Using remote telemonitoring to detect early decline in lung function and streamline clinics in adults with cystic fibrosis

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ABSTRACT

Background:

As the adult cystic fibrosis (CF) population increases, low-burden and innovative ways to manage and continually monitor people are crucial. This thesis aims to explore whether breathing parameters automatically recorded by the I-neb® correlate with acute lung function changes allowing earlier detection of pulmonary exacerbations, and to develop a set of clinic attendance criteria using pre-clinic data to optimise clinic use.

Methods:

This thesis encompasses two main studies. First, the development (using a retrospective dataset, N=61, 797 FEV1 readings) and internal validation (prospective dataset, N=34, 327 FEV1 readings) of a predictive model for acute FEV1 decline using I-neb® breathing parameter data and hospital FEV1 readings (the Lung Health study). Second, the development of a set of clinic attendance criteria using multi-stage consensus methods.

Results:

The most promising I-neb® breathing parameter identified was minimum Treatment Time (TT). Values exceeding the 75th centile of the retrospective dataset (adjusted for baseline FEV1 and I-neb® mode) had a sensitivity of 0.31 (95% CI 0.20-0.49) and false positive rate of 0.32 (95% CI 0.17-0.43) for acute decline in FEV1 of ≥5% from baseline within a ±7-day window in the prospective dataset (with random effects model to account for clustered data). The consensus combined results from an online survey (CF clinician response rate 15/36) and face-to-face meeting (involving 8 CF experts) using the nominal group technique developed a set of criteria which included 14 categories (including acute change in FEV1/BMI) deemed important in decision-making.

Conclusion:

The novel use of I-neb® breathing parameters to function as a predictive model to detect acute changes in FEV1 may be a potential passive sensor for continual lung health monitoring but there are limitations and further testing is required. The set of clinic attendance criteria requires further evaluation but may provide a stepping stone to streamlining clinics in the future.

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Declaration

I, Rachael Emma Thompson (nee Curley), confirm that the Thesis is my own work. I am aware of the University's Guidance on the Use of Unfair Means (www.sheffield.ac.uk/ssid/unfair-means). This work has not been previously been presented for an award at this, or any other, university.

Publications/Conference presentations arising from the thesis:

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CHAPTER 1: INTRODUCTION

This chapter summarises the relevant literature to provide a background on cystic fibrosis, including disease management, service provision, and future challenges.

1.1 What is cystic fibrosis?

Cystic fibrosis (CF) is one of the most common life-threatening genetic diseases.[1] It is caused by a mutation in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene on the long arm of chromosome 7.[2] This leads to dysfunction of the apical membrane CFTR protein, which regulates sodium and chloride transport in secretory epithelial cells throughout the body. The abnormal movement of ion concentrations in these cells causes the body's secretions to become viscous.[3] The clinical consequences are multi-system, characterised by progressive inflammation, infection, and structural damage of hollow organs; in particular the lungs and gastrointestinal tract are affected.[3] This process leads to the prominent respiratory component of the disease; bronchiectasis, which is responsible for the majority of the morbidity and premature mortality as a result of recurrent chest infections and progressive respiratory failure.[2] Other complications occur due to problems with gut motility and malabsorption, pancreatic dysfunction leading to diabetes, liver disease which can advance to cirrhosis, and osteoporosis. Almost all males with CF are infertile due to atresia or congenital bilateral absence of the vas deferens.[3]

CF is an autosomal recessive condition with two abnormal CFTR genes required to cause the disease.[1] In Europe, the asymptomatic carrier frequency is 1 in 25 and the incidence of having CF is 1 in 2500 live births.[2] At least 80,000 people with CF (PwCF) are recorded on registries in Europe, North America, and Australia, with numbers elsewhere in the world being less complete.[4] In the UK 10,908 people are currently diagnosed with CF.[5]

A diagnosis is made based on a combination of characteristic clinical symptoms, genetic testing, and abnormal sweat chloride tests.[2] This is often in early childhood but can be delayed even into late adulthood with some cases being identified through infertility screening. Over 2000 different mutations in the CFTR gene exist which are thought to lead to varying degrees of severity of the disease.[1, 2] Different CF genotypes can be grouped into six functional classes which are expected to have similar clinical phenotypes and mortality.[1, 6] The most common gene mutation found in approximately 70% of PwCF is Phe508del.[7] Those who are homozygous for class I-III mutations which includes Phe508del generally have a more severe clinical phenotype than those who are heterozygous with at least one mutation in class IV-VI.[1, 6, 7] This is thought to be due to the different effects that the CF genotype

has on the CFTR protein production and function.[6] There can however still be phenotypical variations amongst people with the same CF genotype due to the influence of other modifier genes and environmental and immunological factors.[8, 9]

1.2 The importance of detecting changes in lung function in CF

At birth PwCF predominately have structurally normal lungs. Over time abnormalities develop due to repeated inflammation and infections leading to obstructive airways disease.[10] In clinical practice the forced expiratory volume in one second (FEV1) measured with a spirometer, in litres per second, is used to quantify the severity of obstruction and as a disease monitoring tool.[3] Annually it is expected that PwCF should lose no more than 2 percentage points of their predicted %FEV1.[10] Though predicted %FEV1 already adjusts for age, the accelerated rate of FEV1 decline among PwCF in comparison to the general population means that %FEV1 decline over time is an important marker of disease progression as a person with CF ages.[11, 12] Retrospective studies in CF have found that several factors are associated with FEV1 and are thought to influence long-term decline.[13-16] These include CFTR genotype, age at diagnosis, gender, body mass index (BMI), baseline variability in FEV1, chronic infection with *Pseudomonas aeruginosa* or *Burkholderia cepacia*, pancreatic insufficiency, CF diabetes (CFD), and CF-related liver cirrhosis or portal hypertension.[13-16] The frequency of pulmonary exacerbations and intravenous (IV) antibiotic courses per year have also been found to strongly correlate with FEV1 decline.[14] It has been suggested that those with three or more exacerbations per year could lose more than 157ml FEV1, and that for every course of IV antibiotics, more than 30ml FEV1 is lost per year.[14] As many of these factors are potentially preventable and treatable it is crucial that early identification and aggressive treatment is initiated to delay deterioration in lung function.

Pulmonary exacerbations are one of the most important clinical events in CF. They are usually characterised clinically by an acute episodic increase in pulmonary symptoms and changes in spirometric parameters.[17] Their mechanism of onset is thought to be due to an imbalance in the complex relationship between host defences and airway microbiology. This leads to infection and inflammation which impacts on sputum production and airflow obstruction. Events may be initiated by viral infections, acquisition of a new organism, or more commonly a change in bacterial density of colonised flora. In CF there is currently no definitive consensus to define a pulmonary exacerbation however various definitions have been used in research studies.[17-20] These commonly highlight that a significant indicator of a pulmonary exacerbation is a short-term fall in FEV1.[18] Fuch's criteria suggests an acute decline in FEV1 of 10% or more from baseline is a determining feature in the diagnosis of a pulmonary

exacerbation.[21] It has also been shown that those with an FEV1 decline of 10% are more likely to receive therapeutic intervention.[22]

Day-to-day physiological variability in FEV1 measurements have been demonstrated in obstructive lung diseases including CF.[23] FEV1 tests are sensitive not only to comorbid factors but also time of day, mood, fatigue, and medical instruction. It is therefore important clinically to consider an FEV1 result in context and observe the absolute change rather than relative change over time.[24, 25]

1.3 Management strategies in CF

The clinical management of CF involves a multidisciplinary team (MDT) approach.[4] The main aims of treatment are to prevent complications and slow disease progression by reversing acute deteriorations in lung function using rescue IV antibiotic therapy. This is achieved by maintaining airway clearance, use of antibiotics to treat infections and reduce inflammation, and ensuring optimal nutritional status.[26] To stay well and enjoy prolonged survival PwCF are therefore required to take a multitude of oral and inhaled treatments, undertake daily chest physiotherapy and exercise, and maximise intake of a high-fat high-calorie diet.[3, 26]

In the last 10 years, genetic modulators have been developed that can target specific genotypes in order to facilitate defective CFTR processing or function.[1] Ivacaftor a CFTR potentiator was first developed for those with class III, class IV, and some residual function mutations. This was followed by the introduction of CFTR correctors; lumacaftor and tezacaftor, resulting in lumacaftor/ivacaftor and tezacaftor/ivacaftor combinations for those homozygous to Phe508del More recently tezacaftor/ivacaftor combined with elexacaftor (Kaftrio) another form of CFTR corrector is effective for individuals with at least one Phe508del as well as some other specific single mutations.[1, 27, 28] These drugs have shown increasing success in improving quality of life, FEV1, and BMI, along with reducing pulmonary exacerbations.[27, 28] Since August 2020 the UK now have CFTR modulators available for approximately 90% of the CF population.

Over the years, advances in the management of CF have transformed survival for PwCF. These treatments are effective if taken regularly[29] however physical, psychological, and social constraints can undermine engagement.[1] The median age of death for PwCF is 38 years with most people dying of respiratory failure[5], however those who can develop successful habits of adherence have the potential to live much longer.[30]

1.3.1 Nebulised treatments in CF

Nebuliser treatments are an important part of CF care. A nebuliser is a device used to administer inhaled treatments to the lungs. There are different nebuliser systems available with newer devices delivering drugs more quickly and efficiently.[31] In CF inhaled antibiotics and mucolytics (to loosen sputum) are potent treatments that reduce pulmonary exacerbations and by preventing lung function loss can be expected to increase survival.[32, 33] A UK CF study showed self-reported adherence to these inhaled treatments to be 80% compared to an objective adherence of only 36%.[34] Adherence is therefore often invisible and overestimated by PwCF and the clinical team. Despite the availability of potent preventative therapy for PwCF suboptimal adherence means that patients continue to have frequent pulmonary exacerbations resulting in an avoidable need for rescue antibiotic therapy.[30] Rescue intravenous antibiotics are associated with renal damage[35], drug allergy and toxicity, difficulties with venous access, and multi-resistant infections.[36]

1.3.2 What is the I-neb®?

The I-neb® (Adaptive Aerosol Delivery (AAD) system) is a handheld battery-powered 'intelligent' nebuliser. It is commonly used to administer inhaled treatments in CF. It automatically collects objective adherence data and breathing parameters (inhalation flow and time) which can be analysed retrospectively.[37] On receipt of the device PwCF are consented to allow this data to be collected and reviewed by the MDT as part of routine clinical practice. Anecdotal evidence suggests that during a pulmonary exacerbation, PwCF breathe differently and will need time to cough during treatment which will affect the data captured by the I-neb®. It is expected that the inhalation flow and time of each breathing effort will reduce, and rest time will increase. These parameters can be obtained from the I-neb® for every time the device is used with data being stored. The I-neb® can be Bluetooth enabled to the Bi-neb allowing automatic data transfer (Figure 1.1). This enablement does not interfere with the existing function of the I-neb®. The Bi-neb is currently not commercially available but is suitable for testing in a clinical trial having been used in other unpublished research studies.

Figure 1.1: Images of the Bi-neb (I-neb® with Bluetooth bridge attached to the bottom and side of the device).

1.4 Current service provision for CF in the UK

There are now many effective treatments for CF which has led to increased life expectancy. The improved survival has resulted in an increasing prevalence of PwCF with an estimated increase of 200 individuals transferring to adult services each year in the UK.[5, 38] More than 60% of PwCF in the UK are over the age of 16 and there are more than 1000 over the age of 40 years.[5] With the recent development of mutation-specific therapies survival can be expected to rise further in the future.[36] It is predicted that a child born today can live until at least 53.3 years of age.[5] Increasing patient numbers mean that adult centres are struggling to cope with demand.[36] If the efficacy of CFTR modulators are translated into the real world, we may see fewer exacerbation episodes and potentially a reduced need for hospitalisation. Improving lung function may mean that PwCF are healthier and may therefore require less intense monitoring. Both of these could help reduce the demand, but it is uncertain how long these effects will last given that the lung function of people on ivacaftor returned to baseline after around five years.[39] It is also important to consider that as PwCF live longer the demands for healthcare may subsequently increase due to a greater incidence of extra-pulmonary complications related to ageing such as cardiovascular disease, metabolic syndrome, malignancy, and even the emergence of more drug resistant infections.[40] Therefore strategies that can support self-management, adherence, and enable clinics to more effectively deal with the increased workload are still urgently required.[36]

PwCF managed in specialist centres have better outcomes than patients managed elsewhere.[41] In the UK there are 26 specialist Adult CF centres that provide care for patients from a wide catchment area.[5] The CF Standards of Care European Consensus recommends PwCF should be seen in clinic every 1-3 months preferably monthly. If they have more severe disease it is expected that they will be seen more often, and if they have a mild phenotype or have atypical CF they may be seen less often every 3-6 months.[42] Some PwCF will travel long distances to clinic and this can cause considerable disruption to school and employment.

The UK CF Standards of Care and more recently the National Institute for Health and Care Excellence (NICE) CF Guidelines stipulate that PwCF should have their weight, spirometry, and oxygen saturations measured, and that microbiology culture (sputum or cough swab) should be obtained at each clinic visit. These measures along with available objective adherence data provide important diagnostic and monitoring information for PwCF and the MDT.[26, 42] Specialist centres should prevent cross-infection by segregating face-to-face PwCF in clinic, including coordinating the use of communal areas such as diagnostic, treatment, and pharmacy facilities.[26]

Staff time is one of the most expensive resources in the National Health Service (NHS) and CF units will invest significant amounts of that time in out-patient clinics. CF clinics are complex because patients are usually seen by all members of the MDT as mandated by the UK commissioning process.[42] Typically, all patients will be allocated an identical slot in clinic that takes no account of the patient's current status since that status is not available prior to clinic arrival.

Since the COVID-19 pandemic in early 2020, there has been an impact on how CF care is now being delivered. In the UK this led to the cancellation of routine clinics and monitoring with the rapid uptake of remote self-monitoring, increased home visits, and virtual clinics. Alongside this PwCF were told to shield due to being extremely vulnerable.[43] The consequences of the lockdown measures for many shielders included a decline in mental health due to isolation, fear, anxiety, depression, lack of routine, and the stigma of being labelled as vulnerable.[44] Since PwCF were inevitably monitored less closely during shielding, this reduction in contact with the CF team may have led to a sense of freedom from the disruption of face-to-face clinic reviews and an escape from the reminder of having a chronic condition, which may potentially result in an avoidance of regular engagement over the long-term. With less intense monitoring for some PwCF a decline in lung function may have gone unnoticed for some time resulting in an inability to regain lost lung function.[45] Over time it is therefore likely this temporary disruption will have a long term negative impact on PwCFs' wellbeing and outcomes.[43] Going forward some of the new ways of working may influence future care and guidance but it is important to consider that when the virus threat level declines or disappears these may not be satisfactory unless a structured approach is taken to ensure they provide efficient and effective care.[46]

1.4.1 Clinic variation & queues

When we make a visit to the hairdressers we don't expect to wait. We ring ahead for an appointment and the hairdresser allocates a slot length depending on whether we need a quick trim for a 6-year-old boy or a wash, colour, and style for the bride in preparation for a wedding. In healthcare, we have not tended to allocate different slots to different patients. The reasons for this are typically conceptualised as related to a lack of information and may include a belief that patients do not know what they need, and clinicians cannot anticipate that need as they may lack information about a patient's status when the appointment is planned. In any system, it is important to balance demand and capacity in order to maintain flow.[47] In healthcare systems, this flow can become disrupted when demand exceeds capacity and due to variation, leading to queues.[47] In the clinic setting if patients are seen in set appointment slots there may be adequate time for some, but for others, there will be insufficient time to deal

with complex issues or a requirement for an unplanned process (such as an unforeseen investigation needed) causing a delay in the system. At the same time did not attends (DNA, i.e. patients who fail to turn up) may result in gaps and wasted resources. One method to address this problem is to process map, measure demand and variation, and then using Erlang's rule of thumb plan a service to 80% of the maximum time required (Variation x 0.8 + lowest value)[48] Although matching capacity and demand may have advantages it does not address any variation mismatch, hence is not an effective use of resources, and patient's needs may not be fully met. The more predictable the demand and variation the better the system can be planned and consequently flow.[48]

There are different types of variation in a system.[47] Some of the artificial variation can be planned for such as staff leave and availability of clinical equipment. Natural variation however is an inevitable characteristic of any healthcare system.[47] This includes differences in the co-morbidities and clinical needs of patients presenting, the socio-economic or demographic differences between patients, and the times of the day that emergency patients require review.[47] A Pareto analysis can be used to subgroup patients based on their individual characteristics (i.e. red stream: unstable complex patients, green stream: stable less complex patients) allowing streamlining in clinics.[48] As outlined above using the analogy of the hairdressers if a client requires a 'colour and cut' this will have been determined in advance and a 90-minute slot given, however, if only a 'short back and sides' is required the slot could be reduced to 15 minutes. In healthcare, if pre-clinic data are available a similar approach can be taken, with this being particularly useful in CF since patients are seen regularly and become well known to their MDT.

1.4.2 Remote monitoring in CF

Remote monitoring is a form of telemedicine. The term telemedicine was first described in the 1970's meaning "healing at a distance".[49] Telemedicine is the use of electronic communication to exchange medical information from one site to another with the aim of improving a patient's clinical health status.[50] Numerous terminology and definitions can be used to describe this form of intervention.[50] The key goals however include: 1) To provide clinical support, 2) To overcome geographic barriers, 3) To involve the use of various types of information communication technology (ICT), and 4) To improve health outcomes.[49] This technology emerged over 40 years ago and has been advancing since with the growing number of applications and services using two-way video, email, smartphones, wireless tools, and other forms of telecommunications technology.[50] Its uses are vast with services broadly including[50]:

- *Remote monitoring* - devices collecting and sending clinical and physiological information to be used by health professionals to monitor chronic conditions, and allow patient self-management
- *Real-time interactive services* – consultation between patients and specialists, and amongst patients; similar to a face-to-face visit
- *Store-and-forward* – involves collected medical data (e.g. imaging) to be transmitted for review at a convenient time offline by other doctors or medical specialists

In CF telemedicine may encompass PwCF monitoring parameters such as home lung function and symptoms to self-manage and support adherence or communicate with the CF centre. It may also involve videoconferencing to review PwCF and prevent them from having to attend centres or allow PwCF to get peer support via a forum. A systematic review exploring telemedicine in CF suggested that PwCF were able to use the technology but struggled with high levels of non-compliance ranging from 43-63%.[51] One highlighted barrier is the burden of performing frequent measures on top of an already high volume of daily treatment. This is not surprising since adherence to prescribed therapies is often poor amongst PwCF.[30, 34, 52] Despite this there are still felt to be some potential benefits for telemedicine in CF, with several studies using home spirometry to detect early pulmonary exacerbation.[53-55] It has also been suggested that PwCF are more likely to perform home spirometry when symptomatic.[56] A further recent review of telemedicine in CF for home monitoring, adherence, and self-management again highlighted that technology must be acceptable, sustainable, not add significant burden, and be of benefit to PwCF and the MDT.[57]

1.4.3 Complexity theory: introducing changes in clinical practice

Human lives are complex, and systems made up of humans even more so. To successfully introduce changes within a healthcare system it is therefore important to first consider complexity theory. Healthcare has become increasingly more complex in the 21st century due to a combination of shared decision-making, more evidenced-based treatments, and the interplay of genetic predisposition, environmental factors, and lifestyle choices. The outcomes resulting from treatments used may therefore be imprecise, equivocal, or conflicting. This makes healthcare systems non-linear with components being interconnected and the outcome of interventions that aim to influence system performance potentially difficult to predict. An important determinant of this unpredictability is the impact of human factors where actions can be driven by instincts, constructs, and mental models that are not necessarily logical to an outside observer.[58-61]

Improvement science is an emerging field that at its best acknowledges the unpredictability of complex systems and attempts to develop tools that can allow engagement with a context that is often difficult to fully characterise. A powerful method to engage with complexity is the use of Plan-Do-Study-Act (PDSA) cycles which acknowledge that a given intervention may well not achieve its intended objective but by recognising the possibility of "failure" and reframing that as an opportunity to learn, repeated "trials" or tests of change can incrementally allow interventions to be revised until they fit better with the revealed environment. The repeated tests of change help those wishing to change systems to have a humble and resilient approach in which "failure" is expected and not resented and therefore not demoralising.[62, 63] PDSA cycles in many ways mirror the Medical Research Council (MRC) Complex Intervention Framework which highlights the importance of taking a structured approach to intervention development.[64] The MRC Complex Intervention Framework involves a development phase that becomes much more powerful when it is iterative and recognises complexity, limited predictability, and the need for frequent revision. When PDSA cycles are explicitly incorporated into intervention development feasibility testing and piloting are seen as critical and on occasion may take considerable time but are crucial to ensuring that interventions that progress to a more formal evaluation are fit for purpose. The MRC also emphasises that a conceptual framework is needed when developing a complex intervention since this allows predictions about what might work and why to be made and increases the probability that intervention components are harmonised.[64] Since change in clinical practice predominately requires behaviour change the Michie Behaviour Change Wheel provides a suitable coherent conceptual framework and Michie who was pivotal in developing the MRC complex interventions pathway clearly recognised the need to create a systematic distillation of the behaviour change literature to allow behaviour change to inform system change.[64] Michie pulled together a consensus group that identified the common active ingredients in a whole range of disparate behaviour change models and brought them together in the COM-B model. This posits that 'Behaviour' can be understood in terms of the interaction of Capability, Opportunity, and Motivation.[65, 66] A useful shorthand for understanding facets of motivation in regards to adopting behaviours is Horne's Necessity-Concerns Framework which recognises that people who are reluctant to adopt recommended behaviours may be concerned about aspects of the recommended behaviour or may not see the necessity for that behaviour.[67, 68]

Successfully introducing changes into clinical practice takes time and that is typically the case even when those changes are evidence-based. Gabbay and le May's work looking at the use of medical guidelines in practice led them to propose the concept of "Mindlines".[69] These are "collectively reinforced, internalised, tacit guidelines" developed through a combination of

a clinician's own experience and that of their colleagues, and the informal interactions with opinion leaders, patients, pharmaceutical influences, and others. Mindlines can adapt along with changing organisational demands resulting in a form of “knowledge in practice”. This concept fits in alongside that of improvement science where the complexity of a system may be different in different settings hence any methods of change need to be acceptable, adaptable, and adopted as part of an internalised process.[69-71]

1.5 Conclusions

It is important to monitor PwCF, react to changes early, and prevent a permanent decline in lung function. In an ever-growing CF population with limited additional resources, it is vital to make the most effective use of clinics and any contacts. Innovative ways to deliver care need to be explored however any form of remote monitoring should not add any extra burden on top of an already heavy treatment load.

Most adults with CF are required to use a nebuliser daily to deliver treatment. If the breathing parameters automatically recorded with each treatment by the I-neb® can be correlated with acute changes in lung function it is hypothesised that they could allow the early detection of pulmonary exacerbations without adding any extra measures. Also, if this data can predict changes in lung function it is hypothesised that if this is collected remotely alongside routinely monitored nebuliser adherence it may inform clinics allowing the tailoring of appointments in advance hence streamlining clinics to be most efficient. Any attempts to successfully develop and implement changes in the delivery of clinical care should follow a structured framework taking account of complexity theory.

If these hypotheses are correct the benefits for PwCF and the healthcare system would be great. For PwCF early detection of pulmonary exacerbations may reduce the need for rescue IV antibiotics reducing some of the morbidity and improving quality of life. In the long run, this may also improve mortality. Having automatically recorded measures means no added burden for PwCF and if this data can inform a CF service prior to a clinic it can remove some clinical uncertainty and allow a better chance of predicting outcomes. Hence it should make a clinic process run more efficiently and effectively with the added bonus that PwCF may not always be required to attend for an in-person review saving time and money for all parties, and minimising the risks of cross-infections. The next chapter describes the research questions posed to explore these hypotheses and gives an overview of how the thesis sets out to answer the questions.

CHAPTER 2: RESEARCH QUESTIONS AND OVERVIEW OF THE THESIS

In Chapter 1 it was hypothesised that if the breathing parameters automatically recorded with each treatment by the I-neb® can be correlated with acute changes in lung function, then these parameters could allow the early detection of pulmonary exacerbations. This leads to research question 1.

Research Question 1: Which I-neb® breathing parameter(s), if any, can predict an acute decline in FEV1 of ≥2% from baseline in adults with CF?

To answer this question the following aim was set out: To develop a predictive model for identifying a decline in lung function (equivalent to a decline in FEV1 of ≥2% from baseline, with the baseline being defined as the best FEV1 in the prior 12 months) using routinely gathered I-neb® breathing parameter data.

Since there were no existing studies looking at the role of the I-neb® breathing parameters in predicting FEV1 changes, Chapter 3 systematically reviews the literature exploring how other known breathing parameters recorded during spirometry may correlate with FEV1 to see if any similarities can be drawn.

Chapter 4 describes the development of the predictive model using a retrospective derivation dataset of 61 patients with CF. Following on from the findings in Chapter 4 this leads on to Chapter 5 which compares the accuracy of home versus hospital spirometry and informs Chapter 6. The results from this chapter (Chapter 5) have been published.[72] The predictive model developed is then refined and validated in Chapter 6 using a prospective dataset of 34 patients with CF.

The introduction (Chapter 1) also highlighted the need to look at new innovative ways of managing PwCF due to centres increasing patient numbers, and the importance of tailoring care using remote monitoring. This leads to research question 2 as a first step in making changes to clinical practice.

