Android app. It will be possible for the Site Administrator to change the frequency with which each measure.

Requirement ID	FR15
Requirement Name	View Study Data
Area / Domain	Clinical Monitoring
Source	Adult Study
User	Clinical Research Team
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS
Description	Clinical Research Team users will be able to see anonymised records of patient data as a chart for each measure over time, in order to assess any trends as the study progresses.
Associated Non-functional Requirements	Web app should be fully functional via NHS web browsers Charted data will include usability features to allow panning / zooming into specific data points / ranges of interest.
Acceptance Criteria	Clinical Research Team can view charts for each measure, for each patient in their clinic. All data collected for the relevant patients can be viewed – both in detail and chart form.
Rationale / Benefits	Clinical Research Team can view the data from individual patients without having to export and analyse data from the system.
Expected Delivery	First Release
Additional Comments	

Requirement ID	FR16
Requirement Name	Produce Data Export
Area / Domain	Clinical Monitoring

Source	Adult Study
User	Researcher
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS
Description	It must be possible for researchers to export the data collected during the study to be analysed outside of the web app.
Associated Non-functional Requirements	Exports will be generated in .csv format. Exports can be limited to a date range to restrict data output to a specific period of time. To protect the anonymity of the patients, data exported will include a system ID in place of identifiable data
Acceptance Criteria	Export will include the data collected from each measurement for each patient, and metadata including a timestamp (all metadata - see Appendix A)
Rationale / Benefits	During / at the culmination of the study, data collected can be exported and analysed by researchers to discern whether any biomarkers or health measure trends can be connected to early indicators of pulmonary exacerbations.
Expected Delivery	First Release
Additional Comments	Format must be agreed to fit with the format of data collected from various samples and measures, to ensure consistency for analysis. It must be possible to filter the data export by measure type, to facilitate export to external analysis software: Patient info (demographic data) Patient/Parent input selection Events (patient / clinical research team recorded, categories & free text) Weight Pulse oximetry Lung function Heart rate Respiratory rate Activity Temperature Samples collected Sputum colour Cough severity Sleep quality General wellness Sputum volume Breathlessness/tightness Appetite Tiredness Sample results (sputum etc) Questionnaire scores

Requirement ID	FR17
Requirement Name	Record Questionnaire Scores
Area / Domain	Data Entry
Source	JD / CE
User	Clinical Research Team / Site Admin / System Admin
Requirement Type	Functional
Priority	MUST
Stakeholders	JD
Description	It should be possible for clinical staff to record a score for one of a selection of questionnaires for each patient at varying points of the study.
Associated Non-functional Requirements	Multiple responses to each individual questionnaire can be recorded in the database if the patient is asked to provide these at different points in the study.
Acceptance Criteria	The questionnaire score and corresponding data will be saved to be used in conjunction with the analysis of the measures data. Analysts will be able to make the connection between the questionnaire data and the measures using the same User ID.
Rationale / Benefits	Responses to questionnaires will help to make standardised assessments of the psychological impact of daily monitoring and regular home sample taking.
Expected Delivery	Final Release
Additional Comments	Data required would be Patient ID, Questionnaire Type, date taken, and score. Questionnaire types will be Knowledge of Disease questionnaire: Parent Knowledge of Disease questionnaire: Child, CFQ-R Parent, CFQ-R: Young person, PHQ-8 Parent, PHQ-8 Young person, GAD-7 Parent, GAD-7 Young person, Strengths and difficulties

	questionnaire: Young person, Treatment adherence questionnaire: Parent, Treatment adherence questionnaire: Young person It should be possible for a clinical Research Team to view a history of questionnaire scores in the patient summary, but not for the individual patient to see the scores recorded.

Requirement ID	FR18
Requirement Name	Select Devices
Area / Domain	Patient Set Up
Source	JD
User	Clinical Research Team / Study Administrator
Requirement Type	Functional
Priority	MUST
Stakeholders	Clinical Research Team
Description	It must be possible for the study team to set in the web app which devices and measures are to be used by each patient, therefore affecting what the patient will see in the Android app, and whether they will be inputting data into the Android app or the web app.
Associated Non-functional Requirements	The user profiles that a study administrator can view will be restricted to those within their site The web app will be available during hospital core working hours
Acceptance Criteria	Study administrators will be able to assign any combination of devices / measures to a patient. The patient will only have the option to complete the measures that have been assigned to them. Patients will see instructions relevant to the devices that have been assigned to them. Patients will only be reminded to complete the measures that have been assigned to their user account.
Rationale / Benefits	This will allow the clinical research team to opt patients in or out of the combination of devices they are to use for the study, in particular pulse oximetry and in measuring lung function.
Expected Delivery	Final Release
Additional Comments	Must be available as part of the patient / user account set up process (FR14) Appendix 3 has been provided listing the variables for each device / measure.

Requirement ID	FR19
Requirement Name	Record Clinical Measures
Area / Domain	Data Entry
Source	CE / Study protocol
User	Clinical Research Team
Requirement Type	Functional
Priority	MUST
Stakeholders	Clinical Research Team / Patients
Description	It must be possible for a clinical research team to enter a full range of measures into the patient record using the web app, which will include metadata to indicate that these measures have been recorded in clinic.
Associated Non-functional Requirements	It will be a simple process for a user to reset their password without outside intervention. Patient access will be achieved using an anonymised username and dedicated email address, to ensure that it is not possible to identify individual patients from the data stored on the system. The process of viewing and using the data, either over the web-based facility or on the smartphone, must be easy and straightforward for non-technical people.
Acceptance Criteria	A clinical research team user will be able to manually record all measures that would usually be recorded at home by a patient (including LCI) via the web app, attributed to the relevant patient and date. Metadata in the data export will show that these measures have been recorded in a clinical visit.
Rationale / Benefits	This will ensure that measures taking in a clinical setting can be differentiated from those recorded using home monitoring equipment.
Expected Delivery	Final Release
Additional Comments	This function will be available to clinical research team users as part of the data entry function of the web app.

Requirement ID	FR20
Requirement Name	Record Supplementary Clinical Data
Area / Domain	Clinical Data Entry
Source	CE / JD
User	Clinical Research Team
Requirement Type	Functional
Priority	SHOULD
Stakeholders	Clinical Team
Description	It should be possible for the clinical team to record detailed supplementary data including a patient summary, medication records, comorbidities, microbiology, admissions, IVs and questionnaire scores in the web app, associated with the relevant patient and date.
Associated Non-functional Requirements	This functionality will be restricted by user permissions to be available to clinical research team and administrators only. Clinical research team users and site administrators will only be able to access and edit data from the patients assigned to their site. It will be possible to view the additional data in the data export so that this can be analysed in conjunction with the regular measures recorded.
Acceptance Criteria	Users will be able to record the results of clinical tests and measurements from when the patient visits clinic. The date and type of visit will be included in the recorded data.
Rationale / Benefits	This will ensure that a secondary database of key clinical information that will provide context to the measures recorded will not be required.
Expected Delivery	Final Release
Additional Comments	All data capture requirements are documented in the document "CLIMB-CF data collection proforma V1 april 2016". Further scoping may need to be completed with the clinical team to transform this into a web-appropriate form.

Requirement ID	FR21
Requirement Name	Report Progress
Area / Domain	Study Reporting
Source	BM / CE
User	Clinical Research Team / CFT
Requirement Type	Functional
Priority	SHOULD
Stakeholders	CFT / Lead Study Site / Funders
Description	The web app must provide the ability for the lead site and the project team at CFT to view high level information derived from the live study data.
Associated Non-functional Requirements	This information presented on the dashboard must update in real-time based on the data held in the database.
Acceptance Criteria	CFT and the lead centre will be able to access a dashboard which displays key data from the study as a whole (across all participating centres).
Rationale / Benefits	This will ensure that the lead centre and the CFT project team will be able to access key metrics regarding the progress of the study at any time without having to carry out analysis of the data and without needing access to live or identifiable data.
Expected Delivery	Final Release
Additional Comments	Metrics to include: Total number of patients (per site, with overall total) live on the study. Number of patients having completed the study (post 6 months from their start date). By device, then by site, percentage of users entering data manually rather than through transmission. Percentage of measures missed (based on established frequency of measures for each device – frequency of each measure defined in Appendix 5) For patient recorded measures, ratio of patients recording against parents / guardians.