Research Question 2: What pre-clinic data can decide if adult CF patients should be reviewed in clinic or if the clinic visit can be avoided?

To answer this question the following aim was set out: To develop consensus criteria using pre-clinic data that can help decide whether adult CF patients should be reviewed in clinic or if the clinic visit can be avoided.

The literature review in Chapter 3 identifies factors that might influence clinic attendance decisions in adults with CF and considers how these may be collected remotely. This informs Chapter 7 which describes how a clinical decision-making tool to optimise clinic use was developed, using a nominal group consensus approach. The results from this chapter have been presented as a poster in an international conference and published as an abstract.[73]

The final chapter in this thesis (Chapter 8) draws together the results for both research questions and ends with an overall discussion and conclusions; as well as offering future recommendations and plans for further publications.

CHAPTER 3: LITERATURE REVIEW

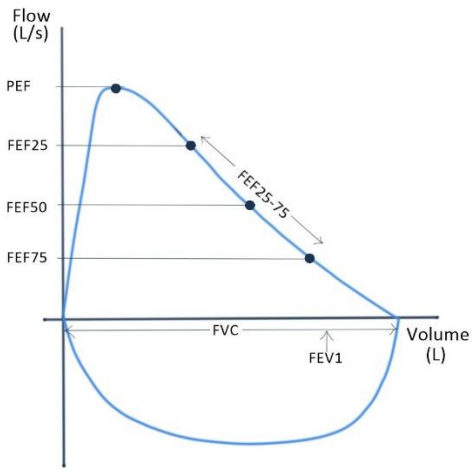
Following the research questions proposed in Chapter 2, this chapter reviews the literature and identifies relevant gaps to be answered.

3.1 Evaluation of surrogate measures of pulmonary function to predict FEV1

3.1.1 Introduction

Current clinical practice in CF involves the use of spirometry at every clinic visit and at times of clinical instability or pulmonary exacerbation. This is a prolonged forced expiratory manoeuvre with the measures FEV1 and forced vital capacity (FVC) being well understood and accepted as the standard for monitoring. The test can only be carried out by patients old enough to form a seal with their lips around the mouthpiece and understand the procedure commands. It is a simple, cheap, and reliable test which is sensitive to change over time. It is also non-invasive and well-tolerated. A series of at least three tests are usually performed until results are deemed acceptable and free from artefact.[74] Although spirometry is repeatable and reproducible there can still be a degree of variability which is higher in PwCF and for flows at lower lung volumes. The results are also highly technique and effort-dependent. Figure 3.1 shows the measures obtained from spirometry. As well as the FEV1 and FVC, mid-flows known as forced expiratory flow at a different point between 25% to 75% (FEF 25-75) are recorded which reflect small airways. The peak expiratory flow (PEF) can also be measured as part of the forced manoeuvre representing the maximal air flow generated during the forced exhalation.[74]

Figure 3.1: Spirometry flow volume loop
(Modified diagram from http://www.spirometry.guru/spirometry.html)



When patients use a nebuliser to inhale a medication this does not involve a forced manoeuvre. Instead, it usually follows tidal breathing patterns (normal inspiration and expiration during rest). When considering if the I-neb® breathing parameters can be used to predict changes in FEV1 it is important to review the spirometry literature in CF and other respiratory conditions to see if there are any known surrogate breathing measurements that can be obtained from simple spirometry and used to predict or correlate with FEV1.

3.1.2 Search strategy

Using the PICOS framework (Population, Intervention, Comparator, Outcome, and Study design or Setting) the different components of the review question were isolated. Using the population and intervention of interest MeSH (Medical Subject Headings) were identified and combined with the Boolean operator "AND":

- *Population* – The condition-related keyword and MeSH terms 'Cystic Fibrosis' "OR" 'Pulmonary disease, chronic obstructive' were used
- *Intervention* – The procedure-related keyword and MeSH term 'Spirometry' was used

To identify all relevant published and unpublished studies (grey literature) the following sources were searched on 29/09/2018:

- Electronic databases Medline (from 1946 onwards) and Embase (from 1947 onwards) via The National Institute of Clinical Excellence (NICE) Healthcare Databases Advanced Search (HDAS)
- Hand searching (electronic/hard copy archives) the past six months (April to September 2018) of the journals: 'Pediatric Pulmonology', 'Journal of Cystic Fibrosis', 'Thorax', and 'Chest'
- Hand searching conference proceedings and abstract books for the past two years (September 2016 to September 2018) for the major national and international conferences: European Cystic Fibrosis Conference, North American Cystic Fibrosis Conference, and the British Thoracic Society Conference
- Google Scholar search using the keywords
- Reference and citation tracking of relevant literature identified
- Expert pulmonary physiology opinion and work sought from Professor Martin Miller Honorary Professor of Medicine, University Hospitals Birmingham and Matthew Austin Respiratory Physiologist, Sheffield Teaching Hospitals

3.1.3 Inclusion and exclusion criteria

Studies were included in the review if they fulfilled the following inclusion criteria:

- The comparison of FEV1 to other breathing parameters obtained from simple spirometry in terms of correlation, reliability, repeatability, or use in clinical practice
- Any study design including review articles
- Studies involving adults or children
- Studies involving any respiratory condition including CF

Studies were excluded if they compared FEV1 with other modalities to measure lung function beyond simple spirometry such as imaging, gas inhalation techniques, forced oscillatory pressure, etc. Searches were limited to studies in humans and those reported in English language due to a lack of resources for translation.

3.1.4 Data extraction and analysis

Initial citations were screened for eligibility based on the title and abstract. Following this full articles were reviewed in more detail against the inclusion and exclusion criteria. Of those deemed suitable the following information was extracted:

- Authors and year of publication
- Study design
- Study population – including if CF or other respiratory condition
- Comparator to FEV1
- Methods use to compare breathing measures
- Correlation to FEV1
- Use of comparator in clinical practice

As the majority of the studies were observational and descriptive the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was used to assess quality.[75] The relevant data extracted from each study was tabulated and due to a lack of heterogeneity amongst studies involving quantitative data a narrative approach was taken to summarise the results.

3.1.5 Results

Figure 3.2 shows the process of the literature search using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. Only seven studies[76-82] were deemed suitable according to the inclusion and exclusion criteria. Of these two were review articles[79, 80], one was a conference abstract[78], and one was unpublished grey literature[82] obtained from an expert who conducted the research study. Table 3.1 summarises the results from the included studies. It was difficult to fully assess the quality of the included literature since there was only one research trial study fully published.

Figure 3.2: PRISMA flow diagram of literature search and study inclusion

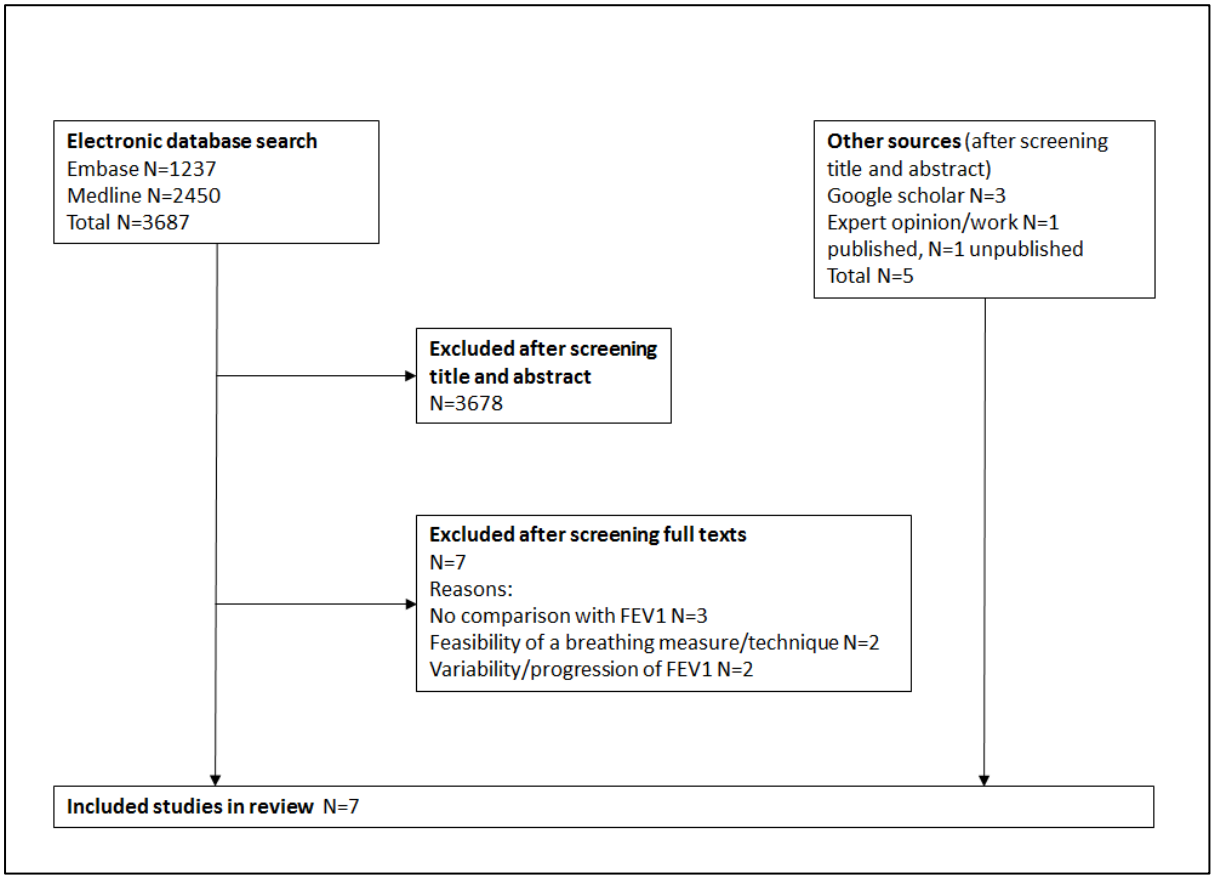


Table 3.1: Summary of study results included in review

Authors, year, Study design	Study Population	Comparator to FEV1	Methods used to compare breathing measures	Correlation to FEV1	Use of comparator in clinical practice
Lukic KZ et al[76] 2015 Canada Single centre retrospective observational study	Children 6-18 years of age CF or asthma N=1175 (CF N=559, Asthma N=616) N=1701 spirometry records originally reviewed but 526 excluded from analysis as FEV1 or FVC below lower limit of normal based on reference equations	FEF25-75 FEF75	Comparison of retrospective spirograms showing normal values for FEV1/FVC and FEF25-75 Z scores of each measure were scatter plotted to explore correlations in each condition	FEV1 is a more sensitive index than either FEF25-75 of FEF75	FEF25-75 or FEF 75 adds no superior interpretative information compared to FEV1/FVC in CF or asthma Advantage of FEV1/FVC is the rigorous standards to ensure quality control FEF25-75 is an index derived from volume time curve so higher coefficient of variation hence less sensitive
Quanjer PH et al[77] 2014 Netherlands Multicentre observational study	White males and females 3-94 years old Mixed respiratory conditions – asthma, cystic fibrosis, investigation of cough, dyspnoea, or miscellaneous Total N=22767 Males N=11654 Females N=11113 FEF75 available in N=8255 males, N=7407 females	FEF25-75 FEF75	Comparison of spirograms for FEV1, FVC, FEV1/FVC ratio, FEF25-75, FEF75 Predicted values and Z scores were correlated with scatter plots	Very little discordance in classifying results Airways obstruction went undetected by FEF25-75 in 2.9% of cases and by FEF75 in 12.3% of cases Most reductions in FEF25-75 and FEF75 in the absence of airway obstruction defined by FEV1/FVC data resulted from reduced lung volume rather than airways disease The low incidence of abnormal expiratory flows with normal FEV1/FVC may represent measurement ‘noise’ therefore reviewing the FVC manoeuvre is performed correctly is important	Maximum mid-expiratory flow and flow towards the end of the forced expiratory manoeuvre do not contribute usefully to clinical decision making above FEV1, FVC, and FEV1/FVC ratio

Authors, year, Study design	Study Population	Comparator to FEV1	Methods used to compare breathing measures	Correlation to FEV1	Use of comparator in clinical practice
Vermeulen F et al[78] 2014 Belgium Single centre retrospective longitudinal observational study Abstract only	CF patients aged 6-76 years at the time of assessment N=268 patients N= 1793 measurements reviewed	FEF25-75	Comparison of retrospective spirograms FEV1, FVC, FEF25-75 Z scores used to correlate measures. Kruskal-Wallis non-parametric tests used for comparison	Discordance between FEF25-75 and FEV1/FVC was uncommon In 811 tests with normal FEV1 and FVC Z scores 95 tests with low FEF25-75 was seen in younger patients with lower FVC Z scores In 971 tests with low FEV1, FEF25-75 was also abnormal in 95.7% and FEV1/FVC in 83.3%	Spirometry with normal FEV1, FVC, and FEV1/FVC but low FEF25-75 was rare and was seen more often in younger patients with a FVC Z score at the lower end of normal
Brand PLP et al[79] 1999 Netherlands Review article	Review of spirometry testing in CF patients with case examples	PEF Mid-Expiratory Flows (MEF25-75)	Descriptive explanations of parameters and how they compare	PEF reflects large airway calibre. Small and medium airways obstruction can occur before PEF decreases – therefore late sign in CF PEF highly effort dependent	PEF popular for day-to-day follow up in asthma but not CF In CF chronic malnutrition and infection may affect PEF effort hence increase the variation of results MEF along with PEF are more variable than FEV1 and VC (Vital Capacity) especially in CF and even in healthy subjects
Horsley A et al[80] 2015 UK Review article	Review of lung function testing techniques in CF	FVC Slow Vital Capacity (SVC) Mid-expiratory flows	Descriptive explanation of the parameters and how they compare	FVC correlates closely with FEV1 but in trials it improves to a lesser extent than FEV1 Relaxed expiration reduces dynamic compression of obstructed airways allowing a lower Residual Capacity (RV) and greater value for SVC than FVC Correlate with FEV1 but poorer repeatability	Although an isolated change in FVC may be relevant in general FVC adds relatively little additional information to FEV1 SVC is not widely used and insufficient studies comparing this and/or FVC as outcome measures No added value of mid-expiratory flows in health subjects or in CF

Authors, year, Study design	Study Population	Comparator to FEV1	Methods used to compare breathing measures	Correlation to FEV1	Use of comparator in clinical practice
Colasanti et al[81] 2004 UK Observational/ descriptive study	Adults with COPD, CF, or healthy lungs, and juveniles with CF N=81 adults (N=25 CF, N=21 COPD) N=46 juveniles	Flow indexes: TPPEF20 (change in post-peak expiratory flow at 20%) TPPEF80 (change in post-peak expiratory flow at 80%)	Comparison of breathing parameters using multiple linear regression – tidal flows (pressure sensor and time measures) to calculate/predict FEV1	Relationship between FEV1, body size, and age in healthy adults. More complex relationship between FEV1, body size, age, and tidal breathing profile in those with obstructive airways disease. In the juvenile CF group body weight influenced the calculation of FEV1 the most. In the healthy only if weight was pathologically increased did it influence FEV1 by limiting inspiration. The importance of TPPEF in deriving FEV1 in the CF juveniles was most relevant in those with severe obstruction. A reduced TPPEF was more common in obstructive disease due to a loss of expiratory flow braking In adults with CF the TPPEF20 was the major contributing factor in determining FEV1. The initial portion of expiratory flow is exponential implying that expiratory flow braking is reduced in the presence of airflow obstruction. The lack of contribution of TPPEF80 shows that this portion does little to characterise the severity of airway obstruction suggesting that lung hyperinflation is not a major factor in adults with CF. This is supported by the observation that resting or tidal expiratory flow limitation (often associated with hyperinflation)	Not used in current clinical practice but postulated that once obstructive airways disease has been diagnosed the data points could be used to monitor changes as time and flow domains become important. Without obstructive disease these would be variable with expiratory flow braking predominating in expiration

				has been shown to be present in only CF patients with severe reduced FEV1<30% predicted. In adults with COPD the major predictor of FEV1 was TPPEF80. Of the parameters important in the development of hyperinflation (pattern of breathing, inspiratory and laryngeal muscle activity) it is the beginning of inspiration before the lungs reach functional residual capacity that is the predominant factor. If the loss of inspiratory muscle activity was more important than TPPEF20 would contribute more to FEV1.	
Authors, year, Study design	**Study Population**	**Comparator to FEV1**	**Methods used to compare breathing measures**	**Correlation to FEV1**	**Use of comparator in clinical practice**
Miller MR, et al[82] 2006 UK Unpublished observational study data abstract	Patients investigated for occupational asthma N=134 Data used from N=127 (83 men) Mean age (SD) 46.6 years (10.8)	Tidal volumes and tidal peak flows	Subjects having a methacholine challenge test as part of investigations. Allowed pre and post FEV1 changes to be correlated with changes in tidal breathing measures (including first and second moments α1 and α2, and moment ratio (MR=√(α2)/α1) calculated from volume-time curves of inspiratory and expiratory tidal breaths)	N=56 FEV1 dropped by >20%. Mean (SD) % drop in FEV1 after methacholine was 16.7% (10.3) Tidal volumes and tidal peak flows pre and post challenge were significantly negatively correlated to the % drop in FEV1 r=-0.3, p<0.001 From the post methacholine tidal breaths the drop% was best correlated with inspiratory MR (r=0.3) although this did not correlate pre-challenge. Only the change in inspiratory MR significantly correlated with drop% (r=0.2, p<0.01), absolute drop and log dose slope from the challenge	Not used as generally weak correlations so limited usefulness to identify change in FEV1 from tidal breathing, but changes in inspiratory pattern of breathing need further study

Despite various sources being searched there is a lack of research exploring whether other surrogate breathing measurements obtained from simple spirometry can be used to predict or correlate with FEV1. Among studies where the correlation coefficients are reported, the correlation between FEV1 and other surrogate measures is weak.[83] All studies[76-82] looked at forced mid-flow measurements which is particularly important in this study since nebuliser measurements obtained during tidal breathing may be expected to be similar to mid-flow readings. Across the studies they did involve large numbers (at least >100 participants per study, and >1000 participants in two studies[76, 77]), with various age ranges (3-94 years), and conditions (CF, asthma, COPD, those investigated for cough, dyspnoea and occupational asthma, and healthy individuals). Apart from the unpublished study breathing measures were directly compared based on one spirometry result per individual or longitudinal results in individuals over time. In all studies although there was some correlation between FEV1 and forced mid-flows there was no definite evidence to support the use of mid-flows due to them being less sensitive with a higher degree of variability. Lower mid-flows with normal FEV1 were noted to be related to lower FVC particularly in younger patients with the comment that incorrect technique can affect this result.[78] PEF was discussed in one review article[80] which highlighted that this measure is highly effort dependent and reflects large airway calibre so again is more variable compared to FEV1 and is only really used in asthma.

Expert opinion from Professor Martin Miller and the grey unpublished study[82] suggest that there is little evidence that tidal breathing patterns can be used to predict changes in FEV1. Any associations found were weak although it was noted that changes in the inspiratory pattern of breathing may be worth further review. The study looked at absolute drops in FEV1 (pre and post) induced by the methacholine challenge in correlation with tidal breathing timings, flows, and moment analysis. This method of assessing acute changes in close succession will have helped reduce confounding factors which can influence longitudinal FEV1 readings such as day-to-day variability and spirometry technique. As the change in FEV1 was also >10% this should have been sufficient to identify any correlating signal change in tidal breathing patterns. As the study was negative with little interest shown for its results it was not published. Tidal breathing patterns have also been investigated in infants since evaluating airway obstruction is more complex due to lack of patient cooperation. Findings show that tidal breathing parameters are not sensitive enough to reliably detect or predict less severe expiratory airflow obstruction.[84] The same is likely to be true among adults, corroborating with the grey literature results.

Specialist Respiratory Physiologist Matthew Austin's perspective of lung function testing in CF highlighted the limitations of FEV1 in assessing early lung changes with newer techniques such as hyperpolarised Magnetic Resonance Imaging (HP-MRI) and Lung Clearance Index being researched and used. His thoughts on the literature on Forced Oscillation Technique (FOT) is that there is not much evidence to support its use. FOT measures the impedance of the respiratory system during tidal breathing. In practice this test is used in children under 6 years of age who are unable to adequately perform spirometry. This technique was excluded from the literature review since it involves the application of a low-frequency pressure oscillation generated by a loudspeaker through a mouthpiece to calculate changes in flow and pressure.[80] This is different to the types of measures obtained through tidal breathing using the I-neb® as no external pressure is applied via the device.

3.1.6 Conclusions

There is some evidence that forced expiratory mid-flows mirror FEV1 but with poorer repeatability and reliability. It is thought that mid-flows reflect the dynamic collapse of medium and small airways during forced expiration however at lower lung volumes this does seem to impact on results which may well be due to the heterogeneous lung disease found in conditions such as in CF.[74] Although mid-flows are thought to be effort independent if there is insufficient effort this will lead to reduced expiratory flows across the whole expiratory phase regardless of airway patency so results will be affected.[74] There is therefore merit in investigating whether the I-neb® breathing parameters correlate with FEV1 in particular looking at the inspiratory results recorded but also considering potential confounders.

3.2 Review of factors that might influence clinic attendance decisions in adults with CF

Several studies in CF have explored the use of telemedicine particularly since the COVID-19 pandemic but to date there are no published criteria outlining how remote monitoring may be best used to avoid or replace an in-person clinic review.

As CF is a chronic multisystem condition it encompasses many factors that require regular monitoring and review. The reasons for a clinic attendance can be broadly divided up into three categories. These may all take place in a single clinical encounter or independently at different times:

1. Acute illness review: when the patient self-reports signs and symptoms and actively seeks healthcare input.
2. Routine monitoring: involves measures to ensure the condition is stable and no complications have developed. This may identify acute changes in health parameters not necessarily expected by the patient or MDT.

3. Complex discussions/care planning: involves conversations between patients and the MDT about aspects of the condition often with future planning such as fertility, transplant, or end of life care. This communication can be driven by the patient or the MDT.

The UK CF Standards of Care[42], NICE guidelines[26], and ECFS best practice guidelines[85] highlight factors that require regular monitoring and annual assessment to prevent or limit symptoms and complications. These were reviewed to develop a summary of factors that require routine monitoring and how these may be collected remotely (Table 3.2).

Lung health

One of the primary objectives of a routine review is an up-to-date assessment of lung health. This involves objective spirometry data and oxygen saturations, a clinical assessment including subjective symptom reporting, a physical examination, and microbiology sampling. This should be reviewed every 3 months and at times of symptomatic deterioration. The aim is to promptly recognise and treat an acute pulmonary decline but also to track progression of disease. PwCF should be assessed during and post pulmonary exacerbation to ensure lung health has recovered. In those that do not respond to antibiotics other causes for decline should be considered such as allergic bronchopulmonary aspergillosis (ABPA), acquisition of a new organism, gastro-oesophageal reflux disease (GORD) which can lead to pulmonary aspiration, and CF diabetes (CFD). In the 2021 UK CF registry the prevalence of these complications affecting adults (≥16 years) were ABPA 7.7% (incidence 1.3%), GORD 24%, and CFD on treatment 35.2%.[5] It is also important to regularly monitor lung health in those receiving complex treatment regimes for complications such as ABPA, non-tuberculous mycobacterium (NTM) infections, and fungal infections. As part of maintaining lung health airway clearance techniques, exercise programmes, and inhaled therapy should be assessed and modified if needed. At annual review as well as at times of clinical deterioration a chest x-ray should be performed with more detailed imaging being carried out if appropriate. Exercise testing should be considered if clinically indicated. It is also important that complications such as haemoptysis and a pneumothorax are dealt with acutely if they arise.

Nutritional status

Weight is routinely monitored and along with height the body mass index (BMI) is calculated. PwCF are encouraged to maintain their BMI above 20 kg/m^2 aiming for ≥22 kg/m^2 in women and ≥23 kg/m^2 in men.[42] Dietitians provide nutritional input if there is inadequate weight gain or loss by advising increased calories and if this fails supplements are added which may include enteral tube feeding. More recently following the introduction of the new CFTR drug modulators some PwCF have gained excessive weight requiring dietitians to provide weight

loss advice instead. Along with monitoring weight any signs of malabsorption need to be reviewed with the addition of pancreatic enzyme replacement if there is pancreatic insufficiency. Fat soluble vitamins should be monitored at least yearly and replaced as necessary. Bone health is assessed at annual review with bone density scans and blood monitoring. Those with significant abnormalities should be referred on to a bone specialist or endocrinologist. Other gastroenterology complications should be considered and managed including distal intestinal obstructive syndrome (DIOS), GORD, recurrent acute pancreatitis predominately in those with pancreatic sufficiency, and eating difficulties.

Adherence

Improving adherence is a key challenge to prevent disease progression. The ECFS best practice guideline recommends discussing adherence at every visit using a collaborative, nurturing and holistic approach. Successful psychosocial interventions involve identifying barriers and actively supporting PwCF to form habits of adherence.

Impaired glucose metabolism and CF diabetes

PwCF are annually screened to identify impaired glucose metabolism or CFD since early treatment can improve outcomes. This can involve an oral glucose tolerance test, random blood glucose profiles or continuous glucose monitoring. A diagnosis of CFD should be considered if there is unexplained weight loss, deterioration in lung health including a decline in lung function and increased frequency of pulmonary exacerbations, or if there is excessive tiredness. Urine should be tested for glucose in those with weight loss or if receiving regular or frequent oral corticosteroids. CFD control should be monitored and optimised, including assessment for end organ complications.