Requirement ID	FR22

Requirement Name	Record Patient User
Area / Domain	Mobile App
Source	JD / CE
User	Patient / Parent
Requirement Type	Functional
Priority	SHOULD
Stakeholders	Clinical / Analysts
Description	It must be possible for a user of the Android or web app to record whether they are the person with CF recruited in the study, or if they are that person's parent or guardian.
Associated Non-functional Requirements	Data recorded here will be written back to the database and it will be possible to view this in the data export.
Acceptance Criteria	A patient user will not be able to record a measure within a session without having first confirmed whether they are the patient or the parent. The data export will show which sub category of patient user recorded measures on that date.
Rationale / Benefits	This will ensure that data provided can be viewed in the context of whether the data was collected by the patient or the parent.
Expected Delivery	Final Release
Additional Comments	This question could be asked as a precursor to recording any measures with either the mobile or web app, and the answer must be associated with the measures recorded in that session. It could also be possible to set a default for this question in the settings section for cases where it will always be the parent, or always be the patient.

Requirement ID	FR23
Requirement Name	Record Sample Results
Area / Domain	Data Entry
Source	JD / CE
User	Clinical Research Team / Site Admin / System Admin
Requirement Type	Functional
Priority	MUST
Stakeholders	JD
Description	It must be possible to use the data entry screen of the web app to retrospectively record data from the analysis of different types of samples.
Associated Non-functional Requirements	The data recorded is included in any data exports from the web app.
Acceptance Criteria	The Clinical Research Team will be able to record the patient, date, sample type and result in the web app. The data recorded will be available in the data export from the web app.
Rationale / Benefits	This will ensure that the retrospective analysis of samples collected as the study progresses can be recorded alongside the measures being recorded. It will also be possible to ensure that all samples indicated by the patient have been analysed.
Expected Delivery	Second Release
Additional Comments	Confirmation of the related units etc that may be relevant for each sample type will be defined by the study team.

Requirement ID	TR01
Requirement Name	Web App
Area / Domain	Technical
Source	Adult Study
User	Clinical Research Team / Researchers / Study Administrators
Requirement Type	Technical
Priority	MUST
Stakeholders	Clinical Research Team / Researchers / Study Administrators
Description	The data collected by patients will be accessible via a web-front end that is fully functional on Firefox, Chrome, and Internet Explorer. Web pages will be transmitted using a secure HTTPS connection. Access to specific functions of the web app will be role based, and these roles can only be assigned by a System / Site Administrator. The web app will be simple for a non-technical person to use without prior training.

Acceptance Criteria	System Administrators will be able to view and add all users, set up clinics, and assign site administrator rights. Site Administrators will be able to set up and view users assigned to their site only. The Clinical Research Team will be able to view all patients' data in the clinic assigned to them, and have the ability to add additional information. Researchers will be able to export all patient data within a specified date range in a suitable format (.csv) for further analysis. Patients will be able to access the web app and view their measure summary. Those patients not being provided with home devices and that are only recording symptom scores and other events on the web app will have access to the data entry tab and be able to record those measures here.
Rationale / Benefits	The web app will be the main portal to study data, used by all non-patient user groups. It must function to allow the management of the study and the ability to view and analyse the data collected.
Expected Delivery	First Release
Additional Comments	

Requirement ID	TR02
Requirement Name	Android App
Area / Domain	Technical
Source	Adult Study
User	Patient
Requirement Type	Technical
Priority	MUST
Stakeholders	Patients
Description	The app provided to patients must be fully operable on the designated device provided for the study (Moto E, running a minimum of Android 5.0) using a home Wi-Fi connection. All device integration must be achieved through Bluetooth 4.0 (LE) and this process must be simple enough for a patient to undertake this with limited initial training. All screens must display in line with Cystic Fibrosis Trust brand guidelines. Dialogue must be displayed to inform the user of the progress of syncing with devices via Bluetooth and syncing data with the database via Wi-Fi. Data must be temporarily stored in the app if it cannot be transmitted to the web database.
Acceptance Criteria	All functions developed for the Android app will be tested and assessed as fully functional on the chosen platform device.
Rationale / Benefits	
Expected Delivery	First Release
Additional Comments	

Requirement ID	TR03
Requirement Name	Connected Devices
Area / Domain	Technical
Source	Adult Study
User	Patient
Requirement Type	Technical
Priority	MUST
Stakeholders	Patients
Description	Devices used in the study must transmit data via Bluetooth 4.0 (LE), have an API that can be made available to the app development team for integration. The devices must transmit data directly to the app, rather than to a dedicated web service.
Associated Non-functional Requirements	Devices will be easy to use with only initial training. Data measured by devices will be clinically accurate (to be assessed by the study team).
Acceptance Criteria	The study team will confirm acceptance of each candidate device. The development team will assess any candidate devices and their APIs to confirm that they are suitable for integration.
Rationale / Benefits	Devices will all communicate with the Android app across a common standard and data collected will remain treated in line with NHS Data Security regulations.

Expected Delivery	Final Release
Additional Comments	The turnaround time to assess and develop integration for any new devices must be factored in to any decisions made about new / alternative devices.

Requirement ID	TR04
Requirement Name	Store All Study Data
Area / Domain	Data Security
Source	Adult Study / NHS Information Security
User	Research Team
Requirement Type	Technical
Priority	MUST
Stakeholders	CFT, JD, PS, NHS
Description	It is imperative that all data submitted by patients is stored in line with the NHS England Information Security Policy, and held with the relevant encryption and protection against unlawful access.
Associated Non-functional Requirements	Access to study data through both the Android and web apps will be restricted by password. User profiles will restrict the functionality available to the user dependent on what is defined appropriate for their role. All storage and transmission of personal data must be compliant with applicable legal and security requirements.
Acceptance Criteria	It will not be possible for a user of the Android app or the web app to access any data without a valid user profile and password. A logged in user will only see the functions appropriate to their user role. It will be impossible for a person to gain access to the database via known penetration methods.
Rationale / Benefits	Data must be stored at a level of security appropriate for sensitive medical data (OFFICIAL). Patients and families must be confident that the data they are submitting is being treated in a fair and appropriate manner.
Expected Delivery	Final Release
Additional Comments	Data transmission and storage must meet the Data Protection Act, NHS England Information Security Policy, HTTPS encryption.

Requirement ID	TR05
Requirement Name	Restrict Access
Area / Domain	Data Security
Source	Adult Study / JD / NHS Information Security Policy
User	All
Requirement Type	Functional
Priority	MUST
Stakeholders	CFT, JD, PS
Description	Each user's access to data and functionality will be restricted based on user roles and individual account permissions, which will act to define what they should be able to see and do.
Associated Non-functional Requirements	It will be a simple process for a user to reset their password without outside intervention. Patient access will be achieved using an anonymised username and dedicated email address, to ensure that it is not possible to identify individual patients from the data stored on the system. The process of viewing and using the data, either over the web-based facility or on the smartphone, must be easy and straightforward for non-technical people.
Acceptance Criteria	Access to the Android and web app will only be possible with a combination of a valid username and password. A patient will only be able to see the data they have recorded. Clinical Researchers and site administrators will only be able to access data from the patients assigned to their site. Only Researchers and the Clinical Research Team will be able to export data, and will not be able to view any identifiable data.
Rationale / Benefits	Suppression of identifiable data is in line with the non-interventional nature of the study.
Expected Delivery	Final Release
Additional Comments	Permission levels will be Patient, Clinical Research Team, Researcher, Site Administrator, System Administrator, and CFT. Functions available for each user type are provided in Appendix 4.