CF liver disease

CF related liver disease affects 18.9% of adults (≥16 years).[5] Monitoring includes a clinical assessment, bloods, and liver ultrasound. PwCF should be referred on to a hepatologist if they develop chronic progressive disease, liver failure, or complications such as portal hypertension, haematemesis, or splenomegaly. Liver function blood tests are now frequently monitored initially every 3 months since the CFTR drug modulators have been widely used as they can cause hepatic impairment and necrosis.

Psychological and social difficulties

Clinical psychologists and social workers should be part of the CF MDT in order to assess and support general mental health and wellbeing, quality of life, factors impacting on adherence,

emerging psychosocial problems, and behaviours that affect health outcomes. Assessments should be carried out at annual review and if issues are identified at other times.

Transplantation, palliative and end of life care

Early discussions and advanced planning should take place when considering transplantation and end of life issues. Post-transplant care is carried out by some CF centres in the UK including regular blood pressure (BP) monitoring. This has to be in close conjunction with the transplant centre.

Fertility and pregnancy

PwCF planning pregnancy should receive pre-conception advice including CFTR genetic screening of partners. Males should be informed about fertility issues and supported with referral on to specialist fertility services if necessary. Pregnant women with CF should be considered as high risk especially if they have poor lung function (FEV1 <50% predicted), CFD, or chronic infection with *Burkholderia cenocepacia*. This is due to potential pulmonary and nutritional/metabolic complications that can occur.

Transition and new diagnosis

Newly diagnosed PwCF should have immediate access to a specialist CF centre and MDT. Transition from paediatric to adult services should involve a joint approach with opportunity to view adult facilities prior to transition.

Other important factors for review

PwCF that have totally implantable venous access devices (such as a portacath) will require flushing every 4-8 weeks to ensure it does not become infected or blocked.

Studies have shown that gastrointestinal malignancies are more common in PwCF and this rate increases further post transplant. More recently screening for colorectal cancer is being recommended from the age of 40 years old.

It is recommended that blood pressure is regularly monitored in those on regular oral corticosteroids.

Annually PwCF have a routine review with a series of tests including bloods and imaging. This is to evaluate the multisystem condition to ensure no complications have occurred.

Other issues which may require review include allergies, sinus disease, renal disease, arthropathy, stress incontinence, delayed puberty (which can be due to malnutrition and chronic disease), hearing problems as a consequence of frequent courses of aminoglycoside use which may require audiology assessments.

Table 3.2: Summary of the factors that require routine monitoring and how these may be collected remotely

Factors that require routine monitoring	Measures recommended	Potential alternative method of collecting or remotely monitoring
Lung health	Spirometry Oxygen saturations Microbiology sampling for culture	Home spirometer Home pulse oximeter Microbiology sampling locally or postal
Nutritional status	Weight/BMI	Home weighing scales
Adherence to treatment	Objective or subjective data	Self-report likely inaccurate but may be used for certain treatments with no objective measures Medicines possessions ratio (MPR) may not indicate actual adherence but may be used for certain medications Bluetooth or download of devices at home for nebulisers Adherence to other treatments: exercise trackers, insulin Bluetooth pens caps, etc.
Impaired glucose metabolism & CF diabetes (if applicable to patient)	Blood sugar monitoring End organ damage monitoring	Bloods locally or postal Home continuous glucose monitoring Diabetic eye and foot checks locally Urine albumin creatinine ratio (ACR) locally or postal Home BP monitor
Liver monitoring (if applicable to patient)	Blood monitoring	Bloods locally or postal
Totally implantable venous access devices (if applicable to patient)	Devices require access and flushing every 4-8 weeks	Requires in-person procedure at home or in clinic by trained staff (Some PwCF/their families may be able to manage this at home with suitable training)
Annual review investigations	Bloods Imaging hospital only	Bloods locally or postal

3.2.1 Conclusions

The current guidelines in CF have taken a consensus approach when recommending how clinical care should be delivered. One of the challenges in providing CF care is the

multisystem manifestations and complications which require specialist MDT input. Any alternative to an in-person clinic review should minimise perceived clinical risk and optimise quality outcomes. There are a number of objective measures which can now be remotely collected although this relies on patients recording the data and submitting it for review. It is clear that some investigations or elements of a review cannot be performed outside of a face-to-face review or in a hospital setting such as imaging and a physical examination. Understanding how to integrate remote monitoring into clinical care is therefore crucial to transform how CF care is delivered. Since the COVID-19 pandemic some CF centres have reported how they reactively used remote monitoring and virtual clinics to replace an in-person review although at present there are no clear consensus criteria as to how this can best be done in practice outside a pandemic. In particular there is no guidance on what outcome results should prompt a review virtually or in-person.

3.3 Summary of gaps in the literature

The published literature reviewed explores how other breathing parameters recorded during spirometry may correlate with FEV1 although it does not consider if changes in these can predict absolute changes in FEV1. Only the grey literature study attempts to demonstrate this comparing changes in tidal breathing measurements with absolute changes in FEV1. Since this question has not been looked at in detail in the literature it is important to investigate whether the breathing parameters recorded by the I-neb® can identify clinically relevant changes in FEV1. If this is the case it could allow pulmonary exacerbations to be detected earlier and may become a remote surrogate for FEV1 informing the routine monitoring pathway and clinic process.

Revolutionising routine CF care delivery is critical to deal with increasing prevalence. Advances in technology provide a potential solution allowing remote monitoring to inform a CF team of real time changes. This has intensified over the COVID-19 pandemic and with the introduction of the CFTR drug modulators many PwCF are now more empowered to self-manage. Consequently CF clinics need to be reactive to this change to ensure that PwCF continue to engage and achieve the best clinical outcomes using innovative methods. The literature exploring the purpose of a clinical encounter provides key areas for review but does not provide a criteria for when a patient may avoid or replace an in-person review. Specifically, for a routine clinic there are no objective measure ‘cut-off’ values agreed whereby this process may be informed. It is therefore important for a consensus approach to be taken to develop a clinic attendance criteria. By creating a clinical decision-making tool this can aid clinic restructuring using service improvement methodology.

CHAPTER 4: LUNG HEALTH STUDY: DEVELOPMENT OF A PREDICTIVE MODEL

This chapter describes how a predictive model was developed to detect an acute FEV1 decline.

4.1 Introduction

An important part of healthcare is being able to make predictions about future outcomes. Whether to determine prognosis or predict results the purpose is to guide better clinical decision making. Predictive models can standardise and assist with the decision-making process.[86] The advent of telemonitoring has allowed predictive modelling to become more sophisticated combining real-time data from multiple sources. Telemonitoring is increasingly used in chronic conditions to optimise control of disease trajectory and prevent exacerbations.[87] Being able to detect a potential deterioration early can enhance the usefulness of telemonitoring in making predictions allowing improvements in quality of care and reduced healthcare costs.[88] Some of the challenges of using telemonitoring measures in predictive models have included a lack of useful early predictors, suboptimal adherence to monitoring, and poor performance of conventional algorithms to detect meaningful changes within a reasonable timeframe.[89, 90]

Remote telemonitoring to identify CF pulmonary exacerbations early has been the focus of several studies since the 1980s. These have predominantly used home spirometry and remote symptom monitoring to detect acute changes. The eICE large multicentre RCT recruited 267 patients aged ≥ 14 years old (n=135 early intervention arm, n=132 usual care arm) and monitored home spirometry and symptom diaries twice a week over 12 months.[53] They demonstrated that pulmonary exacerbations could be detected earlier with telemonitoring compared with usual care (time to first exacerbation hazard ratio 1.45, 95% CI 1.09 to 1.93, p=0.99). Despite this adherence to home spirometry was poor (once weekly 50%, twice weekly 19%).[53] Similar results were seen with the HOME-CF study a randomised controlled mixed-methods pilot study.[54] They recruited 88 adult patients (n=44 home monitoring intervention arm, n=44 routine care arm) and monitored home spirometry and symptom diaries twice a week over 12 months. The home monitoring group detected a mean of 4.4 (95% CI 3.7-5.1) pulmonary exacerbations per person over 12 months, compared to 3.8 (95% CI 3.2-4.5) in the routine care group. Adherence to home spirometry was 50% once weekly but significantly lower than eICE at 2% twice weekly.[54] Qualitative results in this trial suggested suboptimal adherence to the home spirometry was due to the burden of frequent measures with patients reporting they forgot, had insufficient time, and for some they avoided

measures as worried results would be abnormal.[54] It is therefore of benefit if routinely recorded measures that can infer or predict an exacerbation can be remotely used to minimise the high reporting burden of additional measures. An FEV1 advantage was not seen in either study (eICE or Home-CF) despite early exacerbation detection, probably because of the inability to effectively treat an exacerbation without a cohesive behaviour change strategy.[91]

The concept of using routinely recorded surrogate breathing parameters to detect exacerbations has been explored in other chronic lung conditions. Borel et al. developed a predictive model using parameters recorded by home non-invasive ventilation software to detect exacerbations of chronic obstructive pulmonary disease (COPD).[92] This study calculated the 25th and 75th percentile for each parameter to determine an 'abnormal value' then used stratified conditional logistic regression models to estimate the risk of exacerbations within 5 days of an abnormal reading. When the predictive parameters (respiratory rate and percentage of respiratory cycles triggered by the patient) showed 'high abnormal' results on two or more days out of five consecutive days (i.e. above the 75th of a moving window value) this correlated with an increased risk of an exacerbation.[92] Following this, other studies have also explored whether changes in breathing parameters recorded on home non-invasive ventilation can predict exacerbations of COPD.[93, 94] Similar to Borel et al, Blouet et al highlighted that the daily monitoring of parameters may be too variable to be useful in clinical practice hence explored the number of days with abnormal values over different windows. Blouet et al. used four different methods to evaluate the change in breathing pattern over varied moving windows.[93] Methods A and B like Borel's method classified abnormal values as below the first quartile or above the third quartile. These abnormal values had to occur on two consecutive days over a 5-day or 4-day window respectively. Method C looked at the standard deviation (SD) of the parameter for two consecutive days and if the SD varied >5% the following day the value was deemed abnormal and had to occur for two consecutive days to be significant. For method D the SD was calculated over a ten-day period.[93] Results showed respiratory rate was consistently higher in the exacerbation group regardless of the method used. For 2 consecutive days a respiratory rate outside the interquartile limit calculated over the preceding 4 days was associated with an increased risk of an exacerbation. Variability in the daily use of non-invasive ventilation was also a significant predictor when assessed by methods C and D.[93] Jiang et al. used the same concept as Borel to determine an abnormal value but looked at the number of days this occurred within a 7-day window.[94] They identified that the seven-day mean respiratory rate, abnormal values of daily usage, leaks, and tidal volume within 7-days pre-exacerbation may be indicators for exacerbation detection.[94] Surrogate breathing parameters can also be obtained routinely for those using long term oxygen therapy through a medical device called TeleOx® (Srett,

Boulogne-Billancourt, France). This device is placed on the oxygen circuit in patients using nasal cannula. It contains a pressure sensor and a fluidic oscillator flow sensor. It is designed to monitor adherence but also enables a proxy for oxygen flow rate and respiratory rate at regular intervals. This has been investigated looking at exercising data in healthy subjects and those with COPD to see if the parameters could identify changes in breathing pattern which may indirectly predict exacerbations.[95]

It is crucial in CF to detect an acute decline in FEV1 as early as possible to identify pulmonary exacerbations. This can then allow the rapid implementation of therapeutic interventions to reverse the decline. Acute FEV1 change is an important outcome used when diagnosing an exacerbation since it is an objective reliable measure.[21] FEV1 trend is also strongly associated with survival, therefore it is imperative to maintain a stable FEV1.[96, 97]

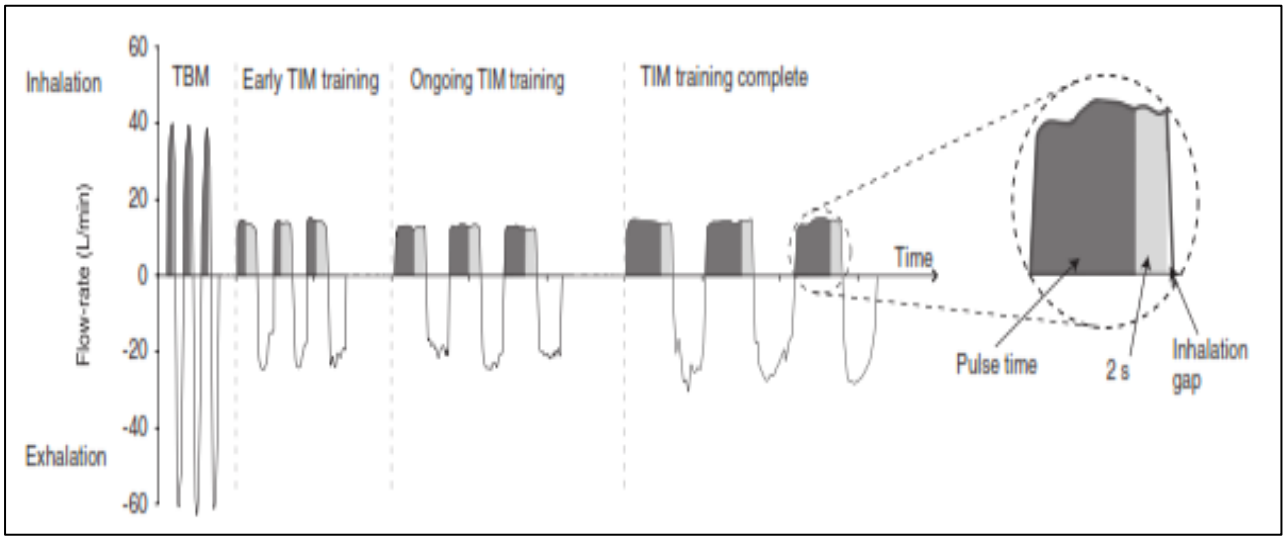
The systematic review in Chapter 3 suggests that forced expiratory mid-flows may correlate with FEV1. Most adults with CF are prescribed a daily nebuliser. For those with an I-neb® this automatically records breathing parameters with every use. Nebulisers usually require tidal breathing which may be considered similar to a mid-flow breathing pattern. Based on the hypothesis that a change in the breathing parameters may reflect a change in FEV1, the aim of this study was to assess whether daily variations in breathing parameters recorded by the I-neb® could predict an acute decline in FEV1 of ≥2% from baseline. Hence developing a predictive model which could serve as an early warning signal of a pulmonary exacerbation. Being able to do this remotely with no active involvement or additional measures required from patients is of great advantage as it minimises burden and allows real-time data to be readily available.

4.2 The breathing parameters measured by the I-neb®

The I-neb® can be used in two different breathing modes: Tidal Breathing Mode (TBM) and Target Inhalation Mode (TIM). TBM is low resistance with patients trained to keep the device in their mouth throughout the inhalation and exhalation. TIM is high resistance to promote higher flow rates and aims to reduce treatment times (vibrates to encourage longer inhalation; aims for 8 seconds per breath, with a minimum target that should be reached. Following each breath, the device will try to lengthen the vibration to aid this as needed). TIM is more sensitive to changes in inhalation length as patients inhale for longer as the device controls flow rate and gives “targets to” achieve on each inhalation and the device remembers where the inhalation target was from one treatment to another (see Figure 4.1).[98-100] However unlike the TBM, patients using the TIM are trained to remove the mouthpiece during exhalation due

to resistance. As the breathing technique for each mode is different this means the TIM mode does not record any expiratory times therefore an accurate rest time cannot be calculated. The I-neb® breathing parameters recorded during each use involve measures of time and flow. Inhalation time and volume inhaled per breath is lower using the TBM than the TIM, however the total treatment time and the number of breaths needed to deliver the drug will be lower using the TIM than the TBM. Since the TIM requires slower deeper inhalations this tends to be more easily achieved when individuals have better lung health (greater respiratory reserve) as indicated by a higher baseline FEV1 than those who have severe airway obstruction. Patients should therefore be advised which mouthpiece they should use to provide most effective drug delivery. The device should be held in a horizontal position when in use and after a few breaths the I-neb® will start to deliver medication. The treatment can be paused at any time by removing the mouthpiece from the mouth. After 2 minutes if there is no breath activation the device will go into pause mode, and if it continues for 10 minutes it will automatically shut down.

Figure 4.1: Graphical presentation of the two breathing modes used with the I-neb® AAD system (reproduced with permission from Mary Ann Liebert, Inc. Publishers see Appendix 1)[99]



The different readings measured by the I-neb® are described in Table 4.1.

Table 4.1: Readings measured by the I-neb®

Reading	Explanation
Rec No.	Each set of parameters for a given treatment
Time (hh:mm:ss)	Time of day of treatment as recorded by I-neb®
Date (dd/mm/yy)	Date of the treatment
Drug ID	As provided by the drug disc supplied with the prescription
Dose (Full/Incomplete)	Denotes whether the treatment was finished, or the drug chamber was only partly emptied
Disc ID (Serial No.)	Disc identifier
Mode (TBM/TIM)	Denotes which treatment mode was used
Time Spent Inhaling (TSI) (seconds)	Cumulative time spent inhaling during the treatment
Time Spent Exhaling (TSE) (seconds)	Cumulative time spent exhaling during the treatment May be artificially low if mouthpiece removed when using TBM No data measured for TIM as the mouthpiece should be removed during exhalation
Treatment Time (TT) (seconds)	Time from the start of the first inhalation to the end of treatment (i.e. drug chamber fully emptied defined by high pitched bleep and smiley face on device) TT = TSI + TSE + RT
Duration (minutes)	TT rounded up to the nearest minute
Mean Time Spent Inhaling (MTSI) (seconds)	Average inhalation time MTSI = TSI/Total number of breaths recorded for treatment
Mean Peak Inspiratory Flow (MPIF) (litres/min)	Pressure sensor measuring peak inhalation flow averaged per breath over the treatment Non-linear as laminar and turbulent flow Each measurement needs to be adjusted depending on the mouthpiece used TBM mean flow = MPIF/0.76 litres/min TIM mean flow = MPIF/5 litres/min With TIM peak inhalation flow likely to be lower as encouraging longer inhalation
Horn On Time (HOT) (seconds)	Amount of time the 'horn' is actively producing aerosol during treatment
Out of Angle (OOA)	Denotes a non-horizontal and therefore non-optimal orientation detected at least once during treatment. Not expected to have any impact on the breathing parameters recorded
Valid (Yes/No)	Denotes whether a valid treatment has been recorded
Rest time (RT) (seconds) Not directly measured but can be calculated for TBM	Amount of time during a treatment when there is a break for example due to coughing TBM RT = TT – (TSI + TSE) TIM RT unable to calculate as the mouthpiece is removed during exhalation (impossible to accurately distinguish between rest and exhalation even if assumptions are made about inspiration to expiration ratios)

4.3 Building a predictive model

It is important to first consider the generic steps involved in building a predictive model. The aim should be to develop an accurate and clinically useful predictive model considering multiple variables using comprehensive datasets. There is no agreed standard for constructing a predictive model although the Prognosis Research Strategy (PROGRESS) group have recommended several methods to improve development quality and impact[101, 102] which Lee et al. summarised as a five-stage process.[103]

Stage one defines the target outcome/event being predicted, target group of the model, and the target user of the prediction model. This informs the dataset used for the model and determines the selection and handling of variables.[103]

Stage two considers the dataset selection which is the most important component since it determines the quality and credibility of the model. There is no perfect dataset or model and no general method to assess the quality of the data. Ideally the best-suited dataset should be selected although this is often outside the control of the model developer. Depending on the purpose of the model, different datasets may be used. For example, cross sectional data can be used to detect a concurrent event, whilst longitudinal or prospective data may predict a future event. It is important to consider that a model derived from the data of one target group may not directly apply to a group with different characteristics. There are no absolute requirements in deciding the dataset sample size. Generally, a large representative dataset should be used which closely reflects the characteristics of the target group. This enhances the relevance, reproducibility, and generalizability of the model. Ideally, two datasets are required when building a predictive model – a development dataset and a validation dataset. The model is derived from analysis of the first dataset and its predictive performance is assessed using the derivation dataset. Where available an external study population or cohort should be used for validation. If this is not the case a dataset may be randomly split into two if the sample size is large, or statistical techniques may be used such as bootstrapping or jackknife resampling. In practice more subjects should be allocated to prediction model development than validation.[103]

Stage three involves handling of the variables used in the predictive model. Datasets need to be evaluated to select the most predictive and clinically relevant predictors. This may require subjective expert judgement. The aim should be for less than ten variables to improve efficiency, feasibility, and convenience.[103] Predictors found to be significant are considered candidate variables. If variables highly correlate with others these may be excluded as they would not contribute anything further. When coding variables categorical and continuous

variables must be managed differently. Continuous parameters can be complex and difficult to use so categorising some continuous predictors can make a model more user friendly. Handling missing data is another important aspect in this stage of development. Data may be missing for various reasons such as not collected, not available or applicable, or refusal from an individual to supply data, or if they drop out during a study. Techniques to handle missing data may involve imputation, dichotomizing an answer, or allowing an 'unknown' category.[103]

Stage four is model generation using various strategies and statistical tools. The full model approach includes all candidate variables in the model which has the benefit of avoiding overfitting and selection bias. Although it can be impractical to do and instead a stepwise selection method may be used to remove insignificant candidate variables. Regression data analyses are widely used but other methods may include classification and regression tree analysis (CART) or recursive partitioning analysis (RPA). Depending on the model and its intended use predictors may also be weighted to generate an overall outcome.[103]

Stage five involves the final model evaluation and validation. Once a model has been developed its predictive power should be tested using an independent dataset. If available, an external dataset should be used. The ability of the model to distinguish events versus non-events is important and known as discrimination. Calibration is also another key aspect which refers to the agreement between observed and predicted outcomes.[103]

Clinical prediction models are useful to screen asymptomatic high-risk individuals for a disease, to predict a future event, or to assist with medical decision making. A recommended method for reporting the development and validation has been established by the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) study which provides a summary checklist.[104]

4.4 Model development using the retrospective dataset

4.4.1Aim

To develop a predictive model which can identify an acute decline in FEV1 of ≥2% from baseline using I-neb® breathing parameters.

4.4.2 Objectives

1. To identify which breathing parameter(s) may be clinically useful to predict an acute decline in FEV1 of ≥2% from baseline.

2. To determine what the normal and abnormal threshold values are for each breathing parameter classified by baseline FEV1 category.
3. To understand how the breathing parameter(s) should be used as a predictive test.

4.4.3 Methods

This is a retrospective analysis of breathing parameter data from the I-neb® used to develop a predictive model for an acute decline in FEV1.

Source of data

Retrospective observational data was collected from a single adult CF centre. The following steps describe how the retrospective breathing parameter data was obtained, processed, and organised into a suitable format for analysis alongside other relevant variables. When considering the use of I-neb® breathing parameters to predict changes in FEV1, an *a priori* clinical judgement was made to analyse the different breathing mode datasets separately to determine the relevant thresholds for a positive test, since different breathing modes will require different breathing patterns and have different breathing parameter readings.

Obtaining the raw breathing parameter and demographic data

Participants with a post-2008 I-neb® device (extended breathing parameter data were not recorded on older models) were recruited and consented to the collection of their retrospective data. They were then set up with an Insight Online account by emailing their name and I-neb® serial number (displayed on the bottom of the device) to Philips Patient Support Programme (PSP) using a secure nhs.net account. Participants were then posted a unique username and password for their Insight Online account. Once participants had an Insight Online account they were asked to bring their I-neb® to be downloaded. The I-neb® was attached to a USB cradle of a laptop with Insight Online software. The participant then logged into their account using their username and password to extract the data. If they had forgotten these details they could phone Philips PSP (this confirmed they had given consent). All available data recorded on the device was obtained and processed. After the data extraction was complete Philips PSP were contacted by email and ask to send on the anonymised extended breathing parameter data for each participant. Alongside the breathing parameter data the demographics for each participant were collected at the time of recruitment: age, gender, CFTR genotype, co-morbidities (pancreatic insufficiency, CF diabetes), *Pseudomonas aeruginosa* status as defined by the Leeds criteria[105], from the preceding year: the best FEV1 and BMI, total IV days, and total routine clinic appointments attended, and the average daily prescribed nebuliser doses). All the FEV1 and BMI readings from the previous year were collected and the best was calculated as the highest readings.

‘Cleaning’ the raw breathing parameter data

The extended breathing parameter data was supplied as a text document with an individual sheet for each participant. Breathing parameters were available for every dose of nebuliser used, which was date and time stamped. Data in date order from every individual was transferred into and combined in a single Excel® spreadsheet for further processing. Some participants used their I-nebs® in both modes: TIM (Target inhalation mode) and TBM (Tidal breathing mode). Where this was the case, the data was separated as per the *a priori* clinical decision made.

Corresponding FEV1 and IV days data for the breathing parameters

For each participant all FEV1 readings recorded over the time span of the breathing parameter dataset were collected. The FEV1 volume was obtained from the medical notes (paper and electronic) and clinic letters, then converted to percentage predicted using the Global Lung Initiative (GLI) equation.[106] GLI is now generally accepted as the standard equation for calculating %FEV1 among PwCF since it is seamless across all ages and helps with the interpretation of FEV1 decline across the lifespan. The FEV1 data was collected by two researchers (RT and ZHH) independently to ensure accuracy. All disagreements between the researchers were resolved by going back to the original data to reach a consensus.

FEV1 readings were paired to corresponding breathing parameters using the following approach. FEV1 readings were paired with breathing parameters on the same date. If there was no exact date match, FEV1 readings were paired with breathing parameters within ±3 days with priority given to breathing parameters closest to the date of the FEV1 reading. For example, if there were breathing parameters on day -2 of the FEV1 reading and day 3 of the FEV1 reading, the FEV1 reading was matched to the breathing parameter on day -2. If there were equal days on either side of a reading priority was given to the preceding day. An *a priori* clinical decision was made not to pair FEV1 readings with breathing parameters beyond 3 days of spirometry since it is likely lung health might have changed to the extent that the breathing parameters no longer correspond to the FEV1 reading. This is consistent with Ramsey’s pulmonary exacerbation definition which includes a window of 3 days.[107] A 3-day window has also been used in another study comparing video-coaching remote spirometry with in-person spirometry in patients with asthma.[108]

Baseline FEV1 was determined for each breathing parameter as the best (highest) FEV1 in the last 12 months of each breathing parameter. The highest FEV1 in the last 12 months is generally accepted as reflecting the true baseline lung health of an individual with CF.[109] For each participant, the dates of intravenous antibiotic courses received over the period of

the breathing parameter retrospective data span were also extracted from medical notes (paper and electronic) and clinic letters, as a surrogate for pulmonary exacerbation. This is because people with CF on intravenous antibiotics are most likely to be receiving treatment for a pulmonary exacerbation. For each day with breathing parameter data, participants were noted as either being on intravenous antibiotics or not.

Participants

The predictive model target group was adult CF patients using an I-neb® and the target users of the model were the CF clinician and multidisciplinary team (MDT). As part of routine clinical practice on receipt of an I-neb® patients sign a form giving consent for data to be recorded on the way they use the device. This data is automatically collected and stored directly on the device. Participants were recruited from the Sheffield Adult CF Centre between May 2015 to September 2016. All eligible patients were invited to provide their retrospective I-neb® data if they fulfilled the inclusion criteria below (Table 4.2). Those who were post lung transplant were excluded. Ethical approval for the study was obtained from the Yorkshire & the Humber, South Yorkshire Research Ethics Committee, NHS Health Research Authority (15/YH/0131) and research and development approval was received from Sheffield Teaching Hospitals NHS Foundation Trust (STH18185).

Table 4.2 Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
• Confirmed diagnosis of cystic fibrosis via genetic testing • Aged 16 or above • Using inhaled mucolytics or antibiotic treatments via an I-neb® for all or part of their treatment • Capacity to give informed consent • I-neb® device post 2008 model	• Post lung transplant

Participants were categorised by their baseline FEV1 into four groups: FEV1<40%, FEV1 40-69.9%, FEV1 70-99.9%, and FEV1>100%. This was because patients with different baseline FEV1 may have different breathing patterns.[110] Clinically it was presumed that these distinct groups may have different breathing parameter thresholds which would need to be factored into the model. The FEV1 thresholds have been frequently used in other CF studies to describe groups of people with different levels of lung health.[110] Participants could have data over a prolonged period, hence they may have multiple different baseline FEV1 readings and contributed data to different FEV1 categories.

Outcome

FEV1 is a maximal effort reading and an acute decline from a baseline FEV1 is a clear outcome which has objective thresholds that can be set as an event. Using a change in FEV1 to identify an exacerbation avoids variability in clinician assessment and ensures a minimum threshold of clinical importance is set. The target event was an acute decline in FEV1 of ≥2% from baseline. An *a priori* decision was made to look at three different thresholds of percent predicted FEV1 (ppFEV1) decline: an acute decline in FEV1 of ≥2 percentage point, ≥5 percentage point, and ≥10 percentage point. These were agreed as clinically relevant thresholds to decision making in the clinic consensus criteria described in Chapter 7.

Predictors

Some *a priori* clinical assumptions and decisions were made although it was unclear at stage three of development which breathing parameters would be most relevant, so each breathing parameter was considered (Table 4.3). A decision was taken to use all available retrospective data with each individual contributing different amounts. Some individuals had multiple breathing parameters per session (same time of the day) if they used a mucolytic and antibiotic or if they had to double load a drug, and multiple sessions throughout the day if they were on regimes more frequently than once a day. The thresholds for "normal" and "abnormal" are unknown for each of the different breathing parameters. Equally there is no standard guidance on what is normal for tidal breathing in a given individual. Consequently, it was unclear which of the 'average value' should be used for each parameter if several readings per day were available. The 25th centile, median and 75th centile are all potential candidates based on a study looking at breathing parameters from domiciliary non-invasive ventilation machines.[92] The model development therefore explored the 25th centile, median and 75th centile for each parameter.

Table 4.3: The potential candidate breathing parameters using in model development

I-neb® mode	TIM	TBM
Breathing parameters	Duration (sec)	Duration (sec)
	Treatment Time (TT) (sec)	Treatment Time (TT) (sec)
	Time Spent Inhaling (TSI) (sec)	Time Spent Inhaling (TSI) (sec)
	Mean Time Spent Inhaling (MTSI) (sec)	Mean Time Spent Inhaling (MTSI) (sec)
	Mean Peak Inspiratory Flow (MPIF) (l/min)	Mean Peak Inspiratory Flow (MPIF) (l/min)
		Time Spent Exhaling (TSE) (sec)
		Rest Time (RT) (calculated) (sec)

sec = seconds, l/min = litres/minute

Sample size

The sample size was pragmatic and all available data was analysed. No published study has previously analysed I-neb® breathing parameters in detail that could provide data for a sample size calculation. Based on previous Sheffield Adult CF data a sample size of 50 participants would be expected to have 100 exacerbation events in a one-year period.[111] With 100 exacerbation events, a logistic regression model would be able to accommodate ten variables and only a maximum of seven breathing parameter variables were available to analyse.

Missing data

Complete-case analysis was performed without any data imputation. It was recognised that not every breathing parameter could be paired to a FEV1 reading since the dataset used was retrospective in nature and daily lung function readings were not routinely collected among PwCF. In the same vein, adherence to the nebuliser treatment would also impact on data availability, because adherence to inhaled therapies is only around 30% among PwCF.[112] To maximise the amount of data for the model development, every suitable FEV1 reading was linked according to an *a priori* convention. Incomplete treatment doses were excluded from the dataset as it was expected that these would have an artificially short treatment time that could bias the results. Out of Angle (OOA) breathing parameter readings were retained in the dataset as Philips Respironics did not expect that the orientation of the I-neb® during inhalation to impact on the breathing parameters recorded. [T Spencer 2015, personal communication, 27 April].

Statistical analysis methods

The minimum, maximum, and mean breathing parameter values per day were calculated. Each FEV1 was paired to one breathing parameter, and the difference between that particular FEV1 and the baseline FEV1 (i.e. the highest FEV1 reading in the previous 12 months) was calculated. An example of how this was calculated was: if the baseline FEV1 for the breathing parameter was 70%, and the actual FEV1 reading recorded on the day was 65%, the acute FEV1 decline would be 5% (70% - 65% = 5% difference). Incomplete doses were removed. The extent of missing data and the number of FEV1 declines ≥2%, ≥5% and ≥10% were described.

To understand the normal range for each breathing parameter at a particular baseline lung function (FEV1) the median, 25th centile, and 75th centile were calculated for each breathing parameter according to baseline FEV1 categories (<40%, 40-69.9%, 70-99.9%, ≥100%). The weighted median, 25th centile and 75th centile were calculated because each individual had varying amounts of data. Weighting was by the design effect DE = n/[1+(n-1)rho], where n =

number of observations of each cluster, rho = ICC (Intraclass correlation coefficient). Weighted median was calculated with the formula [(m1*n1) + (m2*n2) + ...] / [n1 + n2 + ...], with the same formula also applied for the weighted 25th & 75th centiles.

All FEV1 data linked to breathing parameters were used as an outcome in a mixed-effect logistic regression model (random effect at individual level) to determine the association between three FEV1 outcomes (FEV1 decline ≥2%, ≥5%, ≥10%) with:

- Breathing parameters as continuous variables in three categories (mean, maximum, minimum). For each breathing parameter value, deviation from median was calculated. The difference between the parameter value and median was used as the covariate.
- Breathing parameters as binary variables in three categories (mean, maximum, minimum). Each breathing parameter value was considered 'normal' if it was within the interquartile range (IQR).

If there was a statistically significant relationship, then this was adjusted for the following variables: whether FEV1 was matched (i.e. the FEV1 reading was matched to a breathing parameter within a ±3-day window or the FEV1 reading was taken on the same day as the breathing parameter)), whether the FEV1 reading was recorded on a day the patient was on IV antibiotics or not, and the number of breathing parameter readings per day.

In the statistical model only one breathing parameter was considered at any point. The different breathing parameters were not analysed in a single multivariate model due to collinearity. For example, the breathing parameter TT encompasses the other parameters; TSI, TSE, and RT. Therefore, analysing TT and TSI (which are not independent) as covariates in the same regression model could result in biased estimations and misleading interpretations.[113]

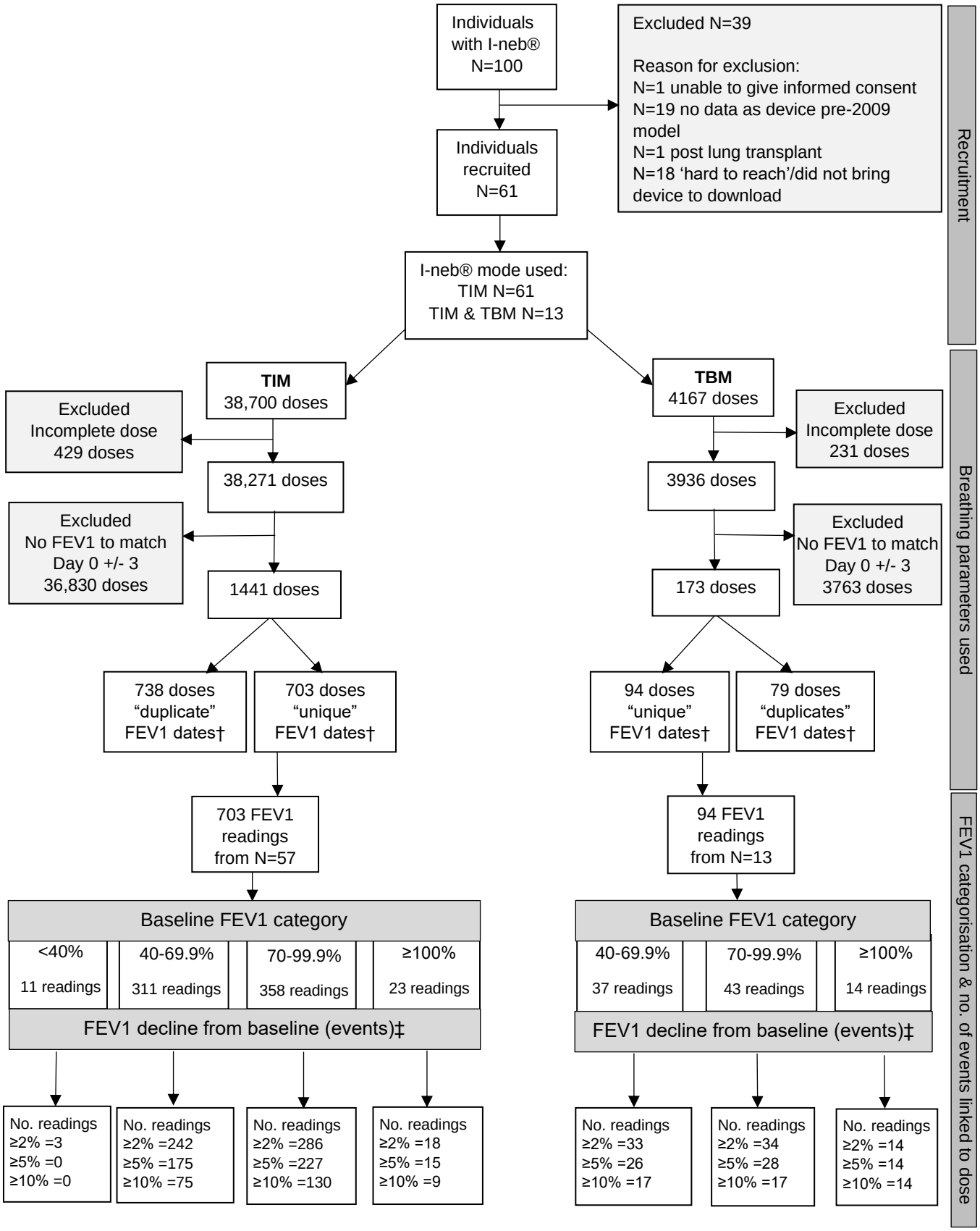
Following the logistic regression analysis, breathing parameter(s) that were strongly associated with FEV1 decline (p-value <0.05) were further analysed to determine their diagnostic accuracy values. The diagnostic accuracy values should allow a clinician to judge the clinical relevance of using the breathing parameter(s) as a screening test for acute FEV1 decline. In calculating the diagnostic accuracy values, the outcome of interest was acute FEV1 decline. In light of a pattern that emerged from the analysis and exercising clinical judgement, the breathing parameter results within ±3 days of the FEV1 reading were considered abnormal ('positive test') if the values were beyond the 75th centile and considered normal ('negative test') if the value was within the 75th centile. Each participant contributed varying amounts of data. The diagnostic accuracy values were calculated using two methods. The first method simply assumed that all data points were independent of each other.

Therefore, each paired FEV1-breathing parameter reading was analysed independently regardless of which participant contributed that paired reading (unadjusted diagnostic accuracy value). The second method takes into account the potential correlation in results from the same participant contributing more than one paired FEV1-breathing parameter reading (adjusted diagnostic accuracy value). This analysis using random effects modelling was performed by a senior statistician (MJC) with full details described in the Appendix 2. All statistical analysis was performed using SPSS v24 (IBM Corp) except the calculation of diagnostic accuracy values with clustering effect which was performed in STATA v13.

4.4.4 Results

Sixty-one patients were recruited to the retrospective study. A participant flow diagram constructed as per the STARD guidance is displayed in Figure 4.2.[114] In 2015 there were 100 patients using the I-neb® in the Sheffield Adult CF Centre. Over a third of these patients were excluded from the study. This was predominantly due to 19 having a pre-2009 I-neb® which prevented extended breathing parameter data extraction and a further 18 did not bring their device to clinic for download via Insight Online. Breathing parameter data spanned from November 2010 to February 2016. Since individuals contributed data over a long time span, their baseline FEV1 could have changed i.e. they may have several baseline FEV1 categories. The flow diagram also highlights the lack of FEV1 readings available to match to every breathing parameter (>95% of breathing parameter data were unmatched).

Figure 4.2: Retrospective participant flow diagram



† There were more I-neb® doses than FEV1 readings. On occasions there was only one I-neb® dose matched to an FEV1, on other occasions there were multiple I-neb® doses matched to one FEV1 reading. Where there were multiple I-neb® doses matched to an FEV1 reading this was regarded as a "duplicate" dose.

‡ These are not mutually exclusive readings. A decline in FEV1 ≥10% means the decline was also ≥2% and ≥5%.

Baseline demographics and clinical characteristics are described in Table 4.4. The majority of participants were colonised with *Pseudomonas aeruginosa* and prescribed three daily doses of nebulised medication via the I-neb®. Despite the high prevalence of chronic Pseudomonas among the cohort, median FEV1 was high at 79% as participants were young with a median age of 27 years.

Table 4.4: Baseline demographics and clinical characteristics

Retrospective study demographics at recruitment (n=61)	
Age in years, median (IQR)	27 (22-34)
Female, n (%)	28 (46)
CFTR Genotype: Heterozygous class I-III or homozygous class IV-VI, n (%) Homozygous class I-III, n (%)	 10 (16) 51 (84)
Pancreatic insufficient, n (%)	55 (90)
CF diabetes (CFD), n (%)	18 (30)
Pseudomonas aeruginosa status: No, n (%) Intermittent, n (%) Chronic, n (%)	 8 (13) 9 (15) 44 (72)
Baseline FEV1 - Best FEV1%, median (IQR)	79 (58-90)
Best BMI kg/m2, median (IQR)	22.9 (20.6-24.7)
Average prescribed daily nebulised I-neb® doses median (IQR)	3 (3-4)
Total IV days, median (IQR)	14 (0-28)
Total routine clinic attendances, median (IQR)	4 (3-6)

The number of paired FEV1 and breathing parameter data supplied by participants is displayed in the waterfall diagram (Figure 4.3). This demonstrates the variability in the amounts of paired data from each participant. Of the 61 participants, 13 (21%) contributed TBM and TIM breathing parameter data with most data captured using the TIM mouthpiece only. Figure 4.4 shows the discordance between the duration of data and amount of paired data – Participant #8 had data spanning >1,500 days yet only had 3 breathing parameters that were matched to FEV1 readings.

Figure 4.3: Number of paired FEV1 & breathing parameter data supplied by participant

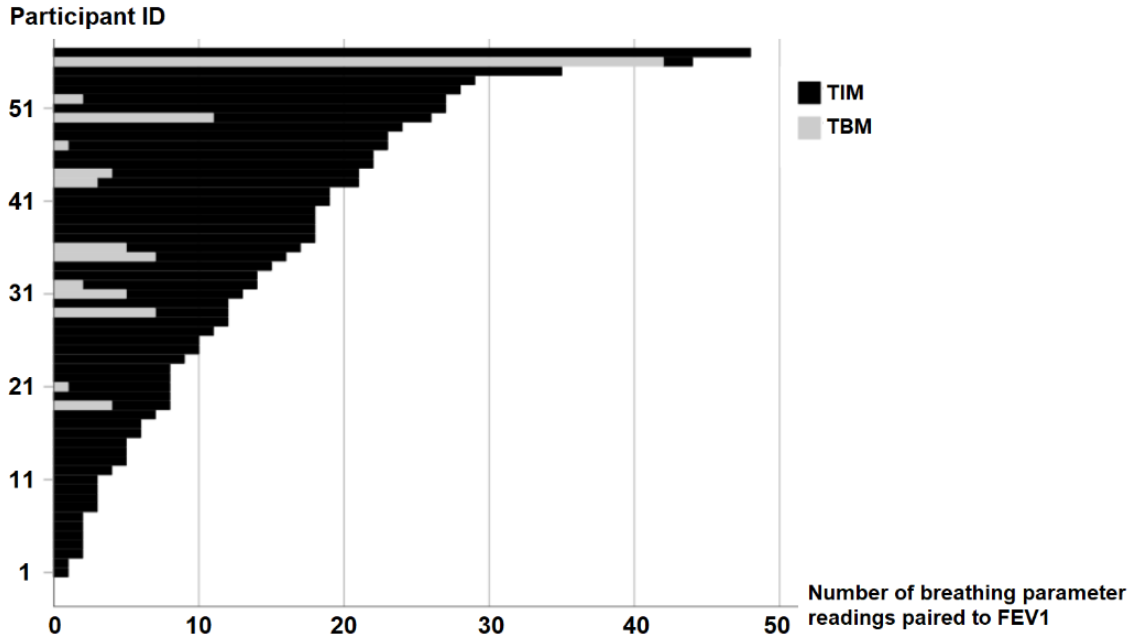
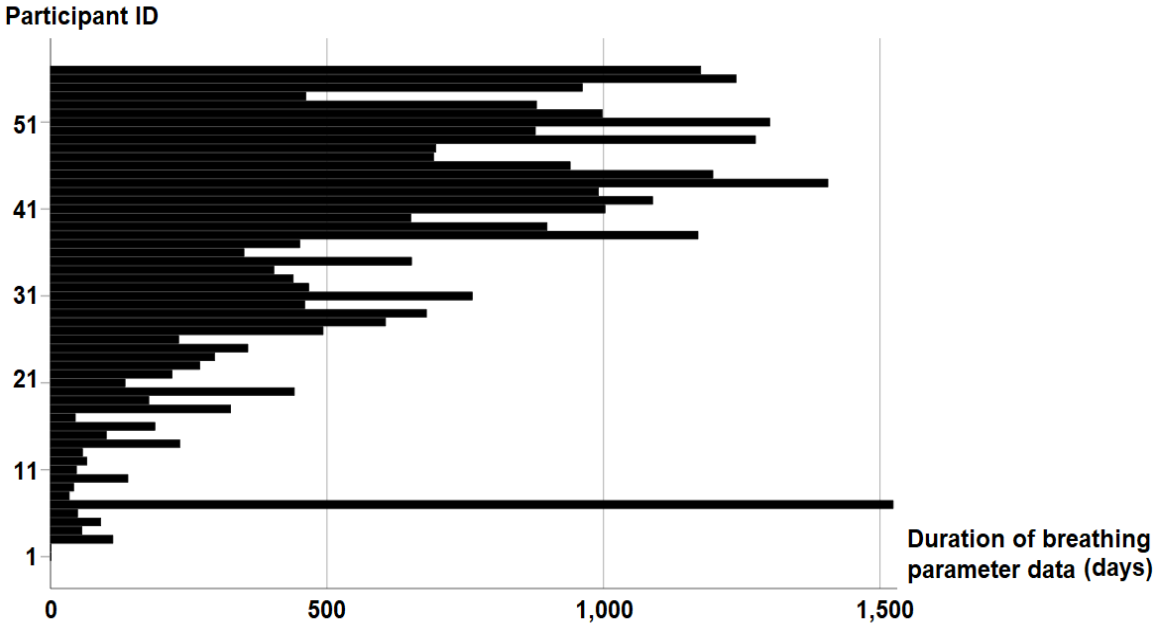


Figure 4.4: Duration of breathing parameter data supplied by participant



The distribution of the baseline %predicted FEV1 for each I-neb® mode is shown in the histograms below (Figure 4.5 and 4.6).

Figure 4.5: Histogram for baseline FEV1 – TIM dataset (213 baseline FEV_1 readings among 60 participants)

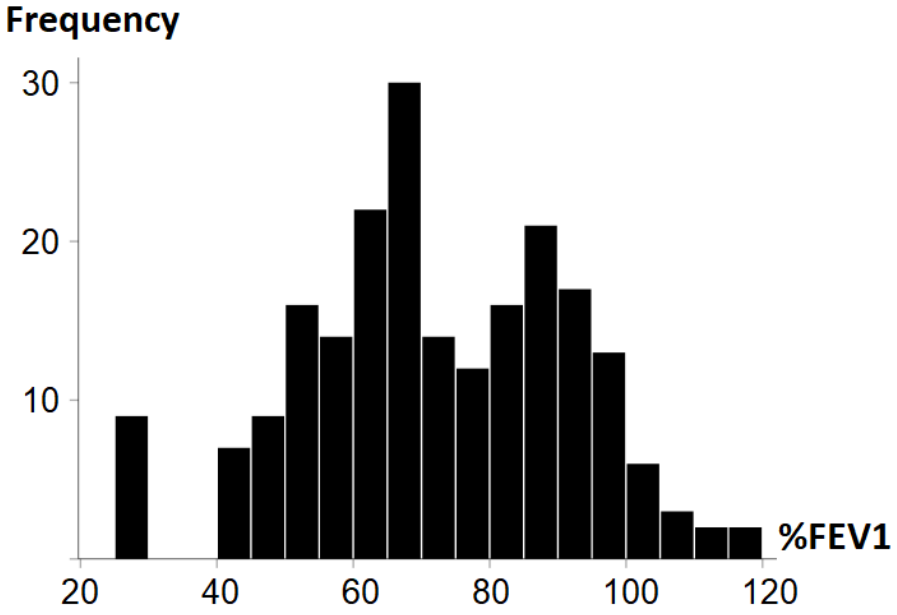


Figure 4.6: Histogram for baseline FEV1 – TBM dataset (34 baseline FEV_1 readings among 14 participants)

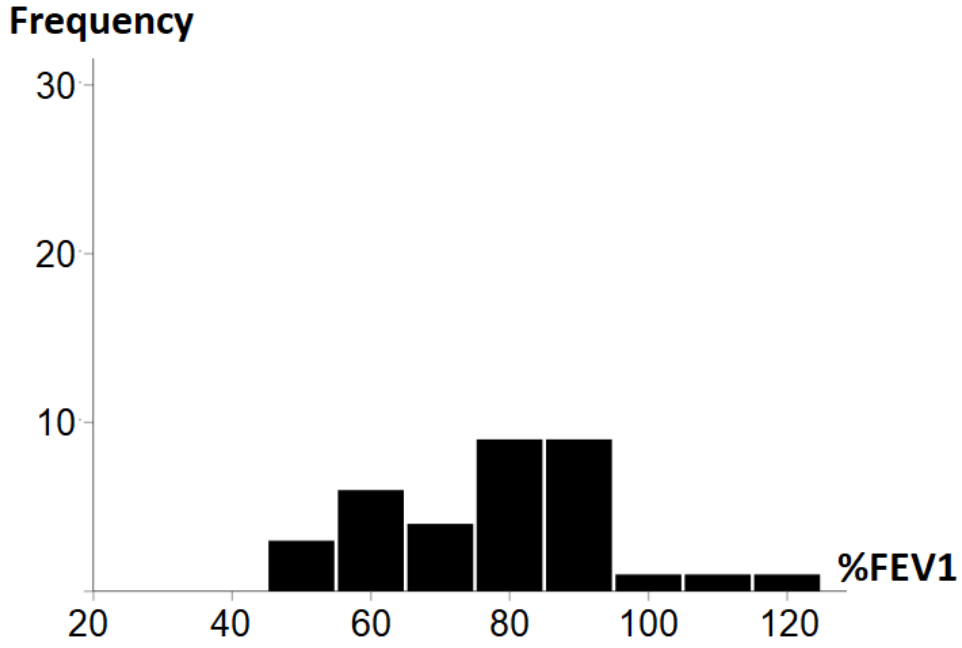


Table 4.5 shows the minimum, mean and maximum values for each parameter. There is variability in the range of values for each breathing parameter, and also according to the two different breathing modes. For example, minimum value was 62 seconds, mean value was 72 seconds, and maximum was 77 seconds for TSI in TIM, whereas the corresponding values for TBM were 88, 101 and 117 respectively. Hence all range of values were initially analysed.