Non-Functional Requirements

Reference No.	Description
NFR001	The solution must provide the following level of availability and support. Transmission Of Data Availability: Upload of single-point data from health monitoring devices at least once a day Supported: M-F, 09:00-17.30. Planned Maintenance can be done anytime outside of supported hours. Display And Analysis Of Data Availability as measured on a monthly basis: 99.5% within core hours (M-F, 08.30-17:30) Supported: M-F, 09:00-17.30. Planned Maintenance can be done anytime outside of supported hours.
NFR002	The developer will provide ongoing support to the technical aspects of the study (see Appendix 2).
NFR003	There must be effective monitoring of system components (both system/hardware and application layers), excluding health devices and phones, to allow pro-active fault resolution and avoid first notice of a problem coming from the systems.
NFR004	Sufficient logs for the solution must be maintained to permit prompt and effective diagnosis of issues. A description of the key logs and proposed housekeeping procedures for these should be provided by the supplier.
NFR005	Support documentation must be in place for the solution.
NFR006	Response times for display and analysis of the data must be no longer than 3 seconds, except where large data manipulation is required such as complex searches.
NFR007	Display and analysis of the data must be straightforward and simple for a non-technical person to use.
NFR008	Error messages must be meaningful to a non-technical person
NFR009	Full training and user documentation must be provided for the use of the data display and analysis tools.

Appendix 2 – Paediatric sprint timetable by week

SmartCare Paediatric Sprints

FatFractal, Inc.

June 15, 2016

Sprint	Phase	Weeks	Key	Description	Effort
1	1	26, 27			
			R	Refactor	40
			MD	Metadata	16
				Total	56
2	1	28, 29			
			PKG	Packaging	20
			FR01	Pulse-Ox device	16
			FR02	Lung device	4
			FR03	Activity device	4
			FR04	Weight device	4
			FR05	Temperature device	12
				Total	60
3	1	30, 31			
			FR06	Symptom entry	6
			FR07	Sleep entry	12
			FR08	Respiratory entry	12
			FR10	Indicate Samples	16
			FR11	Supp. Info	4
			FR13	Historic data	4
			FR15	Study data (web)	4
			FR16	Data export (web)	10
				Total	68
4	1	32, 33			
			UAT	Acceptance testing	40
				Total	40
5	2	34, 35			
			FR09	Pleth trace	28

Continued on next page

Sprint	Phase	Weeks	Key	Description	Effort
			FR14	Create user acct (web)	36
				Total	64
6	2	36, 37			
			FR18	Select devices (web)	8
			FR19	Clinical measures (web)	8
			FR22	Patient user	2
			UAT	Acceptance testing	12
				Total	30
7	3	38, 39			
			FR12	Reminders	12
			FR17	Questionnaires (web)	18
			FR20	Clinical data (web)	16
			FR21	Report progress (web)	8
			FR23	Sample results (web)	4
				Total	58
8	3	40, 41			
			LV	Patients leaving	20
			UI	UI adjustments	24
			UAT	Acceptance testing	20
				Total	64

Appendix 3 – Participant proforma

*Cli*nical *M*onitoring and *B*iomarkers to stratify severity and predict outcomes in children with *C*ystic *F*ibrosis (*CLIMB*-CF).
Stage 1: Data collection and Feasibility assessment
Enrolment Visit Worksheet
PATIENT'S INTIALS_____ Hospital ID _____ Study ID_____
DATE_____
INCLUSION CRITERIA
Cystic fibrosis confirmed by standard criteria
Males and females aged 0-17 years
Written informed consent obtained
Permission to inform GP of participation in study
EXCLUSION CRTIERIA
Clinical instability at screening defined by:
Not on any additional antibiotics (excluding routine, long-term treatments) for the previous 2 weeks
No increase in symptoms such as change in sputum production/colour, increased wheeze or breathlessness over the previous 2 weeks
No change in regular respiratory treatments over the previous 4 weeks
If any of these apply, entry into the study can be deferred
This exclusion applies only to study entry and will not affect the status of individuals already enrolled
Repeated non-attendance at scheduled clinic visits (or, once the study has commenced, at study related visits or booked phone calls)
Current participation in an interventional clinical trial
Participation in any trial of a CFTR modulating drug within the previous 60 days
Patients receiving a CFTR modulating drug will be unable to join Arm 2 or Arm 3 (Royal Brompton Hospital only)
Inability, after training by study team, to operate the smart technology or devices
Pregnant or breast feeding
Which arm of the study would they like to join:
☐ Smart app and home monitoring
☐ Web based symptom diary and biomarkers
☐ Clinic contact and biomarkers
CHECKLIST
☐ Consent
☐ GP Letter
☐ Remote Monitoring App UserID _____/ ☐ Website user ID_____
☐ Study email _____@gmail.com
Equipment provided at enrolment visit (if required):
Rucksack
Mobile phone
Phone charger
Pulse oximeter
Lung Monitor
Activity Monitor
Scales
Equipment provided after 2 months (if required):
Cooler bag
Sample pots
Clinell wipes
Nose clips, nasosorption devices, throat swabs, tissues etc
Freezer required yes / no
INDIVIDUAL PATIENT SUMMARY
Background:
DOB: Age:
Gender: Ethnicity:

CFTR genotype_____
No of hospital admissions in last 6 months/IV antibiotics at home_____
No of courses of oral antibiotics in last 6 months _____
Any previous history of:
Pseudomonas Aeruginosa (if cultures now negative) Yes ☐ No☐ Date_____
Mycobacterium abscessus Yes ☐ No☐ Date_____
ABPA treatment Yes ☐ No☐ Date_____

Parent smoking Yes ☐ No ☐ How many a day_____
Patient smoking Yes ☐ No ☐ N/A ☐ How many a day_____

Alcohol intake Yes ☐ No ☐ N/A ☐ How much a week_____
Home address postcode_____
Nursery/School/Work address and postcode_____
_____
Mode of Transport to Nursery/School/Work (tick all that apply)
Tube ☐ Bus ☐ Train ☐ Walk ☐ Car ☐ Cycle ☐
Average journey time_____
Highest level of Maternal Education
Some secondary school or less ☐ GCSEs/O Levels ☐ A/AS Levels ☐ Other higher education ☐ University degree ☐
Professional qualification or post-graduate study ☐
Highest level of Paternal Education
Some secondary school or less ☐ GCSEs/O Levels ☐ A/AS Levels ☐ Other higher education ☐ University degree ☐
Professional qualification or post-graduate study ☐
Maternal occupation_____
Paternal occupation_____
Number of people in household Adults_____ Children (including Participant)_____
CURRENT MEDICATION

Medication	Patient taking (circle as indicated)	Dose / Frequency	Medication	Patient taking (circle as indicated)	Dose/Frequency
Azithromycin	Y/N		Dornase Alpha	Y/N	
Co-amoxiclav	Y/N		Hypertonic saline	Y/N	
Flucloxacillin	Y/N		Ivacaftor	Y/N	
Ciprofloxacin	Y/N		Salbutamol	Y/N	
Clarithromycin	Y/N		Vitamin D	Y/N	
Co-trimoxazole	Y/N		Creon	Y/N	
Amikacin	Y/N		fat soluble vitamins	Y/N	
Colomycin	Y/N		Ranitidine	Y/N	
Promixin	Y/N		Omeprazole	Y/N	
Colobreathe	Y/N		Domperidone	Y/N	
Meropenem (neb)	Y/N		Ursodeoxycholic acid	Y/N	
Tobi	Y/N		Vitamin K	Y/N	
Tobi podhaler	Y/N		Other:		
Itraconazole	Y/N		Other:		
Posaconazole	Y/N		Other:		

Voriconazole	Y/N		Other:		
Ambisome	Y/N		Other:		

NEW/CHANGES TO MEDICATION WHILE ON STUDY

Medication	Start Date	Stop Date	Reason for Change

Please list all patient comorbidities and new diagnoses during the time the patient is in this study:

Diagnosis	Pre-existing (P) or new (N) diagnosis since entering the study?