Table 4.5: Minimum, mean & maximum values for each breathing parameter in TIM & TBM

Breathing parameter	**TIM** (703 data points from 61 subjects)			**TBM** (94 data points from 13 subjects)		
	Minimum value Median (IQR)	**Mean value** Median (IQR)	**Maximum value** Median (IQR)	**Minimum value** Median (IQR)	**Mean value** Median (IQR)	**Maximum value** Median (IQR)
Duration (sec)	120 (60-80)	120 (96-180)	120 (120-240)	240 (180-630)	355 (240-730)	420 (240-840)
TSI (sec)	62 (48-82)	72 (55-94)	77 (59-110)	88 (73-157)	101 (84-168)	117 (90-200)
TSE (sec)	N/A	N/A	N/A	102 (71-181)	125 (84-243)	143 (99-251)
TT (sec)	107 (78-150)	131 (93-180)	145 (101-228)	267 (205-623)	342 (242-751)	420 (252-844)
MTSI (sec)	6.5 (4.4-8.0)	6.8 (4.8-8.3)	7.2 (5.1-8.6)	0.8 (0.6-2.9)	0.9 (0.7-3.0)	0.9 (0.7-3.0)
MPIF (l/min)	90 (56-127)	99 (63-127)	107 (68-127)	16 (12-39)	16 (13-39)	17 (14-39)
RT (sec)	NA	NA	NA	62 (35-281)	109 (53-306)	154 (54-350)

sec=seconds, l/min=litres/minute

Since different participants contributed varying amounts of data, the intraclass correlation (ICC) for each parameter was calculated so that the clustering effect could be accounted for. The ICC values according to baseline FEV1 categories and breathing mode are displayed in Table 4.6. The ICC differs for different FEV1 baselines, for example MPIF via TBM had ICC values of 0.64 (95% CI 0.33-0.95) for FEV1 40-69.9% and 0.83 (95% CI 0.65-1.02) for FEV1 70-99.9%. For both breathing modes the MTSI and MPIF have higher correlation coefficients across all FEV1 baselines.

Table 4.6: Intra class correlation coefficients (ICC)[$] for each breathing parameter stratified by baseline %predicted FEV1
[$]Higher ICC values represent more correlated data

TBM mouthpiece

Baseline FEV1 %predicted 40-69.9% N=8							
	Duration	**TSI**	**TSE**	**TT**	**MTSI**	**MPIF**	**RT**
ICC	0.43	0.32	0.40	0.43	0.84	0.64	0.48
95% CI	0.10-0.75	0.03-0.61	0.08-0.73	0.10-0.75	0.66-1.02	0.33-0.95	0.15-0.82
Baseline FEV1 %predicted 70-99.9% N=9							
	Duration	**TSI**	**TSE**	**TT**	**MTSI**	**MPIF**	**RT**
ICC	0.36	0.41	0.52	0.37	0.92	0.83	0.28
95% CI	0.05-0.67	0.09-0.74	0.19-0.86	0.06-0.68	0.82-1.02	0.65-1.02	0.01-0.55
Baseline FEV1 %predicted ≥100%* N=1							
	Duration	**TSI**	**TSE**	**TT**	**MTSI**	**MPIF**	**RT**
ICC	-	-	-	-	-	-	-
95% CI	-	-	-	-	-	-	-

*Since only 1 individual with baseline FEV1 ≥100% no data for ICC

TIM mouthpiece

Baseline FEV1 %predicted <40%* N=1					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
ICC	-	-	-	-	-
95% CI	-	-	-	-	-
Baseline FEV1 %predicted 40-69.9% N=30					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
ICC	0.28	0.18	0.28	0.82	0.76
95% CI	0.14-0.42	0.08-0.28	0.14-0.42	0.71-0.92	0.63-0.89
Baseline FEV1 %predicted 70-99.9% N=37					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
ICC	0.28	0.41	0.28	0.74	0.70
95% CI	0.16-0.40	0.27-0.56	0.16-0.40	0.63-0.86	0.58-0.83
Baseline FEV1 %predicted ≥100% N=4					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
ICC	0.37	0.07	0.40	0.84	0.78
95% CI	0.00-0.82	0.00-0.21	0.00-0.86	0.58-1.10	0.44-1.11

*Since only 1 individual with baseline FEV1 <40% no data for ICC

The summary measures for each breathing parameter weighted using the ICC results showed variation across different FEV1 baselines and between the two breathing modes. As would be clinically expected, lower TT readings were obtained in participants with higher baseline FEV1. For example, in TBM, median TT was 398.8 seconds for FEV1 40-69.9% and 347.0 seconds for FEV1 70-99.9% (Table 4.7). Correspondingly, the RT Is higher in those with a lower baseline FEV1. There were only a small number of participants with baseline FEV1 <40% and ≥100%, hence these group-level breathing parameter readings may lack precision.

Table 4.7: Summary measures for each breathing parameter (Weighted based on ICC readings)

TBM mouthpiece stratified by baseline %predicted FEV1

Baseline FEV1 %predicted 40-69.9% N=8							
	Duration	**TSI**	**TSE**	**TT**	**MTSI**	**MPIF**	**RT**
25th centile	277.51	79.34	104.66	277.03	1.23	14.92	76.28
Median	398.24	108.79	149.28	398.77	1.38	16.89	126.19
75th centile	522.34	127.30	186.33	521.01	1.54	19.42	211.71
Baseline FEV1 %predicted 70-99.9% N=9							
	Duration	**TSI**	**TSE**	**TT**	**MTSI**	**MPIF**	**RT**
25th centile	219.92	80.12	68.41	223.50	2.05	28.38	61.12
Median	336.91	109.84	108.77	347.04	2.70	37.36	118.17
75th centile	455.35	137.64	145.30	461.58	3.24	48.88	188.03
Baseline FEV1 %predicted ≥100% N=1							
	Duration	**TSI**	**TSE**	**TT**	**MTSI**	**MPIF**	**RT**
25th centile	240.00	68.00	95.75	240.75	0.70	12.00	60.00
Median	360.00	94.00	135.00	341.5	0.90	16.00	103.00
75th centile	480.00	125.00	178.25	461.00	1.00	19.00	163.50

TIM mouthpiece stratified by baseline %predicted FEV1

Baseline FEV1 %predicted <40% N=1					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
25th centile	120.00	41.00	117.00	5.70	44.00
Median	180.00	54.00	162.00	6.70	56.00
75th centile	240.00	65.00	220.25	7.40	72.00
Baseline FEV1 %predicted 40-69.9% N=30					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
25th centile	119.09	56.56	117.72	4.71	73.54
Median	161.17	69.41	158.77	5.32	83.17
75th centile	227.15	89.85	232.00	5.88	93.08
Baseline FEV1 %predicted 70-99.9% N=37					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
25th centile	105.96	62.40	109.08	6.04	80.16
Median	154.91	77.53	151.83	6.87	90.33
75th centile	231.77	106.98	237.51	7.53	101.44
Baseline FEV1 %predicted ≥100% N=4					
	Duration	**TSI**	**TT**	**MTSI**	**MPIF**
25th centile	89.68	56.53	103.86	5.51	82.87
Median	134.84	66.09	127.85	6.00	99.42
75th centile	175.64	83.42	169.51	6.65	107.22

The number of FEV1 readings with acute decline with more than or equal to 2%, 5%, 10% were displayed at the end of the STARD diagram (Figure 4.2). The results for the mixed effect logistic regression models are displayed in Tables 4.8. The statistically significant results are bolded in each row of the table. If the TT minimum in TIM as a binary variable exceeded the 75th centile, the odds of a 10% acute decline in FEV1 increased by 67% (95% CI 11%-151%), p= 0.014. After adjusting for the date of FEV1, IV antibiotic use, and the number of breathing parameters per day, the odds still increased by 65% (95% CI 9%-150%), p= 0.019.

Tables 4.8: Associations (odds ratio) between binary outcome, FEV1 change from baseline, and breathing parameters from mixed effect logistic regression models

TBM - FEV1 ≥2% change			
Breathing parameter	**Odds ratio[#] (OR)**	**95% CI for OR**	**P-value**
Duration mean continuous	1.001	1.000-1.002	0.143
Duration max continuous	1.001	1.000-1.002	0.131
Duration min continuous	1.001	0.999-1.002	0.241
Duration mean binary	0.640	0.191-2.144	0.466
Duration max binary	0.634	0.188-2.141	0.459
Duration min binary	0.390	0.115-1.320	0.128
TSI mean continuous	1.004	0.995-1.013	0.362
TSI max continuous	1.002	0.993-1.011	0.620
TSI min continuous	1.005	0.997-1.013	0.230
TSI mean binary	1.651	0.468-5.824	0.431
TSI max binary	1.002	0.993-1.011	0.620
TSI min binary	1.529	0.406-5.748	0.526
TSE mean continuous	1.002	0.996-1.008	0.533
TSE max continuous	1.000	0.994-1.006	0.997
TSE min continuous	1.003	0.997-1.008	0.314
TSE mean binary	0.730	0.213-2.503	0.613
TSE max binary	0.488	0.140-1.699	0.257
TSE min binary	0.553	0.159-1.924	0.348
TT mean continuous	1.001	1.000-1.002	0.151
TT max continuous	1.001	1.000-1.002	0.140
TT min continuous	1.001	0.999-1.002	0.255
TT mean binary	0.541	0.161-1.819	0.317
TT max binary	0.459	0.135-1.560	0.210
TT min binary	0.261	0.076-0.898	**0.033**
TT min binary adjusted	0.207	0.051-0.831	**0.027**
MTSI mean continuous	1.053	0.738-1.504	0.772
MTSI max continuous	1.035	0.724-1.479	0.849
MTSI min continuous	1.072	0.752-1.528	0.698
MTSI mean binary	1.356	0.257-7.150	0.717
MTSI max binary	1.128	0.212-5.994	0.887
MTSI min binary	0.925	0.170-5.017	0.927
MPIF mean continuous	1.002	0.975-1.030	0.883
MPIF max continuous	1.001	0.975-1.028	0.949
MPIF min continuous	1.004	0.977-1.032	0.777
MPIF mean binary	1.559	0.302-8.044	0.592
MPFI max binary	2.071	0.406-10.565	0.377
MPFI min binary	2.033	0.400-10.330	0.388
RT mean continuous	1.001	1.000-1.003	0.134
RT max continuous	1.001	1.000-1.003	0.118
RT min continuous	1.001	0.999-1.003	0.289
RT mean binary	1.924	0.469-7.883	0.359
RT max binary	1.387	0.336-5.720	0.648
RT min binary	0.696	0.160-3.041	0.627

TBM - FEV1 ≥5% change			
Breathing parameter	**Odds ratio[#] (OR)**	**95% CI for OR**	**P-value**
Duration mean continuous	1.002	1.000-1.003	**0.026**
Duration mean continuous adjusted	1.001	1.000-1.003	0.080
Duration max continuous	1.001	1.000-1.003	**0.050**
Duration max continuous adjusted	1.001	1.000-1.003	0.081
Duration min continuous	1.002	1.000-1.003	**0.027**
Duration min continuous adjusted	1.001	1.000-1.003	0.122
Duration mean binary	1.534	0.564-4.171	0.398
Duration max binary	1.951	0.693-5.494	0.203
Duration min binary	1.394	0.486-3.998	0.533
TSI mean continuous	1.007	0.999-1.015	0.085
TSI max continuous	1.005	0.998-1.013	0.165
TSI min continuous	1.007	1.000-1.015	**0.043**
TSI min continuous adjusted	1.005	0.997-1.014	0.221
TSI mean binary	1.272	0.467-3.462	0.635
TSI max binary	1.187	0.432-3.263	0.737
TSI min binary	0.638	0.232-1.754	0.379
TSE mean continuous	1.002	0.997-1.007	0.402
TSE max continuous	1.000	0.995-1.006	0.888
TSE min continuous	1.003	0.998-1.008	0.185
TSE mean binary	1.955	0.702-5.445	0.197
TSE max binary	0.918	0.331-2.550	0.869
TSE min binary	1.704	0.573-5.071	0.334
TT mean continuous	1.002	1.000-1.003	**0.026**
TT mean continuous adjusted	1.001	1.000-1.003	0.080
TT max continuous	1.001	1.000-1.003	0.051
TT min continuous	1.002	1.000-1.003	**0.026**
TT min continuous adjusted	1.001	1.000-1.003	0.119
TT mean binary	1.233	0.451-3.371	0.679
TT max binary	1.337	0.472-3.783	0.581
TT min binary	0.914	0.311-2.684	0.869
MTSI mean continuous	1.205	0.881-1.648	0.241
MTSI max continuous	1.208	0.885-1.649	0.230
MTSI min continuous	1.196	0.874-1.636	0.261
MTSI mean binary	3.682	0.721-18.801	0.116
MTSI max binary	3.304	0.629-17.343	0.156
MTSI min binary	1.465	0.335-6.400	0.608
MPIF mean continuous	1.000	0.977-1.024	0.996
MPIF max continuous	1.001	0.978-1.023	0.963
MPIF min continuous	0.998	0.974-1.023	0.894
MPIF mean binary	0.775	0.238-2.525	0.669
MPFI max binary	1.043	0.329-3.308	0.943
MPFI min binary	0.817	0.268-2.491	0.719
RT mean continuous	1.002	1.000-1.004	**0.029**
RT mean continuous adjusted	1.002	1.000-1.004	0.064
RT max continuous	1.002	1.000-1.004	0.058
RT min continuous	1.002	1.000-1.005	**0.029**
RT min continuous adjusted	1.002	1.000-1.005	0.106
RT mean binary	2.124	0.698-6.462	0.182
RT max binary	2.022	0.623-6.563	0.238
RT min binary	1.332	0.348-5.102	0.673

TBM - FEV1 ≥10% change			
Breathing parameter	**Odds ratio[#] (OR)**	**95% CI for OR**	**P-value**
Duration mean continuous	1.002	1.001-1.004	**0.010**
Duration mean continuous adjusted	1.002	0.999-1.004	0.147
Duration max continuous	1.002	1.000-1.004	**0.030**
Duration max continuous adjusted	1.001	0.999-1.003	0.289
Duration min continuous	1.002	1.001-1.004	**0.006**
Duration min continuous adjusted	1.002	1.000-1.004	0.088
Duration mean binary	1.552	0.569-4.237	0.387
Duration max binary	1.433	0.509-4.030	0.492
Duration min binary	1.076	0.378-3.064	0.890
TSI mean continuous	1.013	1.004-1.023	**0.006**
TSI mean continuous adjusted	1.011	0.999-1.022	0.069
TSI max continuous	1.011	1.002-1.020	**0.018**
TSI max continuous adjusted	1.007	0.997-1.017	0.154
TSI min continuous	1.014	1.005-1.023	**0.003**
TSI min continuous adjusted	1.013	1.002-1.026	**0.027**
TSI mean binary	1.208	0.432-3.379	0.716
TSI max binary	0.849	0.308-2.341	0.750
TSI min binary	0.798	0.279-2.281	0.671
TSE mean continuous	1.009	1.002-1.016	**0.010**
TSE mean continuous adjusted	1.006	0.999-1.014	0.103
TSE max continuous	1.006	1.001-1.012	**0.032**
TSE max continuous adjusted	1.004	0.997-1.010	0.274
TSE min continuous	1.009	1.003-1.015	**0.005**
TSE min continuous adjusted	1.008	1.000-1.017	**0.040**
TSE mean binary	1.129	0.405-3.148	0.815
TSE max binary	0.820	0.284-2.367	0.711
TSE min binary	1.473	0.502-4.327	0.477
TT mean continuous	1.002	1.001-1.004	**0.011**
TT mean continuous adjusted	1.002	0.999-1.004	0.159
TT max continuous	1.002	1.000-1.004	**0.032**
TT max continuous adjusted	1.001	0.999-1.003	0.305
TT min continuous	1.002	1.001-1.004	**0.006**
TT min continuous adjusted	1.002	1.000-1.004	0.092
TT mean binary	1.399	0.502-3.897	0.517
TT max binary	1.006	0.349-2.900	0.991
TT min binary	0.980	0.320-3.001	0.972
MTSI mean continuous	1.063	0.714-1.584	0.761
MTSI max continuous	1.045	0.706-1.547	0.824
MTSI min continuous	1.074	0.718-1.607	0.724
MTSI mean binary	4.445	1.005-19.651	**0.049**
MTSI mean binary adjusted	2.159	0.380-12.270	0.381
MTSI max binary	2.934	0.647-13.297	0.161
MTSI min binary	1.895	0.411-8.744	0.408
MPIF mean continuous	0.980	0.953-1.009	0.176
MPIF max continuous	0.980	0.953-1.008	0.153
MPIF min continuous	0.981	0.953-1.010	0.202
MPIF mean binary	0.803	0.242-2.666	0.717
MPFI max binary	0.880	0.280-2.764	0.825
MPFI min binary	1.118	0.358-3.491	0.846
RT mean continuous	1.003	1.000-1.006	0.065
RT max continuous	1.002	0.999-1.004	0.158
RT min continuous	1.003	1.000-1.006	**0.035**
RT min continuous adjusted	1.002	0.998-1.005	0.386
RT mean binary	2.344	0.788-6.967	0.124
RT max binary	2.554	0.794-8.215	0.114
RT min binary	1.732	0.443-6.770	0.426

TIM - FEV1 ≥2% change			
Breathing parameter	**Odds ratio[#] (OR)**	**95% CI for OR**	**P-value**
Duration mean continuous	0.999	0.997-1.001	0.228
Duration max continuous	0.999	0.998-1.000	0.223
Duration min continuous	0.999	0.997-1.001	0.385
Duration mean binary	1.501	1.014-2.222	**0.042**
Duration mean binary adjusted	1.496	1.006-2.224	**0.047**
Duration max binary	1.249	0.852-1.832	0.254
Duration min binary	1.686	1.141-2.492	**0.009**
Duration min binary adjusted	1.695	1.141-2.517	**0.009**
TSI mean continuous	0.999	0.994-1.004	0.800
TSI max continuous	1.000	0.997-1.004	0.861
TSI min continuous	0.998	0.992-1.004	0.461
TSI mean binary	1.212	0.821-1.789	0.333
TSI max binary	1.360	0.915-2.023	0.128
TSI min binary	1.599	1.064-2.402	**0.024**
TSI min binary adjusted	1.644	1.089-2.484	**0.018**
TT mean continuous	0.999	0.997-1.001	0.319
TT max continuous	0.999	0.998-1.001	0.282
TT min continuous	0.999	0.998-1.001	0.558
TT mean binary	1.316	0.889-1.947	0.170
TT max binary	1.254	0.852-1.846	0.251
TT min binary	1.370	0.911-2.059	0.130
MTSI mean continuous	1.087	0.985-1.199	0.097
MTSI max continuous	1.088	0.990-1.196	0.080
MTSI min continuous	1.073	0.974-1.182	0.152
MTSI mean binary	0.782	0.494-1.238	0.294
MTSI max binary	0.756	0.467-1.223	0.253
MTSI min binary	0.662	0.428-1.022	0.063
MPIF mean continuous	0.995	0.989-1.002	0.182
MPIF max continuous	0.996	0.989-1.003	0.218
MPIF min continuous	0.995	0.989-1.002	0.162
MPIF mean binary	0.553	0.337-0.909	**0.019**
MPIF mean binary adjusted	0.544	0.327-0.904	**0.019**
MPFI max binary	0.850	0.496-1.458	0.555
MPFI min binary	1.562	0.855-2.854	0.146

TIM - FEV1 ≥5% change			
Breathing parameter	**Odds ratio[#] (OR)**	**95% CI for OR**	**P-value**
Duration mean continuous	0.999	0.998-1.001	0.488
Duration max continuous	1.000	0.999-1.001	0.693
Duration min continuous	0.999	0.998-1.001	0.497
Duration mean binary	1.840	1.288-2.631	**0.001**
Duration mean binary adjusted	1.869	1.301-2.685	**0.001**
Duration max binary	1.457	1.031-2.057	**0.033**
Duration max binary adjusted	1.546	1.086-2.201	**0.016**
Duration min binary	1.565	1.099-2.229	**0.013**
Duration min binary adjusted	1.586	1.108-2.270	**0.012**
TSI mean continuous	1.002	0.997-1.006	0.477
TSI max continuous	1.001	0.998-1.005	0.385
TSI min continuous	1.001	0.996-1.006	0.690
TSI mean binary	1.261	0.890-1.786	0.192
TSI max binary	1.396	0.982-1.985	0.063
TSI min binary	1.287	0.901-1.836	0.165
TT mean continuous	1.000	0.998-1.001	0.651
TT max continuous	1.000	0.999-1.001	0.795
TT min continuous	1.000	0.998-1.001	0.673
TT mean binary	1.635	1.149-2.327	**0.006**
TT mean binary adjusted	1.635	1.141-2.342	**0.007**
TT max binary	1.461	1.035-2.061	**0.031**
TT max binary adjusted	1.530	1.077-2.172	**0.018**
TT min binary	1.218	0.851-1.744	0.281
MTSI mean continuous	1.102	0.999-1.216	0.053
MTSI max continuous	1.110	1.010-1.220	**0.031**
MTSI max continuous adjusted	1.096	0.994-1.208	0.066
MTSI min continuous	1.071	0.975-1.178	0.153
MTSI mean binary	0.854	0.552-1.323	0.480
MTSI max binary	0.819	0.517-1.296	0.393
MTSI min binary	0.808	0.535-1.222	0.312
MPIF mean continuous	0.999	0.992-1.006	0.736
MPIF max continuous	0.999	0.992-1.006	0.837
MPIF min continuous	0.998	0.992-1.005	0.619
MPIF mean binary	0.691	0.430-1.110	0.126
MPFI max binary	0.939	0.571-1.546	0.805
MPFI min binary	1.261	0.764-2.083	0.364

TIM - FEV1 ≥10% change			
Breathing parameter	**Odds ratio[#] (OR)**	**95% CI for OR**	**P-value**
Duration mean continuous	0.999	0.997-1.000	0.140
Duration max continuous	0.999	0.998-1.000	0.264
Duration min continuous	0.998	0.997-1.000	0.084
Duration mean binary	1.211	0.810-1.809	0.350
Duration max binary	1.067	0.723-1.576	0.743
Duration min binary	1.394	0.929-2.091	0.109
TSI mean continuous	1.002	0.997-1.008	0.379
TSI max continuous	1.003	0.998-1.007	0.252
TSI min continuous	1.001	0.995-1.006	0.759
TSI mean binary	0.982	0.664-1.450	0.926
TSI max binary	1.135	0.772-1.670	0.519
TSI min binary	1.066	0.712-1.595	0.756
TT mean continuous	0.999	0.997-1.001	0.187
TT max continuous	0.999	0.998-1.000	0.276
TT min continuous	0.999	0.997-1.000	0.128
TT mean binary	1.148	0.772-1.709	0.494
TT max binary	1.207	0.818-1.780	0.342
TT min binary	1.670	1.110-2.511	**0.014**
TT min binary adjusted	1.646	1.085-2.496	**0.019**
MTSI mean continuous	1.278	1.132-1.443	**0.000**
MTSI mean continuous adjusted	1.263	1.118-1.427	**0.000**
MTSI max continuous	1.263	1.124-1.419	**0.000**
MTSI max continuous adjusted	1.226	1.088-1.381	**0.001**
MTSI min continuous	1.238	1.103-1.389	**0.000**
MTSI min continuous adjusted	1.273	1.132-1.433	**0.000**
MTSI mean binary	0.824	0.489-1.387	0.466
MTSI max binary	1.034	0.608-1.758	0.903
MTSI min binary	0.919	0.567-1.492	0.733
MPIF mean continuous	1.001	0.993-1.010	0.780
MPIF max continuous	1.003	0.995-1.011	0.455
MPIF min continuous	1.000	0.992-1.008	0.987
MPIF mean binary	0.995	0.585-1.692	0.985
MPFI max binary	1.322	0.757-2.309	0.326
MPFI min binary	2.030	1.193-3.452	**0.009**
MPFI min binary adjusted	2.063	1.198-3.552	**0.009**

Odds ratio unadjusted unless otherwise stated. Since a participant could contribute several data points to the model, participant was included as a random effects in the model. Adjusted odds ratio accounts for FEV1 date matched, IV antibiotic use, and number of breathing parameter readings per day

Across a range of FEV1 decline and different breathing modes, TT minimum as a binary variable was associated with FEV1 decline though the odds ratio may not necessarily reach statistical significance. For example, TT minimum was associated with an increased odds of 22% (95% CI -15% to 74%) for ≥5% acute FEV1 decline and 37% (95% CI -9% to 105%) for ≥2% acute FEV1 decline. During episodes of pulmonary exacerbation TT would be expected to increase as a consequence of reduced breathing effort and increased rest time from coughing. Taking into account this clinical picture and the results from the logistic regression models, it makes sense to select TT minimum as the breathing parameter of interest for further testing. Clinically, an acute FEV1 decline of ≥5% would be considered relevant and worthy of

additional or a change in treatment. Therefore, the sensitivity and specificity for the ability of TT minimum as a binary variable to detect an acute FEV1 decline of ≥5% were calculated. The sensitivity, for detecting a true 5% decline in FEV1, for TT minimum in TIM was 0.091 (95% CI 0.067-0.123) and the specificity was 0.902 (95% CI 0.868-0.937), see Table 4.9. Following adjustment for clustering effect, the sensitivity was 0.097 (95% CI 0.062-0.151) and the specificity was 0.896 (95% CI 0.851-0.943). Similar results were observed in TBM with adjusted sensitivity of 0.147 (95% CI 0.054-0.399) and adjusted specificity of 0.725 (95% CI 0.515-1.021).

Table 4.9: Sensitivity & specificity results for the TT minimum variable for predicting a true 5% decline from baseline in %predicted FEV1

	TIM 703 observations N=61		TBM 94 observations N=13	
	Not clustered (unadjusted)	Clustered (adjusted)	Not clustered (unadjusted)	Clustered (adjusted)
Sensitivity 95% CI	0.091 0.067-0.123	0.097 0.062-0.151	0.264 0.178-0.393	0.147 0.054-0.399
Specificity 95% CI	0.902 0.868-0.937	0.896 0.851-0.943	0.615 0.454-0.834	0.725 0.515-1.021
LR(+) 95% CI	0.931 0.59-1.48	0.813 0.525-1.260	0.688 0.368-1.289	0.339 0.133-0.866
LR(-) 95% CI	1.01 0.96-1.06	1.025 0.972-1.082	1.19 0.854-1.671	1.33 1.023-1.727

4.4.5 Discussion

In this retrospective analysis of breathing parameters from the I-neb®, a predictive model was developed to detect an acute decline in FEV1 of ≥5% from baseline. The results showed variability in the individual breathing parameter values recorded for different nebulisations completed on the same day. Logistic regression analysis indicated Treatment Time (TT) as the most promising breathing parameter; with the minimum TT value for the day >75th centile correlating with an acute decline in FEV1 of ≥5% from baseline. Using TT minimum as a predictive test has a sensitivity of ~10% and specificity of ~90% for TIM mode, and sensitivity of ~20% and specificity of ~70% for TBM mode. However, it should be noted that the positive likelihood ratio was <1 whereas the negative likelihood ratio was >1 suggesting that the test (TT value) may not refine the pre-test odds for acute decline in FEV1 of ≥5% from baseline.[115]

When several nebulisations are done on the same day, the median, minimum, and maximum values for each breathing parameter recorded are different even if the nebulisations are done in close succession. This is not surprising since lung function (FEV1) repeated on the same

day or even in the same session can vary, hence why spirometry is done multiple times until acceptable and repeatable results are achieved.[116] Prior to this study, unlike FEV1, there were no known “normal” or “abnormal” thresholds for each breathing parameter. These thresholds have now been estimated by calculating the 25th and 75th centiles for each breathing parameter. As would be expected clinically, these thresholds differed according to baseline FEV1 values and the breathing mode used (TIM or TBM).

The logistic regression results demonstrated an association between the breathing parameter TT minimum and a range of FEV1 declines, therefore this was chosen for further evaluation. As a binary variable it allows the threshold values to be identified, with TT minimum exceeding the 75th centile being deemed as abnormal. It would be expected that people take longer to carry out a treatment if FEV1 has acutely declined and a patient is unwell, as it will be harder to breathe and there will be more rest time from coughing. Similarly, a high baseline FEV1 is an indicator of better lung health which in turn leads to lower TT since it should take less time to complete a treatment. It makes clinical sense for Treatment Time (TT) to correlate with FEV1 since TT incorporates the breathing parameters Time Spent Exhaling (TSE) and Rest time (RT). In the TIM mode, TSE and RT cannot be independently attained but the value of the TT will be affected by these measures during a nebulised treatment. As a shorter TT is a more desirable outcome reflecting better lung health, it is plausible for the minimum value to be a relevant predictor. Similarly, higher FEV1 is a desirable outcome reflecting better lung health, and the maximum value from multiple readings in a session is taken as the value representing lung health.[116]

TT minimum as a binary variable (with 75th centile of the cohort data as the threshold for a positive test) has high specificity but low sensitivity in predicting a ≥5% acute change in FEV1 from baseline. The results are similar for both I-neb® breathing modes and after adjustment for clustering. Clustering does not appear to affect the point estimates in the TIM dataset since no individual contributed more than 7% of the data, however, the standard errors are wide. For the TBM dataset, the point estimates were affected by clustering because this dataset is dominated by one participant who contributed 44% of the data.

Screening tests are widely used in medicine to assess the likelihood an asymptomatic individual in a defined population has a particular disease. Since the screening test cannot diagnose the illness “positive” subjects with an abnormal test result require further evaluation with a diagnostic ‘gold standard’ test.[117] A good screening test should be easy to perform, inexpensive, safe, readily available, and reliable or repeatable. As repeated measures can vary, even in the same subject, the differences around measures should be minimised. The

validity of the test is also important determined by the sensitivity and specificity.[118] When the sensitivity of a test is high there should be few false negatives or missed cases of the disease, and when the specificity is high there should be few false positives, hence few subjects without the disease will test positive (misclassified as having the disease) and receive unnecessary extra tests.[117] Depending on the consequences of both false positives and false negatives it is possible to alter the decision criteria of a test, by trading-off sensitivity or specificity.[117]

Human immunodeficiency (HIV) rapid self-testing is an example of a good screening test with a high sensitivity and high specificity, making it a robust test when compared to the 'gold standard'.[119] In clinical practice, not all screening tests have such impressive diagnostic accuracy yet they can still be of value and used to benefit patient care.[120] An example is the D-dimer used to screen for venous thromboembolism (VTE) which has a high sensitivity but low specificity.[121] Before using this test it is essential to assess an individual's clinical probability for VTE. The lower the clinical probability the more useful the test is to exclude VTE events. It is therefore important to determine whether a screening test can serve its role not exclusively based on its sensitivity and specificity but also on how the test is used clinically and the implications of false positives and false negatives.[122] The opposite diagnostic accuracy can be seen with glycated haemoglobin (HbA1c) as a screening test for diabetes. This has a high specificity and low sensitivity for diagnosing diabetes.[123] Despite the low sensitivity the advantage of this test is that it is minimally invasive, can easily be repeated and is convenient (does not require any fasting prior to the test and does not require multiple samples at different time points) making it a useful screening test in the right circumstances.

Using the breathing parameters automatically recorded by the I-neb® provides a unique method of predicting an acute decline in FEV1 since the screening test can be repeated several times without added burden. An alternative approach is home spirometry, but this has poor uptake.[53, 54] In using breathing parameters from the I-neb® to monitor FEV1 if a "positive" result is detected a patient can be invited to carry out the 'gold standard' spirometry to confirm or refute a diagnosis. This screening test would be of added value in clinical practice since currently FEV1 is generally measured at a routine clinic review or if a patient is symptomatic. If the I-neb® is in frequent use it would provide continual FEV1 monitoring allowing the early detection of a decline. This predictive model explored one FEV1 matched to one breathing parameter per day resulting in a low sensitivity and high specificity. If the focus looked for an abnormal reading on consecutive days this would reduce the sensitivity further. Instead to reduce the threshold for positivity if any positive result over a window was

taken this would increase the sensitivity. This concept is similar to the lateral flow test for COVID-19 which is repeated multiple times to improve its sensitivity.[124]

The CF Standards of Care state that a non-urgent course of treatment should occur within 7 working days of the planned date.[42] Following this guidance detecting an acute decline in FEV1 within 7-days would still be of clinical value. If any positive test in a 7-day window was considered relevant this would increase the sensitivity at the expense of the specificity which would somewhat decline. Since the I-neb® should be used every day there would be leeway to detect an acute change using this concept. Based on this further hypothesis in would be useful to explore this in a separate dataset and validate its diagnostic accuracy.

There were several potential limitations to the predictive model developed in this study. The derivation population sample size target was reached but was still reasonably small compared to the number of patients using an I-neb® in the single centre. Barriers to recruitment included some I-neb® models being incompatible with Insight Online, and the process to obtain data relied on patients bringing their devices for download. The set-up to gain access and receive the data was also time consuming and involved various steps. The number of available retrospective FEV1 readings was limited such that >95% of the breathing parameter data were unmatched. Although the span of the breathing parameter dates for many patients was long, not all available FEV1 readings would be matched to breathing parameters due to low nebuliser adherence. A potential strategy to increase the amount of data for analysis could be multiple imputation to either match all breathing parameters to FEV1 or ensure that all available FEV1 have a breathing parameter to match to. Multiple imputation was not performed for this study because it is uncertain how FEV1 or breathing parameters could be predicted from other available variables. By taking a complete case approach the results may be subject to bias because data are often not missing at random but at the same time the risk of introducing erroneous ‘noise’ may be reduced. The TIM mode was most commonly used by patients (n=61) with some switching between the different modes (n=13) even during the same day. Since TIM mode does not measure the TSE and RT there were very few readings recorded for these using the TBM mode which may impact on the ‘normal’ and ‘abnormal’ threshold values obtained. It had been initially considered that RT could be estimated for TIM mode making some assumptions about inspiratory and expiratory ratios, but unfortunately this is not possible since RT is subject to confounders outside of lung health such as having a break during treatment to answer a phone. The multivariate analysis did highlight some issues since some of the effect sizes were small or in the opposite direction. For example, TT minimum in TBM to detect ≥2% decline in FEV1 has an unadjusted odds ratio of 0.26 (95% CI 0.08-0.90). This indicates that a positive test was associated with a lower probability of

FEV1 decline. An odds ratio of 0.26 could suggest a large effect size, but may also be an artefact of sparse data bias.[125] Another limitation is the fact that different medications were used via the I-neb® and these medications may well have different inhalation duration. An I-neb® is unable to recognise the drug that is being nebulised. One way of controlling for this would be to do a sensitivity analysis among PwCF who are only using dornase alfa. However, most people on the I-neb® are also on inhaled antibiotics hence they are given the rapid nebuliser. With only 5/61 (8%) of the participants using a single nebulised drug there is insufficient sample size for such a sensitivity analysis in this study. To manage these limitations, the results were reviewed as a whole and clinical reasoning was applied in the interpretation. When adjusting for statistically significant results, although IV day was used as a variable it is not always indicative of a pulmonary exacerbation since in some situations IV antibiotics may be given pre-emptively to optimise lung health for example prior to a routine surgical procedure requiring a general anaesthetic. There are also scenarios where a patient is offered IV antibiotics for an exacerbation but declined.[111]

4.4.6 Conclusions

This study has developed a predictive model that may identify an acute decline in FEV1 of ≥2% from baseline using I-neb® breathing parameters. TT minimum was identified as the most promising breathing parameter, but it does have limitations. Using this to detect an acute FEV1 decline of ≥5% would be of clinical value and importantly, imposes no additional burden on the patient since it is obtained automatically when the patient takes their treatment. Further testing with a validation dataset is required to explore this test, which is the focus of Chapter 6. Having more FEV1 readings from home monitoring could add value to the validation study. The accuracy of home FEV1 readings is the focus of the next chapter (Chapter 5).

CHAPTER 5: LUNG HEALTH STUDY: MEASUREMENT ACCURACY OF HOME SPIROMETRY

This chapter explores the accuracy of home spirometry readings and considers whether they should be used in addition to hospital spirometry readings in the prospective dataset to validate the predictive model.

5.1 Introduction

The Lung Health Study set out to use home spirometry in the prospective dataset. This was to provide additional FEV1 readings to inform the predictive model validation. When the study was conducted between 2015 and 2016 there was a scarcity of literature exploring the accuracy of home spirometry in CF. Hospital spirometry is deemed the 'gold standard' measurement since it is performed under the supervision of a trained operator to optimise the quality of results, by ensuring the results obtained are acceptable and repeatable.[116] Even for hospital spirometry there may be between hospital variability if different devices are being used and there may also be discrepancies in calibration accuracy.[116] This could be an increasingly relevant issue as the number of large multicentre and multinational trials have increased over the years.[126]

In asthma and CF previous studies in children prior to 2015 had suggested that home spirometry is similar to hospital spirometry when both are directly carried out in the hospital setting.[127-129] Emerging data in 2016 reported by Peat et al. started to question the reliability of home spirometry in CF. They compared the accuracy of a handheld spirometer (COPD6, Vitalograph, UK) with a standard laboratory-based device (Spirostik, Geratherm, Germany) in 41 adult patients. All test results were performed supervised in clinic although coaching and feedback was withheld from the handheld device. The order in which the device was used was random with three manoeuvres being carried out on each. Acceptable paired results were compared in 36 patients. The mean difference was 120ml with the home device tending to under reading (95% limits of agreement -460ml to 220ml).[130] In 2017 Pedersen et al. also published data suggesting a significant but systematic difference in lung function between home and clinic spirometry. They compared the Vitalograph's handheld bluetooth lung monitor with the CareFusion Jaeger Vyntus SPIRO used as 'gold standard' in outpatient clinics. Participants in clinic were randomised in a crossover study to use the devices with an appropriate pause between the two. Results from 62 adults with CF showed a mean difference in FEV1 of -170ml (95% limits of agreement -210ml to -130ml). Not only was the home device reading lower, but the Bland-Altman plot also showed that higher FEV1 values were associated with a larger difference between the two devices.[131] Given the disparity between emerging evidence and data from pre-2015 it was considered important to analyse

the Lung Health prospective home FEV1 dataset to establish whether home and hospital spirometry measurements are clinically comparable among adults with CF in Sheffield.

5.2 Aim

To determine the agreement between unsupervised home spirometry performed within ±3 days of hospital spirometry conducted under expert supervision in adults with CF.

5.3 Methods

5.3.1 Study administration

A cross-sectional observational study using the Lung Health prospective data was conducted. Since this was a secondary analysis of the study data the sample size was pragmatic and all available data was included. The participants recruited to the Lung Health prospective study were issued a home spirometer (Vitalograph Lung monitor USB model 4000). On receipt of the device, they received an in-person demonstration of how to use and submit an FEV1 reading when requested. Home spirometry was performed unsupervised thereafter and no maintenance of the technique after the initial demonstration was conducted. Details on recruitment are described in Chapter 6. Study data collection was between June 2015 and July 2016 with participants asked to submit a FEV1 reading every 3 weeks and prior to their in-person routine clinic (i.e. minimum of 17 readings over a 1-year period). The 'gold standard' hospital spirometer (CareFusion MicroLab ML3500 MK8) was used in clinics over the same timeframe. A respiratory physiologist supervised hospital spirometry in accordance with ATS/ERS standards.[116] The highest FEV1 value from three forced manoeuvres on each device was collected. Only the hospital spirometer shows expiratory flow volume curves which can be viewed by the participant during the procedure.

5.3.2 Statistical methods

Home spirometry measurements performed within ±3 days of a clinic spirometry were paired. An *a priori* 3-day window was chosen as clinically beyond this time it is likely lung health will have changed making results incomparable. This is also in line with other studies where the window of comparison ranged from 24 hours to 7 days.[132, 133] Cross-sectional FEV1 analysis evaluated pairwise differences for each participant. To account for some participants contributing multiple paired readings the data was fitted to a random effects model using the robust option in STATA v13. The random effects modelling was performed by a statistician (MJC). To quantify inter-individual variability for those with multiple readings over time the absolute discrepancy between minimum and maximum FEV1 was calculated. The correlation in FEV1 readings between both devices was illustrated using a scatterplot. The differences

between FEV1 from each device were illustrated using a Bland-Altman plot. This was plotted with the absolute difference in FEV1 values between the devices on the y-axis and the average FEV1 values on the x-axis. The graphs were produced with SPSS v24 (IBM Corp).

5.4 Results

The Lung Health prospective study (Chapter 6) included 34 participants with 1-year follow-up data. A total of 327 hospital spirometry readings and 43 home spirometry readings were available. The median number of hospital spirometry readings was 9 (IQR 7 to 12) compared with a median of 1 (IQR 0 to 2) home spirometry readings. With 17 home spirometry readings per person per year considered as 'complete data', median data completeness was 5.9% (IQR 0 to 11.8%).

A total of 17 participants were included in the analysis since the majority recruited to the prospective study did not submit home spirometry readings within the ±3 days of clinic when asked. Baseline participant characteristics are described in the Table 5.1. The best FEV1 readings are from hospital pulmonary function tests.

Table 5.1: Baseline participant characteristics

Baseline characteristics (n=17)	
Age in years, median (IQR)	30 (27-33)
Female, n (%)	11 (65)
CFTR Genotype: Heterozygous class I-III or homozygous class IV-VI, n (%) Homozygous class I-III, n (%)	 2 (12) 15 (88)
Pancreatic insufficient, n (%)	15 (88)
CF diabetes (CFD), n (%)	7 (41)
Pseudomonas aeruginosa status: No, n (%) Intermittent, n (%) Chronic, n (%)	 3 (18) 1 (6) 13 (76)
Best FEV1%, median (IQR)	80 (65-88)
Best BMI kg/m2, median (IQR)	23.2 (20.3-24.7)
Average prescribed daily nebulised I-neb® doses median (IQR)	3 (3-4)
Total IV days, median (IQR)	14 (0-25)
Total routine clinic attendances, median (IQR)	5 (3-6)

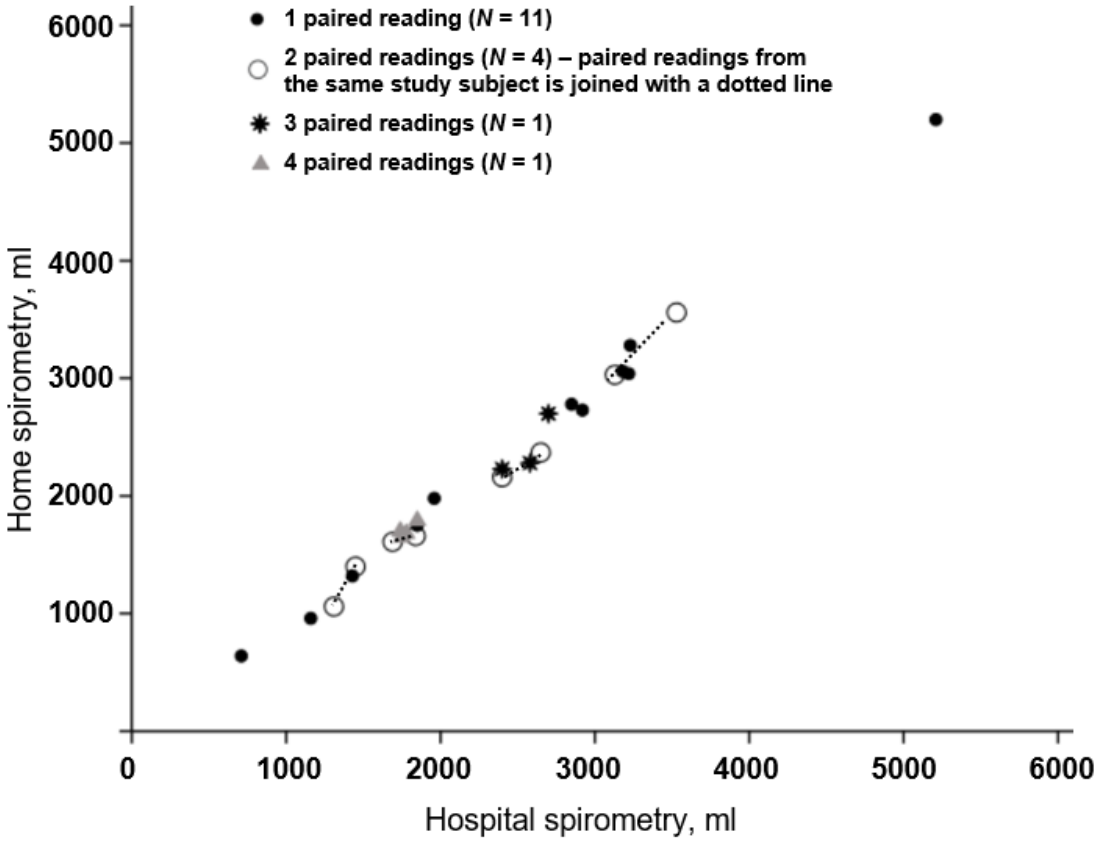
There were 26 paired readings in total with six participants having multiple paired readings on different days. Table 5.2 shows the number of individuals against the number of paired readings they provided on different days.

Table 5.2: The number of individuals with multiple paired readings over time

Number of paired FEV1 readings	Number of individuals
1	11
2	4
3	1
4	1

The scatter plot in Figure 5.1 shows a strong correlation between home and hospital spirometry, r=0.99, p<0.001.

Figure 5.1: Scatter plot of home spirometry FEV1 versus hospital spirometry FEV1



The random effects model showed a very low intraclass correlation coefficient of 0.00345, suggesting that the multiple readings from the same individual are independent. The mean difference adjusted was 0.1114 as opposed to 0.1115 for the raw unadjusted data hence the data was not affected by clustering. Since clustering has not impacted on the data, the Bland-

Altman plot used the unadjusted values (Figure 5.2). The unadjusted standard deviation was 0.0957 and the mean was 0.1115.

The mean difference between home versus hospital spirometry is -111ml (95% limits of agreement -299ml to 76ml) p-value <0.001, with the home device tending to under-read. The intra-individual differences for the multiple paired readings are displayed in Table 5.3.

Figure 5.2: Bland-Altman plot for home spirometry FEV1 versus hospital spirometry FEV1

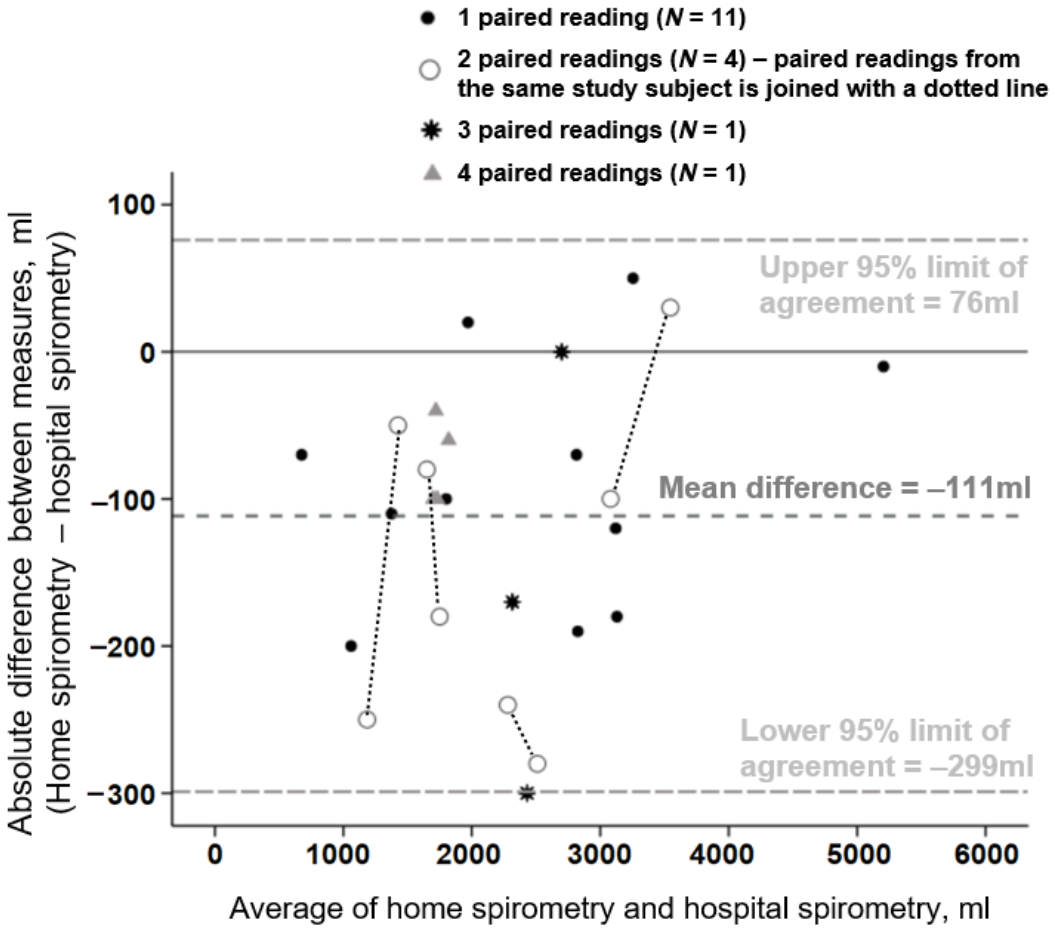


Table 5.3: The intra-individual discrepancies between the home and hospital FEV1 in participants with multiple paired readings over time

Participant	Number of paired readings	Minimum FEV1 discrepancy (ml)	Maximum FEV1 discrepancy (ml)	Absolute difference between minimum & maximum FEV1 discrepancy (ml)
1	2	-50	-250	200
2	2	30	-100	130
3	2	-240	-280	40
4	2	-80	-180	100
5	3	0	-300	300
6	4	-60	-100	40

Among the six participants with at least 2 paired readings, two of them have a discrepancy between paired readings of >150ml.