Please record all positive bacterial growth in the previous 6 months and in the duration of the study (continue on additional comments sheet as required)

Bacteria	Date	Sensitivities

Please record all Clinic attendance dates whilst the patient is in this study:

Date	Date

Please record all hospital lung function measures taken for this patient in the previous 6 months and whilst they are in this study:

Date	FEV_1 (Litres and % predicted)	FVC (Litres and % predicted)	Reference equation used

Hospital Admission Dates for previous 6 months and duration of study (Please also include dates of Home IV therapy):

Reason for admission	Date Admitted	Date Discharged	Antibiotic use (Name/preparation)	Start date	Stop date

Please record all height and weight measurements in last 6 months and for the duration of the study:

Date	Height in CM	Z score (if known)	Weight in kg	Z score (if known)	BMI (if known)

Please record when the patient is given oral or IV corticosteroids during their time in this study:

Name of corticosteroid	Preparation (PO/IV)	Start date	Stop date

ENROLMENT VISIT CLINICAL INFORMATION

HR_____ RR_____Temp_____O_2 Sats_____
Height:_____cms Weight:_____kgs BMI_____
Clinic Spirometry Predicted FEV1:_____(%) FEV1:_____(L) Too young ☐
FEV1 value entered into home lung function monitor_____
LCI Result (if applicable)_____device_____
Samples Taken:
☐ Urine
☐ Sputum
☐ Throat Swab
☐ Nasal secretions
☐ Dried blood spot
Questionnaires:
☐ Knowledge of Disease Questionnaire: Parent Score_____
☐ Knowledge of Disease Questionnaire: Child (6 years and above) Score_____
☐ PHQ-8 & GAD-7 Parent Score_____
☐ PHQ-8 and GAD-7 Scores checked and referred as required
☐ Strengths & difficulties questionnaire (≥3 years) Score_____
Competent using Smart Technology:
☐ Parent (if applicable)
☐ Child (if applicable)

Comments:

SUBSEQUENT VISIT CLINICAL INFORMATION (COPY AS NECESSARY)
VISIT NO: DATE:
☐ Consent checked
☐ Smart app data downloaded checked (if appropriate)
☐ Medicines checked and altered on enrolment sheet as required
☐ Enrolment sheet checked and new information added as required i.e. spirometry, positive culture growth, admissions
Any Admissions or antibiotics since last review _____
_____
Any positive cultures since last review_____
_____
HR_____ RR_____Temp_____O2 Sats_____
Height:_____cms Weight:_____kgs BMI_____
Clinic Spirometry Predicted FEV1:_____(%) FEV1 :_____(L) Too young ☐
FEV1 value entered into home lung function monitor_____
LCI Result (if applicable)_____device_____
Samples Taken:
☐ Urine
☐ Sputum
☐ Throat Swab
☐ Nasal secretions
☐ Dried blood spot
Questionnaires (as per study protocol):
☐ CFQ-R Parent Score_____
☐ CFQ-R Child(6 years and older) Score_____
☐ PHQ-8 & GAD-7 Parent Score_____
☐ PHQ-8 and GAD-7 Scores checked and referred as required

☐ Strengths & difficulties questionnaire (≥3 years) Score_____
☐ Treatment Adherence Questionnaire Parent Score_____

☐ Treatment Adherence Questionnaire Child (6 years and older) Score_____
☐ Acceptability Questionnaire Parent (final visit only)
☐ Acceptability Questionnaire Child (final visit only)

Additional Comments:
(Please date every entry)

PULMONARY EXACERBATION ADMISSION SHEET CLINICAL INFORMATION (COPY AS NECESSARY)
DATE OF ADMISSION:
☐ Consent checked
☐ Smart app data downloaded and checked (if appropriate) + ensuring continuing to record during admission
☐ Medicines checked and altered on enrolment sheet as required
☐ Enrolment sheet checked and new information added as required i.e. spirometry, positive culture growth, admissions
On admission:
HR_____ RR_____Temp_____O2 Sats_____
Height:_____cms Weight:_____kgs BMI_____
Symptoms reported:
☐ Increased cough ☐ Increased sputum volume ☐ Change in sputum colour
☐ Increased breathlessness/tightness ☐ Change in appetite ☐ Tiredness ☐ Fever
☐ Other_____
_____
IV antibiotics/Medicines started:
☐ Tobramycin ☐ Ceftazidime ☐ Amikacin ☐ Meropenam ☐ Tazocin ☐ Teicoplanin
☐ Ambisome ☐ Other (please specify)_____
_____
Cultures taken during admission:

Culture type	Date	Growth and Sensitivities

Spirometry during admission (normally twice a week)

Date	FEV_1 (Litres and % predicted)	FVC (Litres and % predicted)

Weight (normally recorded twice a week during admission)

Date	Weight

Additional Comments:
(Please date every entry)

Appendix 4 -GAD-7 questionnaire and PHQ-8 Questionnaire

Patient Study number: GAD-7 Anxiety

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer"*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Column totals: ___ + ___ + ___ + ___

= *Total Score* _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Centre number:
Patient Study number:

PHQ-8 Depression

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer"*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things.....	0	1	2	3
2. Feeling down, depressed, or hopeless.....	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much.....	0	1	2	3
4. Feeling tired or having little energy.....	0	1	2	3
5. Poor appetite or overeating.....	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down.....	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.....	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual.....	0	1	2	3

Appendix 5- An example of the Strengths and Difficulties Questionnaire: Parents of children aged 4-16

Strengths and Difficulties Questionnaire P 4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name ..... Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes-minor difficulties	Yes-definite difficulties	Yes-severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Appendix 6- An example of the CFQ-R: Children Ages 12 and 13

CFQ-R CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Children Ages 12 and 13 (Self-report Format)

These questions are for children like you who have cystic fibrosis. Your answers will help us understand what this disease is like and how your treatments help you. So, answering these questions will help you and others like you in the future.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Please fill in the answer or tick the box that matches your response to these questions.

A. What is your date of birth?

Date ☐☐/☐☐/☐☐☐☐

Day Month Year

B. Are you?

☐ Male ☐ Female

C. During the **past two weeks**, have you been on holiday or out of school for reasons **NOT** related to your health?

☐ Yes ☐ No

D. Which of the following best describes your racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]
- ☐ Prefer not to answer this question

E. What year are you in now at school?

(If summer, year you just finished)

- ☐ Year 6
- ☐ Year 7
- ☐ Year 8
- ☐ Year 9
- ☐ Year 10
- ☐ Year 11
- ☐ Not in school

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CFQ-R CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Children Ages 12 and 13 (Self-report Format)

Please tick the box matching your response.

In the past **two weeks**:	Very True	Mostly True	Somewhat True	Not at all True
1. You were able to walk as fast as others	☐	☐	☐	☐
2. You were able to climb stairs as fast as others	☐	☐	☐	☐
3. You were able to run, jump, and climb as you wanted	☐	☐	☐	☐
4. You were able to run as quickly and for as long as others	☐	☐	☐	☐
5. You were able to participate in sports that you enjoy (e.g., swimming, football, dancing or others)	☐	☐	☐	☐
6. You had difficulty carrying or lifting heavy things such as books, your school bag, or a rucksack	☐	☐	☐	☐

Please tick the box matching your response.

And during these past **two weeks**, indicate how often:	Always	Often	Sometimes	Never
7. You felt tired	☐	☐	☐	☐
8. You felt mad	☐	☐	☐	☐
9. You felt grouchy	☐	☐	☐	☐
10. You felt worried	☐	☐	☐	☐
11. You felt sad	☐	☐	☐	☐
12. You had trouble falling asleep	☐	☐	☐	☐
13. You had bad dreams or nightmares	☐	☐	☐	☐
14. You felt good about yourself	☐	☐	☐	☐
15. You had trouble eating	☐	☐	☐	☐

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CFQ-R CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Children Ages 12 and 13 (Self-report Format)

Please tick the box matching your response.

And during these past **two weeks**, indicate how often:

	Always	Often	Sometimes	Never
16. You had to stop fun activities to do your treatments	☐	☐	☐	☐
17. You were forced to eat	☐	☐	☐	☐

Please tick the box matching your response.