5.5 Discussion

The ATS/ERS guidelines state a minimally important clinical difference in spirometry is an FEV1 of >150ml in adults.[116] Therefore, a consistent difference of ≤150ml between the home and hospital spirometers is deemed acceptable. When comparing home spirometry against the hospital spirometry it is important to determine whether the difference between the two measures is related to the magnitude of the measurement. This analysis, albeit with a small sample size, shows that home spirometry tends to under-read compared to hospital spirometry. Although a mean difference of 111ml according to ATS/ERS standards is not deemed clinically significant, in practice this can typically equate to a >2% difference in lung function at an individual level depending on their baseline FEV1, which would be clinically relevant. Even though there appears to be a correlation with inter-individuals there is clinically significant intra-individual discrepancy making home spirometry readings unreliable.

There are two potential sources of variability when comparing the spirometry devices. One is that the home spirometry device is of less quality and might systematically under-read FEV1. The other is that individuals might use the home spirometer with variable techniques since not being supervised by a pulmonary function technician. To minimise this the aim should be to use more technically advanced portable home spirometers and perform measurements under expert supervision via a virtual video link to ensure an adequate technique as possible.

Limitations with this analysis are that the dataset is small due to very few home spirometry readings, and FEV1 readings are paired within ±3 days rather than being done on the same day which may have contributed to some variation. The home spirometry results are also unsupervised with no feedback on quality of technique from the device, and participants manually submit their data. This may lead to inaccuracies in spirometry technique and with

data inputting. The adherence to submit spirometry measurements is also low which is consistent with other home monitoring studies.[53, 54, 134]

The measure of agreement between the home and hospital spirometers obtained from the Lung Health dataset is consistent with further evidence published since the research was conducted. More recent studies exploring home spirometry in combination with symptom scores in adults and children with CF found that the accuracy of home spirometry was less clear.[53, 135] The eICE study a large RCT in adults with CF collected unsupervised home spirometry twice weekly over one year using AM2+® Lung Function Monitor (ERT). A secondary analysis paired hospital spirometry readings with the nearest home measure within 7 days in 133 participants randomised to the early intervention arm. Cross-sectional comparison found that the difference in spirometry was variable but that the home devices systematically under-read on average by 70ml (95% limits of agreement -972ml to 832ml). There was also no improvement over time suggesting that experience using a device did not improve the bias.[132] A one-year observational study in children with CF and asthma (36 with CF and 81 with asthma) compared spirometry carried out at home using the AM2+ (CareFusion, Houten, The Netherlands) with that done in hospital on the same day using Masterscreen^{TM} Pulmonary Function Testing Unit (Pneumotachograph, Vyaire Medical, Houten, The Netherlands). They concluded that the home FEV1 measurements were significantly lower than those done under supervision in hospital. Suggesting that the spirometry technique unsupervised at home may affect the results. In CF the FEV1 mean difference was -180ml (95% limits of agreement -270ml to -80ml), p-value <0.001.[136] This is probably not surprising since lung function tests are highly effort-dependent. This study also indicated an absence of a learning effect in multiple measurements performed by the same individual over time. The CLIMB-CF study carried out in children with CF collected home spirometry (Vitalograph BT spirometer) twice a week over six months. They paired clinic spirometry with unsupervised home spirometry done on the same day or one day on either side from 67 participants. The results again highlighted the unreliability of home spirometry carried out unsupervised at home but that the bias was lower in older participants. This study showed that the values from the two devices did correlate r^2=0.85, p<0.001 but that there was substantial bias with home devices under reading (mean+/-SD difference between clinic and home FEV1 6.5%+/-8.2% with wide 95% limits of agreement -9.6% to 22.7%).[137] Bell et al. compared home spirometry results observed and unobserved. They recruited 74 adults with CF to use either Air-Next^{TM} (NuvoAir) or Spirohome^{TM}. Participants were asked to perform a measure within 24 hours prior to clinic and then remotely in clinic supervised by a respiratory scientist. Paired FEV1 from 53 adults showed a mean difference of 0.7ml, however, the 95% limits of agreement (-220ml to 220ml) for the same adult on separate

occasions (observed versus unobserved) were wide and exceeded the ATS/ERS repeatability criteria. In this study, there was also no ‘gold standard’ clinic spirometer making the results more difficult to interpret.[133] Table 5.4 summarises CF home spirometry validation studies in more detail.

Table 5.4: Summary of CF home spirometry validation studies

Study Author, year	**Participants N, Age (years), FEV1(%predicted)**	**Home spirometer device**	**Comparator spirometry device**	**Time between device readings**	**Home device supervised/ unsupervised**	**Outcomes Mean difference (limits of agreement)**
Bastian-Lee, 2002 [127]	N=20 (CF 16, Asthma 4) Age median 8.5 range (7-13) FEV1 mean 80.8 range (56-126)	Clement Clarke VM Plus spirometer	Jaeger Masterscreen spirometer	Same time with devices connected in series to reduce variation	Supervised	80ml (-30ml to 190ml) Combined CF & asthma participants
Peat, 2016 [130]	N=41 Acceptable paired=36 Age mean 39 SD 11.4 FEV1 mean 60 SD 23	COPD6, Vitalograph, UK	Spirostik, Geratherm, Germany	Same time	Supervised (no coaching & feedback)	-120ml (-460ml to 220ml)
Haugen, 2018 [138] (Pederson, 2017 [131] abstract initial data)	N=63 Age mean 28 range (18-50) FEV1 mean 75 range (19.7-114.7)	Vitalograph model 4000 lung monitor (40750)	CareFusion Jaeger Vyntus SPIRO	Same time	Supervised	-170ml (-210ml to -130ml)
Avdimiretz, 2019 [139]	N=76 Acceptable paired=73 Age median 13 range (6-17)	Micro Loop Spirometer (CareFusion)	Vmax Encore System	Same day	Supervised	-65ml (189 to -319ml)
Gerzon, 2020 [136]	N=36 Acceptable paired readings=86 Age mean 9.4 SD 2.8 FEV1mean 87.3 SD 17	AM2+ (CareFusion, Houten, The Netherlands)	Masterscreen™ Pulmonary Function Testing Unit (Pneumotachograph, Vyaire Medical, Houten, The Netherlands)	Same day	Unsupervised	-180ml (-270ml to -80ml)

Study Author, year	Participants N, Age (years), FEV1(%predicted)	Home spirometer device	Comparator device	Time between device readings	Home device supervised/ unsupervised	Outcomes Mean difference (limits of agreement)
Paynter, 2021 [132]	N=133 Age mean 27 SD 12 FEV1 78.9 SD 22	AM2+® Lung Function Monitor (ERT)	Hospital spirometer	+/- 7 days	Unsupervised	-70ml (-972ml to 832ml)
Bell, 2021 [133]	N=74 Acceptable paired=53 Age mean 37+/-11 FEV1 59 (21-108)	Unobserved Air-Next™ (NuvoAir) or Spirohome™	Observed Air-Next™ (NuvoAir) or Spirohome™	24 hours	Unsupervised vs supervised	-0.7ml (-220ml to 220ml)
Barry, 2021 [140]	N=40 Adults	Mir Spirobank Smart	Hospital spirometer	Same time	Supervised	Mean +/-SD -72ml +/-110ml
Berlinski, 2021 [141]	N=52 Acceptable paired=12 Age 12.7 +/-4 FEV1 100 +/-17	Home spirometer	Hospital spirometer	Same day	Supervised	Median (IQR) -155ml (-275ml to -88ml)
Berlinski, 2021 [141]	N=52 Acceptable paired=34 Age 12.7 +/-4 FEV1 100 +/-17	Home spirometer Uncoached	Home spirometer Coached	5 days	Unsupervised vs supervised	Median (IQR) -25ml (-93ml to 93ml)
Edmondson, 2022 [137]	N=67 Age median 10 IQR 7-14	Vitalograph BT spirometer	Hospital spirometer	Same +/-1 days	Unsupervised	Mean +/-SD 6.5% +/-8.2% (-9.6% to 22.7%)

When supervised the quality of the home spirometry technique can be improved which may provide more reliable and consistent measures. Long et al. explored the impact of a Respiratory Physiologist-led virtual spirometry session in adults with CF using MIR Spirobank® portable spirometer. They used ATS grading and found that without coaching only 37% of patients provided a grade A or B spirometry but that this increased to 76% with the online coaching sessions.[142] This was also demonstrated in children with CF by Fettes et al. using the NuvoAir home spirometer. They randomly allocated 61 patients to supervised or unsupervised spirometry following a detailed training session. The supervised group had significantly more quality factor grade A spirometry compared to the unsupervised group (89% vs. 74%; $p<0.001$).[143] Similarly, home spirometers that provide feedback to patients were found to result in good-quality standards.[144]

Research interests in home spirometry in CF had been increasing as new technology emerged and there was a need to improve access, quality of care, and lower the burden for patients and their families. This accelerated when the COVID-19 pandemic struck in early 2020 forcing centres to implement remote home spirometry. This coincided with the wider introduction of highly efficacious CFTR modulators. Now there is a drive in the post COVID and post modulator era to explore new ways of working including the use of home spirometry. Despite this, it is important to consider all the evidence to date highlighting the lack of precision with home spirometry compared to hospital spirometry. In research, FEV1 is an important physiological endpoint for many clinical studies.[145] If home spirometry is used this may give inaccurate results meaning that larger sample sizes are required to achieve a similar statistical power to studies using hospital spirometry. In studies using both home and hospital spirometry due to the discrepancy between results, these readings may not be interchangeable. In clinical practice, home spirometry replacing hospital spirometry may also mean that subtle declines in FEV1 are missed. This could lead to false reassurances and a failure to initiate necessary treatments to maintain lung health. Alongside the long-term outcomes, it is also important to consider the acceptability and adherence to home spirometry measures which may not make this a cost-effective option.

5.6 Conclusions

This study provides further supportive evidence that home spirometry is clinically unreliable and tends to under-read when compared to the 'gold standard' hospital spirometry, particularly when the home spirometry performed is unsupervised. With the emerging evidence that home FEV1 is not necessarily comparable to hospital FEV1, the decision was taken to not include the Lung Health prospective home FEV1 readings in the predictive model validation in the next chapter (Chapter 6).

CHAPTER 6: LUNG HEALTH STUDY: VALIDATION OF THE PREDICTIVE MODEL

This chapter describes how the Lung Health predictive model was refined and validated using an internal prospective dataset.

6.1 Introduction

In Chapter 4 a predictive model was developed to detect an acute decline in FEV1 using a retrospective dataset, in 61 individuals with 797 data points, of I-neb® breathing parameters and hospital FEV1 readings. A single breathing parameter: Treatment Time (TT) minimum (i.e. the lowest reading recorded in a day when multiple nebulisations were performed) was identified as the most promising breathing parameter to predict an acute decline in FEV1 of ≥5% from baseline. The threshold for a positive test was identified for TT minimum which varied according to a patient's baseline FEV1 %predicted and the I-neb® mode used. Based on a pattern that emerged from regression analysis and exercising clinical judgement in the interpretation of results, a test result was considered 'positive' when the TT minimum reading was >75th centile of the group result. Used as a screening test the sensitivity was low (~10% TIM, ~20% TBM), and the specificity was high (~90% TIM, ~70% TBM), with similar diagnostic accuracy for both I-neb® modes.

It is clinically reasonable to detect an FEV1 decline within 7 days of the decline occurring because the CF Trust recommends starting IV antibiotics within 7 days.[42] Therefore, in this chapter, the predictive model was validated using a ±7-day window detection period. Given the low sensitivity of the breathing parameter in a ±3-day window, it may be possible that a ±7-day window with a corresponding increase in the number of daily breathing parameters can increase the sensitivity of the test. Refinement of a prediction model prior to validation in a separate dataset has been done for other diagnostic tests. For example in the T-MACS decision aid, two out of the seven variables were removed following testing in the derivation dataset.[146] In this Lung Health study, a retrospective dataset was used to select the appropriate breathing parameter and determine the threshold for a positive test. On clinical grounds, the method of applying the test was refined. First, a ±7-day window is reasonable in clinical practice (instead of using a ±3-day window to ensure the calculated thresholds are more precise in the retrospective dataset). Second both breathing modes (TBM and TIM) were combined as a single test (instead of both datasets being analysed separately to determine the appropriate thresholds in the retrospective dataset).

One of the limitations of the retrospective dataset in the development of the predictive model was the lack of FEV1 readings leading to a smaller number of available events. It was

originally planned that additional FEV1 measures could be obtained in a prospective dataset using home spirometry alongside hospital spirometry. Chapter 5 describes the potential inaccuracy of home spirometry and the challenges of obtaining data. Based on these results a decision was made not to include the home spirometry FEV1 results in the validation dataset.

6.2 Model validation using the prospective dataset

6.2.1 Aim

To validate the predictive model developed in Chapter 4 using an internal prospective dataset.

6.2.2 Objectives

1. To determine the sensitivity of breathing parameter TT minimum in detecting an acute FEV1 decline of ≥ 5% within a ±7-day window.
2. To determine the false positive rate of the TT minimum test (which is equivalent to 1 – specificity).

6.2.3 Methods

This is a prospective observational study to validate the predictive model for acute FEV1 decline of ≥5%. The development dataset in Chapter 4 identified TT minimum as the most promising breathing parameter variable to predict a ≥5% acute FEV1 decline from baseline.

Source of data

Prospective observational data was collected from the same single adult CF centre as the retrospective data. The following steps describe how the prospective breathing parameter data were obtained, processed, and organised into a suitable format for analysis alongside the FEV1.

<u>Obtaining the raw breathing parameter data & demographic data</u>

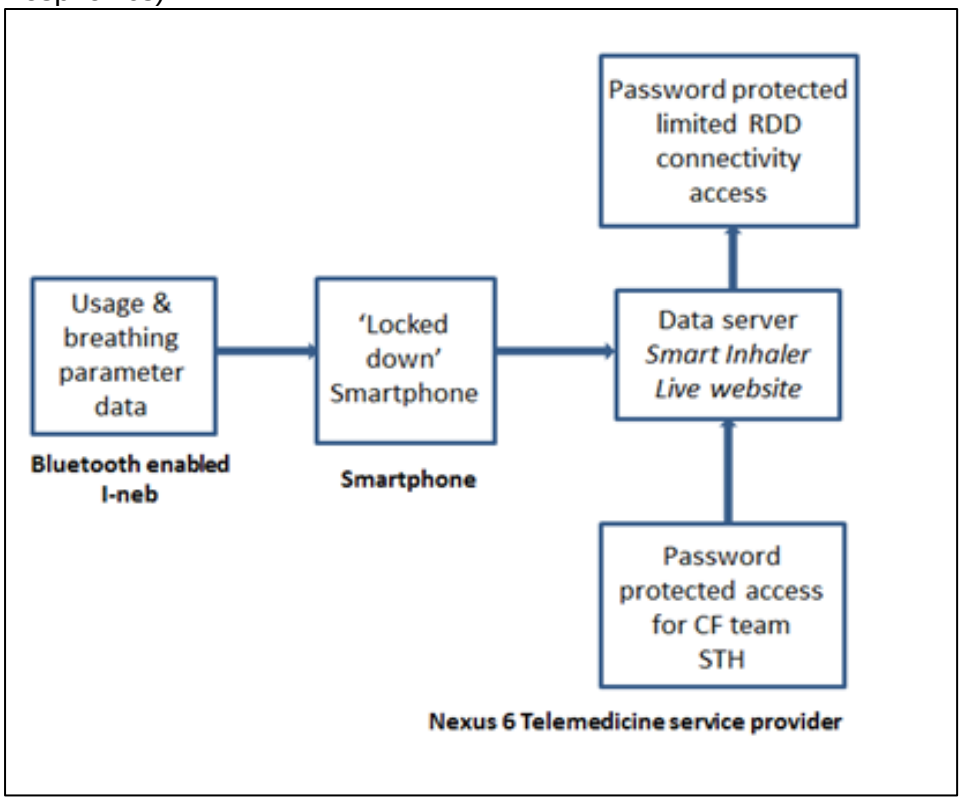
The initial setup was carried out by a Philips Respironics Respiratory Drug Delivery (RDD) trained home healthcare worker in the participant's home. Participants had their existing I-neb® (post-2008 model, or if older were provided with a new I-neb® device) converted to a Bluetooth-enabled investigational I-neb® (Bi-neb). The conversion involved re-assembling the nebuliser by permanently attaching a “Bluetooth Bridge” between the I-neb® body and its base (battery compartment cover). This adjustment was discussed with the MHRA (Medicines and Healthcare products Regulatory Agency) who agreed that the Bi-neb could be used in the study since the adaptation did not affect the usual function of the CE (Conformité Européene)

marked I-neb® device and it was only being used as an investigational device in a single centre.

A Samsung smart-phone was used as a hub to receive data from the Bi-neb and transmit this to a data server. The smart-phone was kept permanently on its charger and was 'locked down' so it had no conventional mobile phone functionality. The Bluetooth range was 100 metres and if the GSM (Global System for Mobile communication) reception within a participant's home was poor the data could be sent over WiFi to their own broadband modem or router to be forwarded to the server via the internet. Bi-neb data was automatically extracted and uploaded once a day when the device was in range and in use. If this was interrupted, data was stored on the device and retrospectively uploaded the next time it was in range and turned on.

The uploaded breathing parameter data was stored in a secure server infrastructure based on Nexus6's *Smart Inhaler Live* web-accessed database. I-neb® data was pseudonymise linked to the participant. This could then be accessed by the CF clinical team from the password-protected website. The RDD team also had limited access to the data during the study to monitor connectivity and manage any technical issues. Figure 6.1 shows an overview of the Bi-neb data transfer process.

Figure 6.1: Overview of Bi-neb data transfer (Modified image from Tim Spencer Philips Respironics)



The demographics for each participant were collected (at the time of recruitment: age, gender, CFTR genotype, co-morbidities (pancreatic insufficiency, CF diabetes), *Pseudomonas aeruginosa* status as defined by the Leeds criteria[105], from the preceding year: the best FEV1 and BMI (as described in Chapter 4), total IV days, and total routine clinic appointments attended, and the average daily prescribed nebuliser doses).

'Cleaning' the raw breathing parameter data

The extended breathing parameter data for each participant was downloaded directly from the *Smart Inhaler Live* platform as an Excel® spreadsheet. The breathing parameter data format was the same as the retrospective data in Chapter 4; with breathing parameters available for every dose of nebuliser used, which was date and time stamped. The data for each individual was combined into a single Excel® spreadsheet for further processing. The TIM (Target inhalation mode) and TBM (Tidal breathing mode) data were initially separated until they could be later adjusted using the thresholds determined in Chapter 4.

Corresponding FEV1 data for the breathing parameter data

For each participant, all hospital FEV1 readings recorded over the time period of the breathing parameter dataset were collected. The FEV1 volume was obtained from the electronic patient record and converted to the percentage predicted using the GLI equation as described in Chapter 4. Home spirometry readings were initially collected but these were later discarded following the results from Chapter 5 which suggested that these were less accurate and could not be reliably compared to hospital spirometry readings. Baseline FEV1 readings were paired with each breathing parameter in the same way as that described in Chapter 4.

All available hospital FEV1 readings were used in the validation dataset. These were paired to corresponding breathing parameters using a ±7-day window approach. The day of the FEV1 reading was classed as day 0. On either side of this 7-day period, all available breathing parameters were linked to the single FEV1 reading. This resulted in up to 15 days of breathing parameter data being linked to an FEV1 reading. This is displayed in the diagram shown in Figure 6.2.

Figure 6.2: How FEV1 reading linked to breathing parameters in a ±7-day window

Day	D-7	D-6	D-5	D-4	D-3	D-2	D-1	D0	D+1	D+2	D+3	D+4	D+5	D+6	D+7
FEV1								**FEV1 reading**							
Breathing Parameter Result	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Participants

Participants were recruited from the Sheffield Adult CF Centre between May 2015 to April 2016 until the targeted sample size was reached. All eligible patients were invited to take part if they fulfilled the inclusion criteria in Table 6.1. Participants who had contributed to the retrospective Lung Health study were able to also take part in the prospective study as this occurred after the completion of the retrospective study. A study information sheet and cover letter from the clinical team were initially sent out to all potential participants in advance. They were then asked in person at a routine clinic visit by the team if they wished to take part. At this point, any questions were answered and they were given further time to decide if necessary. If they agreed they then completed a consent form. Patients were made aware they did not have to take part and could withdraw their consent at any part of the study without reason and with their ongoing clinical care and relationship with the clinical team being unaffected. They were informed that their data was confidential and would be pseudoanonymised. If participants chose to withdraw then information collected with consent remained in the study, but no further information was collected, unless the participant chose to completely withdraw their data. Ethical approval for the study was obtained from the Yorkshire & the Humber, South Yorkshire Research Ethics Committee, NHS Health Research Authority (15/YH/0131), and research and development approval was received from Sheffield Teaching Hospitals NHS Foundation Trust (STH18185).

Table 6.1: Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
• Confirmed diagnosis of cystic fibrosis via genetic testing • Aged 16 or above • Using inhaled mucolytics or antibiotic treatments via an I-neb® for all or part of their treatment • Capacity to give informed consent	• Post lung transplant • On the active transplant waiting list • If pregnant (due to the variability of lung function during pregnancy) • Palliative end stage of life • If using inhaled treatments with no objective adherence measure

Following recruitment, the RDD-trained home healthcare worker arranged a home visit with the participant to set up their Bi-neb. Participants were also given a home spirometry device (Vitalograph Lung monitor USB model 4000) which they were shown to use. They were asked to carry out readings once every 3 weeks and before a clinic appointment. Since the home spirometry device could not automatically transfer results, these had to be manually recorded by participants and submitted to the CF clinical team by secure nhs.net email. Participants were also asked to bring the home spirometer with them to clinics to check the validity of the results against the hospital spirometer. The study period follow-up for each participant was at

least 12 months to account for the impact of seasonality, and funding constraints meant that longer follow-up was not feasible.

Outcome

The outcome of interest based on the results from Chapter 4 (development of a predictive model) was an acute decline in FEV1 of ≥5% from baseline FEV1 %predicted (binary outcome).

Predictors

The sole predictor identified from the development stage was the breathing parameter TT minimum. Taking into account the baseline FEV1 %predicted, a result >75th centile of the retrospective dataset was deemed a 'positive' test, and a result ≤75th centile was deemed a 'negative' test (binary predictor result).

Sample size

A prospective power calculation was not performed since the potential sensitivity and specificity of the breathing parameters were unavailable during the planning stage of the study. It was pragmatically deemed that 50 participants may be sufficient to validate the predictive model, which is in accordance with the rule of thumb that at least 100 events and 100 non-events are required for validating a prediction model.[147] It would be anticipated that 50 participants would have at least 100 events of FEV1 decline ≥5% in the 1-year follow-up, thus reaching the 100 events required.[111]

Missing data

Incomplete doses were removed and Out of Angle (OOA) breathing parameter readings were retained, in the same way as the retrospective dataset was processed in Chapter 4. During a ±7-day FEV1 window, days with missing breathing parameter data were considered to be 'negative' (i.e. did not suggest FEV1 decline ≥5%).

Differences in the analysis methodology between the development and validation datasets

There are differences in the way the diagnostic accuracy was determined in the prospective dataset compared to the retrospective dataset. Based on the result in Chapter 4 which showed low sensitivity of the diagnostic test and from further information from extant literature which suggested that a 7-day window is clinically reasonable for matching, a decision was made to use a ±7-day window to determine if this improved the sensitivity of the diagnostic test. An important difference in the purpose of the model development and model validation

is that the threshold for a positive test was determined in the model development. This requires a more precise estimate of the threshold, hence a shorter window for matching seemed advantageous. This is less important once the threshold has been determined and the diagnostic test with a pre-determined threshold simply needs to be used in a clinical setting. In the validation setting, it seems beneficial to use a longer window to determine if the sensitivity of the test improves, as long as it is clinically reasonable to do so.

The difference in purpose between model development and model validation also drove two other important methodological differences. First, the TIM and TBM datasets were analysed separately for model development so that the thresholds for each breathing mode could be determined with precision. Once the thresholds have been determined, the TIM and TBM dataset could be combined for model validation because clinically the same individual could switch between breathing modes even on the same day. It should be noted that results from Chapter 4 (development of a predictive model) showed a similar diagnostic accuracy for TIM and TBM. Second, an FEV1 reading could only be used for model development if it was matched to a breathing parameter so that the relevant threshold can be determined. For model validation, it is possible to use an FEV1 reading that was not matched to any breathing parameter because the test was assumed to be 'negative' if there was no corresponding breathing parameter.

The Figure 6.3 shows how the ±7-day window was used to determine a 'positive' test. During the ±7-day window, any 'positive' breathing parameter result (i.e. >75th centile of the retrospective dataset value after adjustment for baseline FEV1 %predicted) would identify as a 'positive' test. Where there was no breathing parameter data on any single day, it was assumed that the day was 'negative'. This method also meant that a single breathing parameter datum could potentially be linked to >1 FEV1 readings, depending on the interval between FEV1 readings. In the example (Figure 6.3), the 'positive' breathing parameters on days -2 and +7 for the first FEV1 reading are also linked to the second FEV1 reading because of a short interval (3 days) between those two different FEV1 readings. In the data flow diagram (Figure 6.4) of the results, the term 'overlapping dates' was used to denote the number of days with breathing parameter data linked to >1 FEV1 reading.