During the past **two weeks**:

	Very True	Mostly True	Somewhat True	Not at all True
18. You were able to do all of your treatments	☐	☐	☐	☐
19. You enjoyed eating	☐	☐	☐	☐
20. You got together with friends a lot	☐	☐	☐	☐
21. You stayed at home more than you wanted to	☐	☐	☐	☐
22. You felt comfortable sleeping away from home (at a friend or family member's house or elsewhere)	☐	☐	☐	☐
23. You felt left out	☐	☐	☐	☐
24. You often invited friends to your house	☐	☐	☐	☐
25. You were teased by other children	☐	☐	☐	☐
26. You felt comfortable discussing your illness with others (friends, teachers)	☐	☐	☐	☐
27. You thought you were too short	☐	☐	☐	☐
28. You thought you were too thin	☐	☐	☐	☐
29. You thought you were physically different from others your age	☐	☐	☐	☐
30. Doing your treatments bothered you	☐	☐	☐	☐

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CFQ-R CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Children Ages 12 and 13 (Self-report Format)

Please tick the box matching your response.

Let us know how often in the past **two weeks**:	Always	Often	Sometimes	Never
31. You coughed during the day	☐	☐	☐	☐
32. You woke up during the night because you were coughing	☐	☐	☐	☐
33. You had to cough up mucus	☐	☐	☐	☐
34. You had trouble breathing	☐	☐	☐	☐
35. Your stomach hurt	☐	☐	☐	☐

Please make sure all the questions have been answered.

THANK YOU FOR YOUR COOPERATION!

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Appendix 7 – Knowledge of disease management- CF and My CF treatments questionnaire

ID: _____

Date: _____

Knowledge of Disease Management-CF (KDM-CF)
Parent of Child Version (children ages 6-10)

For each question, please read all the answer choices carefully before choosing the **one** answer you think is **best**.

1) Pulmonary function tests (PFTs) are a fancy name for tests that:
   a. Show how your child's lungs are working
   b. Only need to be done once in a while
   c. Depend on your child's effort in blowing
   d. Answers a and c

2) Most of the food your child eats is absorbed in the:
   a. Stomach
   b. Intestines
   c. Liver

3) Undigested food will pass through your child's digestive system if he/she takes:
   a. Too many enzymes
   b. Too few enzymes
   c. The right amount of enzymes
   d. Enzymes just before he/she eats

4) Which of the following is a sign that your child's body is losing too much salt?
   a. Weakness
   b. Fever
   c. Muscle cramps
   d. Abdominal pain
   e. Answers b and c
   f. All of the above

5) People with CF should eat _____ snack(s) per day.
   a. 1
   b. 2
   c. 3
   d. More than 4

6) Airway clearance:
   a. Keeps your child's body from producing mucus
   b. Helps prevent lung infections
   c. Should be done only when your child is sick
   d. Can be combined with any inhaled treatment

7) Inhaled antibiotics are generally most effective if done:
   a. Before airway clearance
   b. After airway clearance
   c. In the morning

8) Stomach cramps and gas can be signs of hunger and:
   a. Overeating
   b. A lack of vitamins
   c. Poorly digested fat
   d. Do not need treatment

9) When your child exercises, he/she should:
   a. Eat more salt
   b. Pay attention to his/her breathing
   c. Sit down frequently and rest
   d. Drink more water
   e. Answers a and d

10) The CF bacteria in your child's lungs will always be killed with IV antibiotics.
   a. True
   b. False

11) If your child coughs up a small amount of blood on a Friday night:
   a. Your child should do his or her nebulized treatments and airway clearance
   b. Wait and see if it happens again
   c. You or your child should contact the CF doctor on call
   d. You or your child should call the CF clinic to make an appointment

12) Bronchodilators are used to:
   a. Open your child's airways
   b. Reduce mucus
   c. Prevent cough
   d. Clear up a stuffy nose

13) If your child's body is not digesting fat from the foods he/she eats, his/her stools may:
   a. Float
   b. Change color
   c. Sink
   d. Smell bad
   e. Not change
   f. Answers a, b, and d

14) For your child to make the most out of his/her clinic visit, he/she should:
    a. Write down his/her questions before going to the clinic visit
    b. Ask the CF Team to write down changes in your child's treatment plan
    c. Keep a journal or write down changes in your child's health
    d. Ask questions if you don't understand something
    e. Answers a and d
    f. All of the above

15) Which of the following prevents lung damage?
    a. Hypertonic saline
    b. Enzymes
    c. Airway clearance
    d. Exercise
    e. Eating more calories

16) How can your child decrease the number of lung infections he/she gets?
    a. Staying away from people who are sick
    b. Trying to cough less
    c. Keeping up with his/her airway clearance
    d. Answers a and c
    e. All of the above

17) The CF Team is always talking about your child's BMI (body mass index) percentile, which:
    a. Should be the same as your child's age
    b. Comes from measuring your child's weight
    c. Should be at or above the 50^{th} percentile for your child's age
    d. Should be between the 10^{th}-25^{th} percentile for your child's age
    e. Answers b and c

18) Stress, lots of homework, or problems with a friend can affect your child's:
    a. Eating
    b. Mood
    c. Health
    d. Answers b and c
    e. All of the above

19) Exercise can replace regular airway clearance.
    a. True
    b. False

20) Changes in your child's mucus, cough, or energy levels:
    a. Should be watched until the next clinic visit
    b. Can mean he/she is getting an infection
    c. Show that he/she needs to eat more

21) Foods that contain the most energy/calories are:
    a. Fats
    b. Carbohydrates
    c. Proteins

22) Inhaled medications like Pulmozyme® and hypertonic saline:
    a. Treat bacteria in the lungs
    b. Help remove mucus from the lungs
    c. Improve appetite
    d. Can replace airway clearance

23) Your child's CF Team will check his/her blood glucose:
    a. To see if he/she is eating enough
    b. Because people with CF have a higher chance of developing diabetes
    c. To see if your child is doing his/her treatments
    d. To see if your child needs more vitamins
    e. All of the above

24) Timing is everything; what is the right order to take the following treatments?
    a. Airway clearance, inhaled antibiotics, inhaled short-acting bronchodilators
    b. Inhaled short-acting bronchodilators, airway clearance, inhaled antibiotics
    c. Inhaled antibiotics, inhaled short-acting bronchodilators, airway clearance

25) When your child might have a pulmonary exacerbation:
    a. Wait a week and see if he/she gets better
    b. Your child should take extra vitamins
    c. You or your child should call the CF Team when he/she develops a fever
    d. You or your child should call the CF Team right away

26) Children with CF should eat:
    a. Up to twice as much food as children without CF
    b. The same amount of food as children without CF
    c. More fat than children without CF
    d. Less milk and cheese than children without CF
    e. Answers a and c

27) When your child feels stressed, it may help him/her to:
    a. Ignore it
    b. Act out (yelling, hitting)
    c. Do something fun
    d. Talk to someone
    e. Answers a and b
    f. Answers c and d

28) It is best for your child to take enzymes:
    a. As soon as he/she remembers them
    b. At the beginning of a meal or snack
    c. During a meal or snack
    d. Soon after eating

29) With CF, coughing:
    a. Should be controlled with cough medicines
    b. Can make others sick
    c. Makes it harder for your child to fight infections
    d. Helps your child spit mucus out

30) One way to add calories to scrambled eggs is to:
    a. Mix them with 2% milk instead of whole milk
    b. Add grated cheese
    c. Add salt and pepper
    d. Add vegetables

31) It is important for your child to be open and talkative with his/her CF Team because:
    a. Your child knows the most about his/her body
    b. The team is nosy about your child's life
    c. The team needs to get information from your child
    d. It helps the clinic visits go faster
    e. Answers a, c, and d
    f. All of the above

32) Enzymes should be kept in a cool, dark place.
    a. True
    b. False

33) To avoid getting new CF bacteria in his/her lungs, your child should:
    a. Not hang out with others who have CF
    b. Cough into tissues and throw them away
    c. Stay home as much as possible
    d. Answers a and b
    e. All of the above

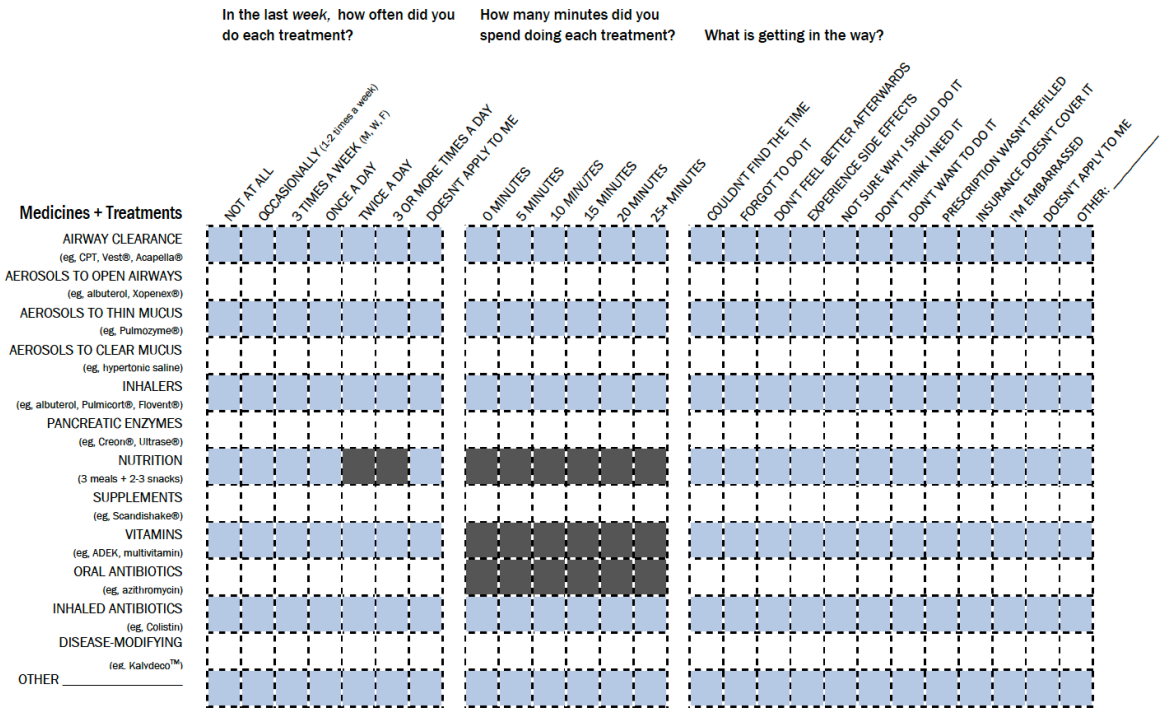
34) Children with CF need to eat more because:
    a. Some energy is lost when food is not properly digested
    b. Their metabolism is faster
    c. They have to fight off infections
    d. Their appetites are naturally bigger
    e. Answers a, b, and c

35) People with CF take vitamins A, D, E, and K because these vitamins:
    a. Can be poorly absorbed from food
    b. Need extra water to be absorbed
    c. Are not found in foods people normally eat
    d. Answers a and b

MY CF TREATMENTS

Treatment Adherence Questionnaire-CF (Quittner et al., 2008)

Most teens find it hard to do all of their treatments each day for good CF care. Please tell us which treatments you have done over the ***last week***. You're not alone if you've been missing some medications and treatments. It is hard to fit it all in everyday. Please answer these questions honestly. Please check the box that is closest to your answer.



Appendix 8 – Acceptability questionnaires for parents, participants, and staff

PARENT SURVEY

How did you find using the monitoring devices?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A child did it
☐	☐	☐	☐	☐	☐

How did you find using the smartphone?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A child did it
☐	☐	☐	☐	☐	☐

How did you find using the Smart app?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A child did it
☐	☐	☐	☐	☐	☐

How often did you have problems with measuring results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A child did it
☐	☐	☐	☐	☐	☐

How often did you have problems with uploading results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A child did it
☐	☐	☐	☐	☐	☐

How often did you have to contact someone for help with measuring results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A child did it
☐	☐	☐	☐	☐	☐

How often did you have to contact someone for help with uploading results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A child did it
☐	☐	☐	☐	☐	☐

If you had to contact someone for help measuring or uploading results, how did you find this process?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A child did it
☐	☐	☐	☐	☐	☐

To what extent did daily home-monitoring interfere with your usual activities?

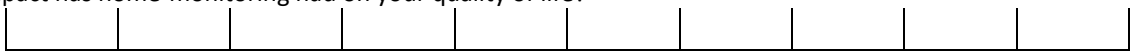
Not at all	Slightly	Somewhat	Moderately	Extremely
☐	☐	☐	☐	☐

Please score the tests on a scale of 1 to 8 (1 = most acceptable, 8 = unacceptable) in terms of acceptability to perform (Tests may have the same score). Leave ones you did not do blank?

☐Weight
☐Sputum collection
☐Urine Collection
☐Nasal Secretion Collection
☐Throat Swab collection
☐Dried blood spot collection

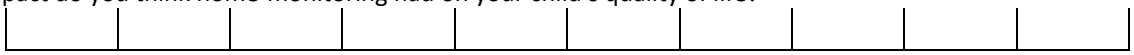
☐Oximetry (heart rate & oxygen saturation)
☐Wellness Score
☐Cough score
☐Spirometry (lung function)
☐Activity/Sleep and Temperature Monitor
☐Free text option for symptoms or events

What impact has home-monitoring had on your quality of life?



0 1 2 3 4 5 6 7 8 9 10
Worse No impact Better

What impact do you think home-monitoring had on your child's quality of life?



0 1 2 3 4 5 6 7 8 9 10
Worse No impact Better

Ideally, how frequently would you and your child like to do home-monitoring?

Daily	Every other day	Weekly	Monthly	Other
☐	☐	☐	☐	☐

If other, please specify

How long on average did it take you to complete the monitoring?

_____

_____

Over the last 6 months, on a normal week, who inputted most of the daily data, yourself or your child?

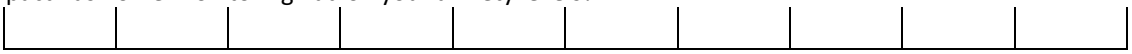
_____

_____

How helpful did you find being able to monitor your child's breathing, activity and weight at home?

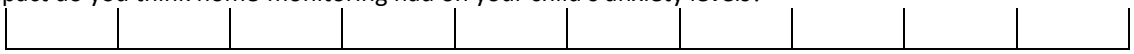
Very helpful	Helpful	Neutral	Unhelpful	Completely unhelpful
☐	☐	☐	☐	☐

What impact has home-monitoring had on your anxiety levels?



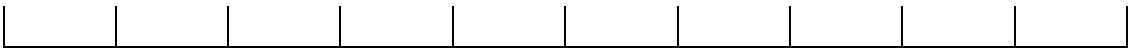
0 1 2 3 4 5 6 7 8 9 10
More Anxiety No impact Less Anxiety

What impact do you think home-monitoring had on your child's anxiety levels?



0 1 2 3 4 5 6 7 8 9 10
More Anxiety No impact Less Anxiety

What impact has home-monitoring had on your ability to cope with managing your child's health?



0 1 2 3 4 5 6 7 8 9 10
Worse No impact Better

Given the choice, would you prefer to use home-monitoring and attend less frequent routine clinics?

Definitely	Probably	Undecided	Possibly	Definitely not
☐	☐	☐	☐	☐

Would you prefer to be able to see the results of the home monitoring on your app immediately rather than just at clinic?

Definitely	Probably	Undecided	Possibly	Definitely not
☐	☐	☐	☐	☐

Please let us know if you had any specific comments about your experience of doing home-monitoring.

Is there anything extra you would like to see incorporated into the home monitoring app?_____
_____

PATIENT SURVEY-AGES 12-17

How did you find using the monitoring devices?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A parent did it
☐	☐	☐	☐	☐	☐

How did you find using the smartphone?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A parent did it
☐	☐	☐	☐	☐	☐

How did you find using the Smart app?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A parent did it
☐	☐	☐	☐	☐	☐

How often did you have problems with measuring results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A parent did it
☐	☐	☐	☐	☐	☐

How often did you have problems with uploading results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A parent did it
☐	☐	☐	☐	☐	☐

How often did you have to contact someone for help with measuring results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A parent did it
☐	☐	☐	☐	☐	☐

How often did you have to contact someone for help with uploading results?

Never	Daily	Weekly	Monthly	Greater than monthly	N/A parent did it
☐	☐	☐	☐	☐	☐

If you had to contact someone for help measuring or uploading results, how did you find this process?

Very easy	Easy	Neutral	Difficult	Very Difficult	N/A parent did it
☐	☐	☐	☐	☐	☐

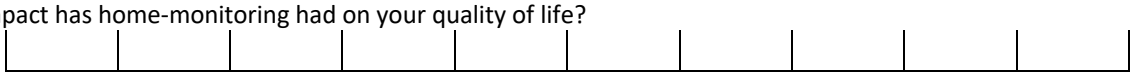
To what extent did daily home-monitoring interfere with your usual activities?

Not at all	Slightly	Somewhat	Moderately	Extremely
☐	☐	☐	☐	☐

Please score the tests on a scale of 1 to 8 (1 = most acceptable, 8 = unacceptable) in terms of acceptability to perform (Tests may have the same score)?

☐Weight
☐Sputum collection
☐Urine Collection
☐Nasal Secretion Collection
☐Throat Swab collection
☐Dried blood spot collection
☐Oximetry (heart rate & oxygen saturation)
☐Wellness Score
☐Cough score
☐Spirometry (lung function)
☐Activity/Sleep and Temperature Monitor
☐Free text option for symptoms or events

What impact has home-monitoring had on your quality of life?



0 1 2 3 4 5 6 7 8 9 10
Worse No impact Better

Ideally, how frequently would you like to do home-monitoring?

Daily	Every other day	Weekly	Monthly	Other
☐	☐	☐	☐	☐

If other, please specify

How helpful did you find being able to monitor your breathing, activity and weight at home?

Very helpful	Helpful	Neutral	Unhelpful	Completely unhelpful
☐	☐	☐	☐	☐

What impact has home-monitoring had on your worry levels?

0 1 2 3 4 5 6 7 8 9 10

More Anxiety No impact Less Anxiety

What impact has home-monitoring had on your ability to cope with managing your health?

0 1 2 3 4 5 6 7 8 9 10

Worse No impact Better

Given the choice, would you prefer to use home-monitoring and attend less frequent routine clinics?

Definitely ☐	Probably ☐	Undecided ☐	Possibly ☐	Definitely not ☐

Would you prefer to be able to see the results of the home monitoring on your app immediately rather than just at clinic?

Definitely ☐	Probably ☐	Undecided ☐	Possibly ☐	Definitely not ☐

Roughly how long would it take you to complete the monitoring in a day?

_____

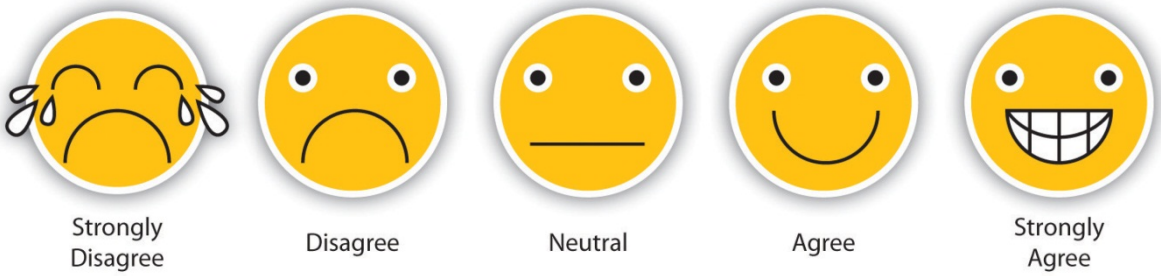
_____

Please let us know if you had any specific comments about your experience of doing home-monitoring.

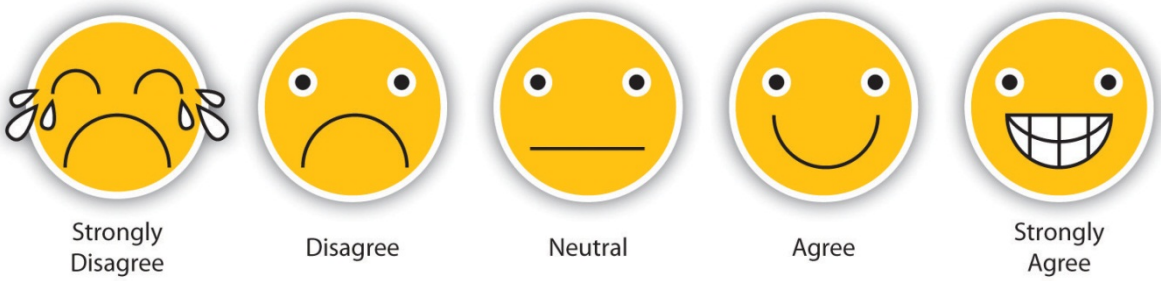
Is there anything extra you would like to see incorporated into the home monitoring app?_____

Patient Acceptability Questionnaire Ages 6-12

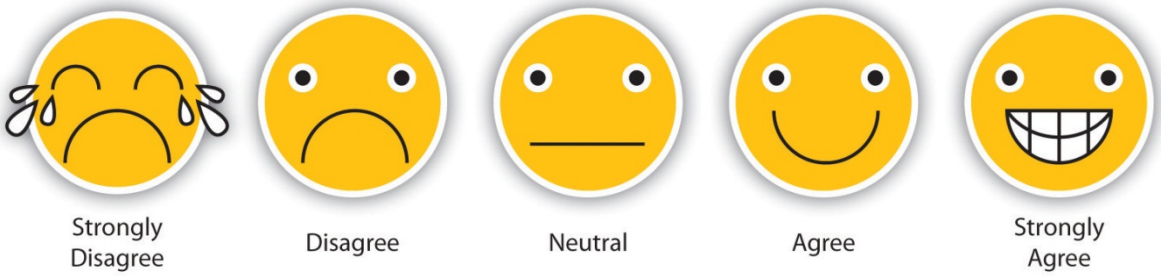
Did you like having your breathing checked every day?



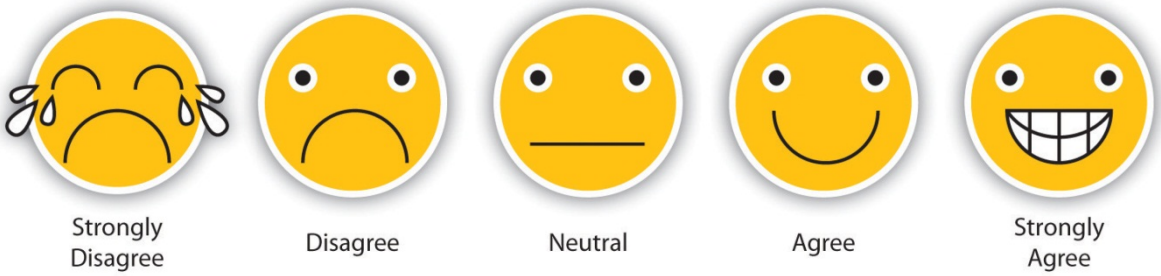
Did you like the look of the app on the phone?



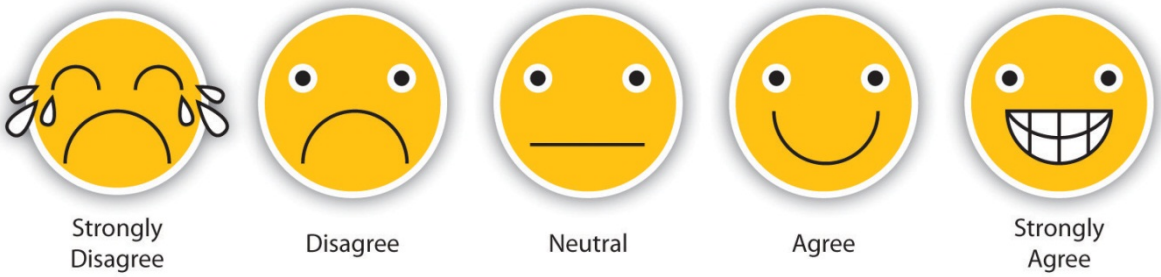
Did you mind collecting extra wee and mucus samples?



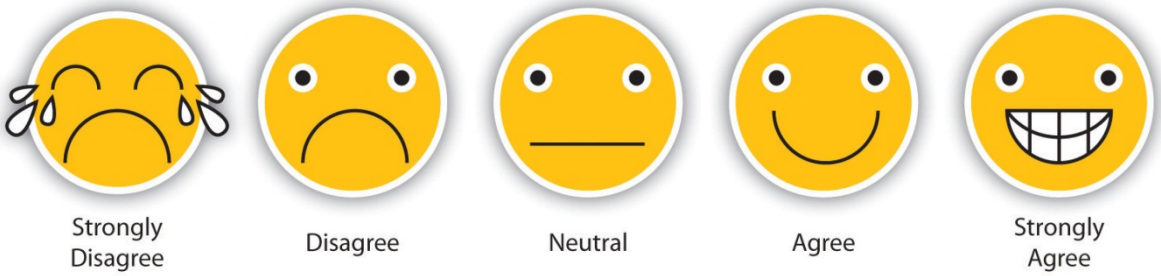
Would you prefer to do these things at home or come to hospital to do them?



Did doing the checks at home make you sad?



Did doing the checks at home make you happy?



CLIMB-CF Staff Views Questionnaire

Are you a:

Doctor □ Nurse □ Physiotherapist □ Pharmacist □ Psychologist □ Dietician □

At which site are you based:_____

Have you had to use the technology?

Yes □ No□

If yes did you find it easy to use? Yes □ No□

Do you feel the technology has increased the amount of contact between the family and the CF team?

Yes □ No□

Any comments_____

Can you see the benefit for patients?

Yes □ No□

Can you see the benefit for staff?

Yes □ No□

Any other comments:_____

_____

_____

_____

_____

Appendix 9 – Monthly phone call proforma

Monthly Phone call – one/two/three/four/five/Six (circle)

Participant ID
Person Calling
Time and Date
Talking to

Any changes of complications since we last spoke?
Yes/No
Comments:

Equipment: Any issues with the following:
Mobile phone/App
Yes/No
Comments:

Lung Monitor:
Yes/No
Comments:

Oxygen Monitor:
Yes/No
Comments:

Activity Monitor:
Yes/No
Comments:

Weighing Scales:
Yes/No
Comments:

Are you collecting samples?
Yes/No
Any Comments or issues:

Any other questions?

Plan of action from staff:

Appendix 10 – Permissions table

Type of work:	Name of work	Source of work	Copyright holder	permission requested on	I have permission yes /no	Permission note
Figure	Figure 1-1 The 6 classes of CFTR mutation. Reproduced from De Boeck and Amaral	De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. The Lancet Respiratory medicine. 2016;4(8):662-74.	Elsevier	20/12/21	yes	Written permission
Figure	Figure 1-2 between different CFTR classes.	Shteinberg M, Haq IJ, Polineni D, Davies JC. Cystic fibrosis. Lancet. 2021;397(10290):2195-211.	Elsevier	20/12/21	yes	Written permission
Figure	Figure 1-3 The proportion of patients with specific lung infections in 2019 registered on the UK CF registry with corresponding ages of infection.	UK Cystic Fibrosis Registry Annual Data Report 2019	CF Trust registry@cysticfibrosis.org.uk	20/12/21	Yes	Written permission
figure	Figure 1-4 Available modulator therapy with the classes of CFTR variants that respond to each treatment	Edmondson C, Course CW, Doull I. Cystic fibrosis transmembrane conductance regulator modulators for cystic fibrosis: a new dawn? Archives of disease in childhood. 2021.	BMJ Publishing group	20/12/21	Yes	Written permission
Table	The UK CF Trust Registry Annual data report 2019 showing the number of patients per age group who required at least 1 course of IV antibiotics in the previous year as reported to the registry	UK Cystic Fibrosis Registry Annual Data Report 2019	CF Trust registry@cysticfibrosis.org.uk	20/12/21	Yes	Written permission

Table	Table *1-2* Fuchs sign and symptoms criteria. A collection of 4 or more of the listed signs and symptoms corresponds to a diagnosis of a pulmonary exacerbation.	VanDevanter DR, Hamblett NM, Simon N, McIntosh J, Konstan MW. Evaluating assumptions of definition-based pulmonary exacerbation endpoints in cystic fibrosis clinical trials. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021;20(1):39-45.	Elsevier	20/12/21	yes	Written permission
Table	Table *1-4* Comparison of signs and symptoms associated with a pulmonary exacerbation in 3 paediatric studies.	Ferkol T, Rosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. The Journal of pediatrics. 2006;148.	Elsevier	20/12/21	yes	Written permission
Figure	Figure *1-5* Some of the body systems affected in CF and the consequences.	Paranjape SM, Mogayzel PJ, Jr. Cystic fibrosis. Pediatr Rev. 2014;35(5):194-205.	American academy of pediatrics	20/12/21	Yes	Written Permission
Figure	Figure *1-6* Digital health tools	IQVIA Institute Report 2017	IQVIA	20/12/21	Yes	IQVIA grants you permission to copy content on the website purely for your non-commercial use.
Figure	Figure *1-7* Schematic illustrating the key differences in asynchronous and synchronous remote monitoring.	Davies B, Kenia P, Nagakumar P, Gupta A. Paediatric and adolescent asthma: A narrative review of telemedicine and emerging technologies for the post-COVID-19 era. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2021.	The authors, Clinical and experimental Allergy published by John Wiley and Sons Ltd.	20/12/21	Yes	Written Permission

Figure	Figure *2-2* Agile development cycle diagram	https://project-management.com/10-key-principles-of-agile-software-development/	Project Management	20/12/21		Open-Source webpage
Table	Table *3-1* Percentages of requested measures collected over the six-month study period for the cohort as a whole and by three different age groups	Edmondson C, Westrupp N, Seddon P, Olden C, Wallis C, Dawson C, et al. The feasibility of home monitoring of young people with cystic fibrosis: Results from CLIMB-CF. Journal of	Elsevier	20/12/21	Yes	Written permission

		cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021.				
Table	Table *3-3* Percentage completed of each measure over the 6-month study period	Edmondson C, Westrupp N, Seddon P, Olden C, Wallis C, Dawson C, et al. The feasibility of home monitoring of young people with cystic fibrosis: Results from CLIMB-CF. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021.	Elsevier	20/12/21	Yes	Written permission
Figure	Figure *3-3* The percentage of completed data per month of the study for the whole cohort and the three different age groups	Edmondson C, Westrupp N, Seddon P, Olden C, Wallis C, Dawson C, et al. The feasibility of home monitoring of young people with cystic fibrosis: Results from CLIMB-CF. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021.	Elsevier	20/12/21	Yes	Written permission
Table	Table *3-10* Combined results from questions from the acceptability questionnaire and percentages of completed measures from parents and participants ≥ 12 years	Edmondson C, Westrupp N, Seddon P, Olden C, Wallis C, Dawson C, et al. The feasibility of home monitoring of young people with cystic fibrosis: Results from CLIMB-CF. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021.	Elsevier	20/12/21	Yes	Written permission
Table	Table *8-1* Considerations for future studies. Learning points from CLIMB-CF and suggestions.	Edmondson C, Westrupp N, Seddon P, Olden C, Wallis C, Dawson C, et al. The feasibility of home monitoring of young people with cystic fibrosis: Results from CLIMB-CF. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021.	Elsevier	20/12/21	Yes	Written permission