Figure 6.3: How the ±7-day detection window is used to link breathing parameter data to FEV1 readings

Day of FEV1 reading 1	D-4	D-3	D-2	D-1	**FEV1 reading**	D+1	D+2	D+3	D+4	D+5	D+6	D+7			
Breathing Parameter Test Result	-	-	+	-	-	-	-	-	-	-	-	+	-	-	-
Day of FEV1 reading 2	D-7	D-6	D-5	D-4	D-3	D-2	D-1	**FEV1 reading**	D+1	D+2	D+3	D+4	D+5	D+6	D+7

Statistical analysis methods

The prospective breathing parameter TT minimum readings were converted to a binary variable using the thresholds determined in the retrospective dataset taking account of the baseline FEV1 %predicted and I-neb® mode used (i.e. 'positive' test result if >75th centile of the threshold, 'negative' test result if ≤75th centile of the threshold). The FEV1 %predicted readings were converted to a binary outcome (≥5% decline or <5% decline) by subtracting each reading from its baseline FEV1 %predicted (for example baseline FEV1=70%, FEV1 reading=63%, decline in FEV1 70%-63%=7%). Baseline FEV1 %predicted is the highest FEV1 reading in the 12-month period preceding each FEV1 reading.

Only participants with breathing parameter data duration ≥1 year were included in the full analysis. The start point of the follow-up was the first date with Bi-neb breathing parameter data, and all included participants had data uploaded to *Smartinhaler Live* (determined as the last Bi-neb contact with the smart-phone hub) at least 12 months after the first breathing parameter datum.

Appropriate descriptive statistics were presented, including the extent of missing data and the number of 'positive' and 'negative' tests cross-tabulated to 'positive' (FEV1 decline ≥5%) and 'negative' (FEV1 decline <5%) events. The diagnostic accuracy values for the test were calculated in the same way as in Chapter 4, including adjustment for clustering effect using a random effects model since participants contributed varying amounts of data. The random-effect modelling was performed by a senior statistician (MJC).

The following exploratory analyses were also carried out to better understand the relationship between breathing parameters and acute FEV1 decline: re-calculating the diagnostic accuracy values by only using 318 FEV1 readings with matched breathing parameter data, re-calculating the diagnostic accuracy values using breathing parameters only on the day of FEV1 reading or within a ±3-day window, and comparing Out of Angle (OOA) breathing

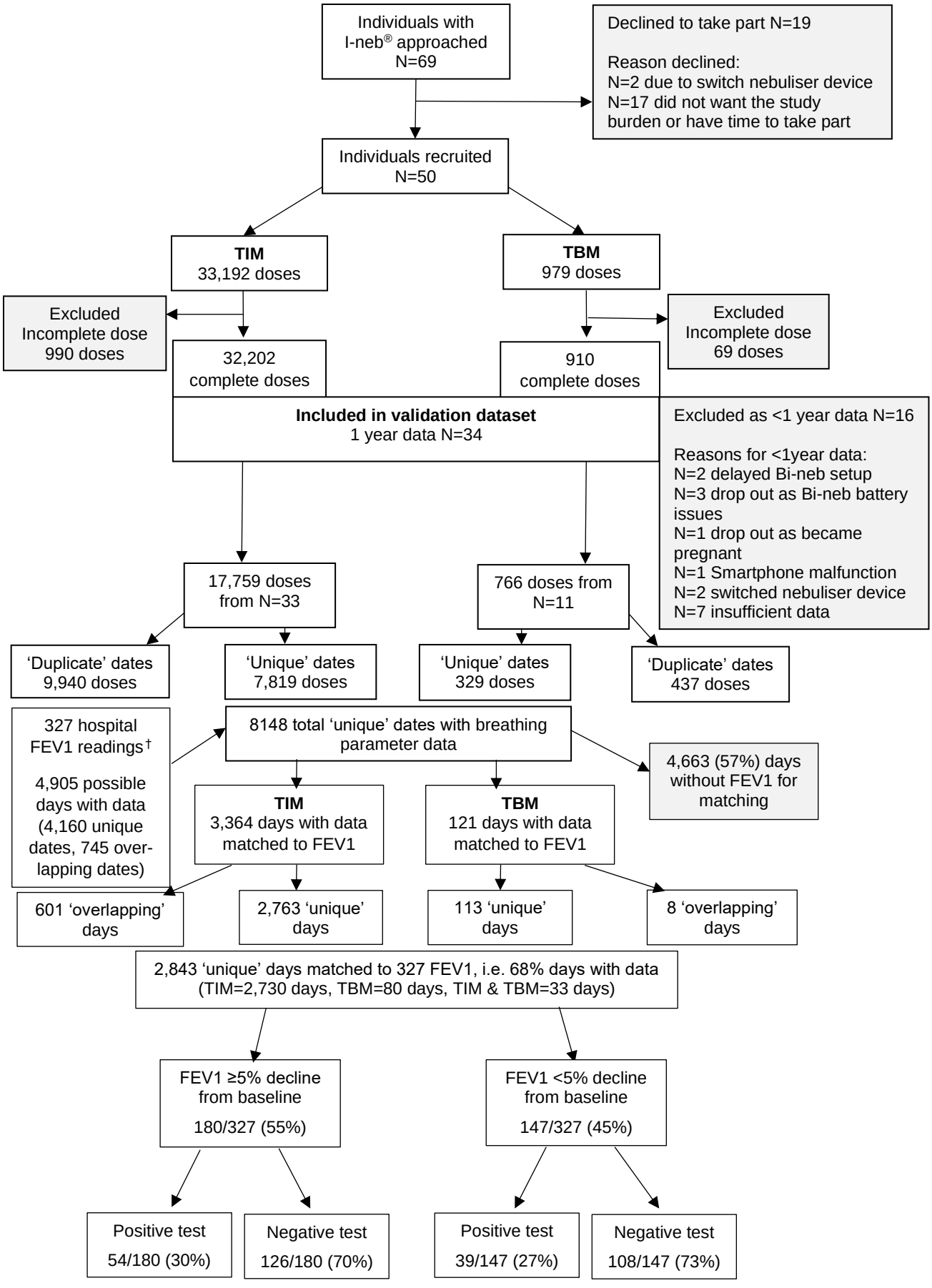
parameter data with in angle data. All statistical analyses were performed using SPSS v24 (IBM Corp) except the calculations of diagnostic accuracy were performed using STATA v13.

6.3 Results

Fifty participants were recruited to the prospective study over the course of a year: 48 of these participants had also contributed to the retrospective study although that dataset was from a different time period. Only 34 participants completed the 1-year follow-up and were included in the full data analysis. The participant flow diagram (Figure 6.4) highlights the reasons why 16 participants failed to complete the study. The majority had breathing parameter data for <1 year.

Of the 34 participants included, 33 used the TIM and 11 used the TBM since an individual can switch between Bi-neb modes. The majority of the breathing parameters are therefore from the TIM=17,759 doses, compared to TBM=766 doses. All 327 hospital FEV1 readings were used in the analysis: of these 9 had no breathing parameters matched during the ±7-day window, resulting in a 'negative' test result being imputed. There were 4663 days (57% of the data) with breathing parameter data but without an FEV1 reading for matching. The 327 FEV1 readings had 4,160 'unique' dates in a ±7-day window but were only matched to breathing parameters for 2,843 days (68%).

Figure 6.4: Prospective participant flow diagram



† Each FEV1 datum was matched to breathing parameter data from day –7 to day +7 of the FEV1 i.e. each FEV1 datum could be matched to 15 days of breathing parameter data. Hence there were 4,905 possible days with breathing parameter data from 327 FEV1 data points. However, some of the FEV1 were measured within ±7 days of each other, resulting in a breathing parameter being matched to >1 FEV1 datapoint, which we termed 'overlapping' days.

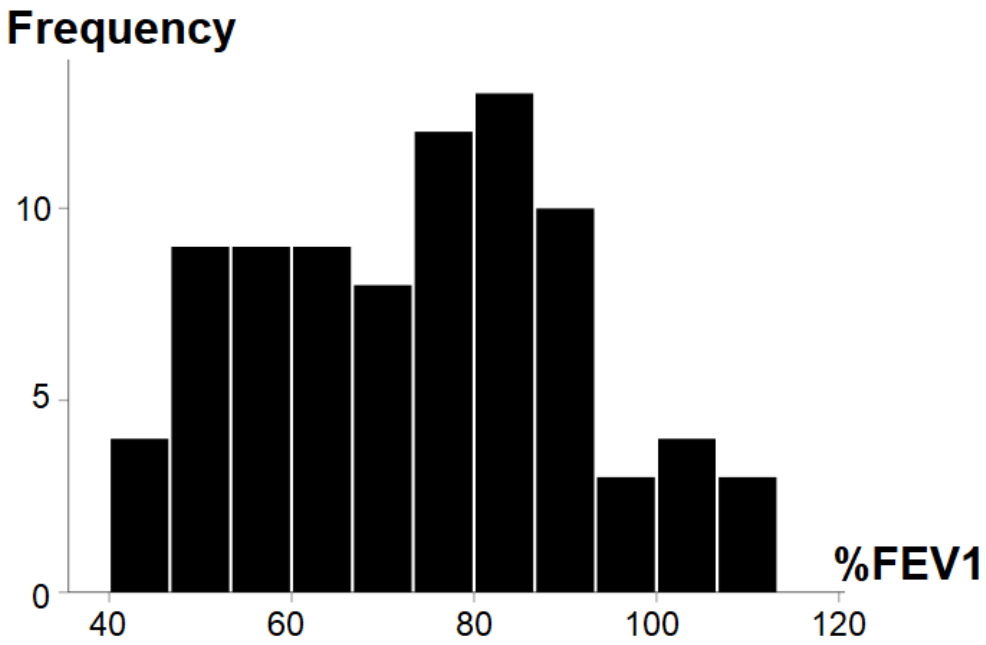
Baseline demographics displayed in Table 6.2 were similar to Chapter 4 as the participants who contributed prospective data also provided data in the retrospective study. Participants were predominately young (median age 26 years), chronically colonised with Pseudomonas and had a high median FEV1 %predicted of 79.5%. Even though the prospective study follow-up only spanned over 12 months participants still had multiple baseline FEV1 %predicted readings.

Table 6.2: Baseline demographics

Prospective study demographics at recruitment (n=50)		
	n=34 Included in analysis	**n=16 Not included in analysis**
Age in years, median (IQR)	26 (23.3-32.8)	28.5 (20-32.3)
Female, n (%)	17 (50)	10 (63)
CFTR Genotype: Heterozygous class I-III or homozygous class IV-VI, n (%) Homozygous class I-III, n (%)	 6 (18) 28 (82)	 3 (19) 13 (91)
Pancreatic insufficient, n (%)	29 (85)	15 (94)
CF diabetes (CFD), n (%)	7 (21)	3 (19)
Pseudomonas aeruginosa status: No, n (%) Intermittent, n (%) Chronic, n (%)	 4 (12) 3 (9) 27 (79)	 1 (6) 0 (0) 15 (94)
Best FEV1% in preceding year, median (IQR)	79.5 (60.5-90)	80.5 (54.8-88.3)
Best BMI kg/m2 in preceding year, median (IQR)	23.1 (20.7-24)	21.3 (19.7-25)
Average prescribed daily nebulised I-neb® doses median (IQR)	3 (3-3.8)	3 (3-4)
Total IV days in preceding year, median (IQR)	14 (0-24)	11 (0-24.5)
Total routine clinic attendances in preceding year, median (IQR)	5 (3.3-6)	4 (3-5)

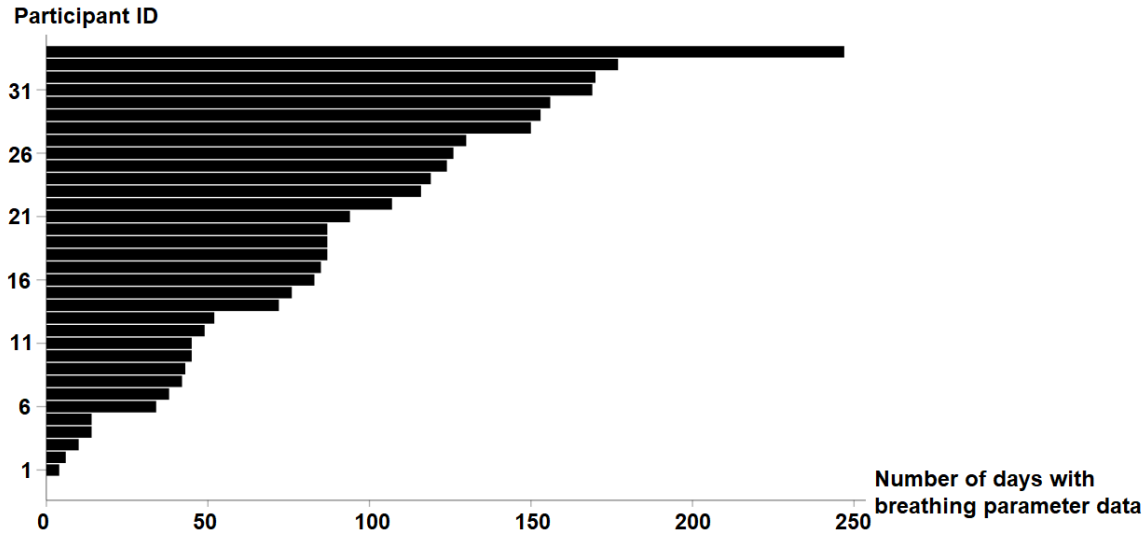
The histogram (Figure 6.5) shows that there were 84 different baseline FEV1 %predicted readings for the 34 participants.

Figure 6.5: Histogram for baseline FEV1 %predicted readings for each participant



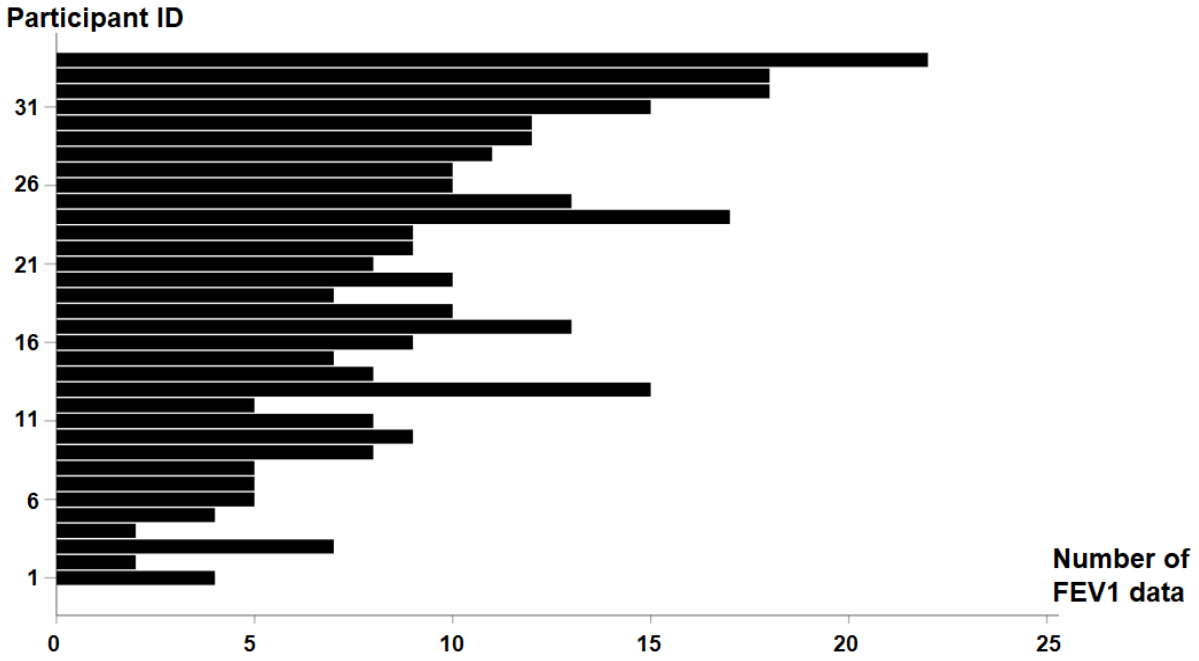
The waterfall diagram (Figure 6.6) shows the number of days with breathing parameter data per participant over the 12-month follow-up. There was variability in the amount of data supplied by each participant, ranging from 4 days to 247 days with breathing parameter data.

Figure 6.6: Waterfall diagram showing the number of days with breathing parameter data



The waterfall diagram (Figure 6.7) shows the number of hospital FEV1 readings for each participant. This ranged from 2 FEV1 readings to 22 readings.

Figure 6.7: Waterfall diagram showing the number of hospital FEV1 readings



Over the 12-month study period, there were 180/327 (55%) acute FEV1 declines ≥5% from baseline. Since participants contributed different amounts of data the diagnostic accuracy values were adjusted for clustering. Despite this the unclustered and clustered diagnostic accuracy results were similar. The sensitivity of the I-neb® breathing parameter in detecting acute FEV1 decline ≥5% (Table 6.3) was 0.31 (95% CI 0.20-0.49) and the specificity was 0.68 (95% CI 0.57-0.83).

Table 6.3: Diagnostic accuracy of the test adjusted for clustering

	Estimate 327 FEV1 readings (N=34)
Sensitivity (95% CI)	0.31 (0.20– 0.49)
Specificity (95% CI)	0.68 (0.57-0.83)
Positive predictive value (95% CI)	0.56 (0.45-0.69)
Negative predictive value (95% CI)	0.49 (0.42-0.56)

Exploratory analysis

Analyses repeated using 318 FEV1 readings with matched breathing parameter data

In the main analysis, all available 327 FEV1 readings were utilised and days without breathing parameter data were assumed to return a 'negative test'. This may reduce the sensitivity of using breathing parameters as a diagnostic test, especially if nebuliser adherence is low. To explore the potential impact of including FEV1 readings without any matched breathing parameter data, the analysis was repeated excluding the 9 FEV1 readings without any matched breathing parameter data.

Among the 318 FEV1 readings with corresponding breathing parameter data, 173 (54.4%) showed decline ≥5% from baseline %predicted. Of those 173 FEV1 declines ≥5%, TT minimum was only able to detect 54 (31.2%) of those events. Of the 93 positive tests, 39 (41.9%) were false positives. The clustered diagnostic accuracy results (sensitivity 0.34, 95% CI 0.22 – 0.53) are similar to the results of the main analysis using all available 327 FEV1 readings (sensitivity 0.31, 95% CI 0.20 – 0.49), see Table 6.4. Therefore, there was minimal impact from including FEV1 readings without any matched breathing parameter data.

Table 6.4: Diagnostic accuracy adjusted for clustering with 318 FEV1

	Estimate 318 FEV1 readings (N=34)
Sensitivity (95% CI)	0.34 (0.22– 0.53)
Specificity (95% CI)	0.68 (0.57-0.83)
Positive predictive value (95% CI)	0.56 (0.46-0.69)
Negative predictive value (95% CI)	0.50 (0.40-0.63)

Analyses repeated by matching FEV1 readings with breathing parameters only on the day of FEV1 reading or within a ±3-day window

In the main analysis, the FEV1 readings were matched to breathing parameter data in a ±7-day window. If the matching window is too wide, the breathing parameter may not correlate with the FEV1 reading. It may be possible that the breathing parameter might return a 'positive test' but the FEV1 has recovered, such that the false positive rate of the test is increased. To explore the potential impact of matching FEV1 readings to breathing parameter data in a ±7-day window, the analysis was repeated by matching FEV1 readings only to breathing parameters on the same day as the FEV1 reading and within a ±3-day window.

Only 241 FEV1 readings had breathing parameter data on the day of the FEV1 reading, of which 121 (50.2%) showed decline ≥5% from baseline %predicted. Of those 121 FEV1

declines ≥5%, TT minimum was only able to detect 19 (15.7%) of those events. Of the 35 positive tests, 16 (45.7%) were false positives.

Only 310 FEV1 readings had breathing parameter data within ±3-day of the FEV1 reading, of which 168 (54.2%) showed decline ≥5% from baseline %predicted. Of those 168 FEV1 declines ≥5%, TT minimum was only able to detect 49 (29.2%) of those events. Of the 80 positive tests, 31 (38.8%) were false positives.

The results suggest that a similar diagnostic accuracy was obtained by matching the breathing parameter data to FEV1 readings in a ±3-day window and a ±7-day window, i.e. the results are not necessarily impacted by the duration of matching window. Matching the breathing parameter in a ±7-day window does have the advantage of ensuring more of the total FEV1 decline events were detected. Matching breathing parameters to FEV1 readings taken on the same day seemed to have the deleterious effect of both lower sensitivity and higher false positive rate, albeit the results may have been impacted by the smaller sample size. Nonetheless, these sensitivity analyses suggest that there was minimal impact from matching FEV1 readings to breathing parameter data in a ±7-day window.

Exploring the potential impact of including Out of Angle (OOA) breathing parameter data

Unlike breathing parameter data from incomplete nebuliser doses that were excluded, the main analysis included breathing parameter data from nebuliser doses used Out of Angle (OOA) because a personal communication from Philips Respironics suggested that the orientation of the nebuliser when in use would not affect the breathing parameters. Using the prospective dataset, the potential impact of OOA nebuliser doses on TT minimum was separately explored for TIM and TBM.

There were 46 individuals with TT readings in TIM mode without any OOA (contributing 25,939 doses) and 44 individuals with ≥1 OOA TT readings (contributing 6,263 doses). The mean TT value without OOA was 159.22 (95% CI 157.43 to 161.00), compared to a mean of 271.69 (95% CI 265.83 to 277.56) with OOA. After adjusting for clustering effect using mixed-effect regression, the mean difference in TT values with and without OOA was 48.92 (95% CI 29.85 to 68.00), p-value <0.001.

There were 10 individuals with TT readings in TBM mode without any OOA (contributing 546 doses) and 18 individuals with ≥1 OOA TT readings (contributing 364 doses). The mean TT value without OOA was 235.90 (95% CI 225.30 to 246.50), compared to a mean of 430.80

(95% CI 397.92 to 463.68) with OOA. After adjusting for clustering effect using mixed-effect regression, the mean difference in TT values with and without OOA was 96.00 (95% CI 44.00 to 148.01), p-value <0.001.

This is an opportunistic exploration of the TT values with and without OOA using routinely available data. The comparison is relatively crude in that differences in the timing for the different doses were not accounted for. The ideal situation may have been to obtain paired TT values with and without OOA in random order, then performed a paired comparison and plot a Bland-Altman plot. Nonetheless, the large differences in TT values for doses used in angle and OOA (amounting to 30-40% of the TT value without OOA) do hint that OOA TT values were higher than in angle TT values. Since the analysis did not exclude OOA breathing parameters, there may be additional variability due to this which can affect the precision of the diagnostic test.

6.4 Discussion

The predictive model using TT minimum to detect an acute FEV1 decline of ≥5% (developed in Chapter 4) was refined and validated using the prospective dataset. A ±7-day FEV1 detection window showed a similar sensitivity (~31%) and false positive rate (~32%). Exploratory analysis using even shorter detection windows (on the day FEV1 window, or ±3-day window) does not significantly reduce the false positive rate but may reduce the sensitivity. Contrary to the initial assumption, further analyses suggest that Out of Angle use (i.e. using the Bi-neb in a non-horizontal orientation) does affect the TT minimum breathing parameter results.

The aim of the Lung Health study was to determine whether the I-neb® breathing parameters could be used to detect an acute decline in FEV1 of ≥2% from baseline %predicted. This study explored the relationship between changes in breathing parameters and FEV1 taking into account different baseline FEV1 %predicted and the I-neb® mode used. A predictive model was developed and validated and found that the diagnostic accuracy of using TT minimum to detect an acute FEV1 decline of ≥5% from baseline %predicted was poor with relatively low sensitivity. Even with a refinement of the predictive model using the ±7-day detection window, the sensitivity still remains low. Therefore, it is likely that solely relying on TT minimum will miss many events of acute FEV1 decline. Since the false positive rate is also relatively high, the test may also result in a higher number of participants being incorrectly asked to attend the hospital for a ‘gold standard‘ spirometry test when there has actually been no clinically significant decline in their FEV1 from baseline %predicted. If this predictive model was used to replace a face-to-face clinic encounter this would be concerning since many acute

FEV1 decline events could be missed, potentially impacting on long-term life expectancy[25]. However, if this was used in addition to routine clinics as a means of continual lung health monitoring remotely, additional events of FEV1 decline over usual care may well be detected. It should be noted that the additional monitoring with I-neb® breathing parameter imposes no extra monitoring burden for a patient because these readings are available as a by-product of their nebuliser treatment. Nonetheless there may be the additional burden of having extra hospital FEV1 readings because of the false positive rates of ~30%. The fact that hospital spirometry, though may be inconvenient, is not an invasive test should be taken into account when considering the pros and cons of this method of remote monitoring for acute FEV1 decline.

It is possible that the poor diagnostic accuracy value of the breathing parameter may be an artefact of the limitations with the study dataset and the methodology used. First, the analysis only included 34/50 (68%) of the recruited participants which is smaller than the planned sample size, though there were 180 events of FEV1 decline ≥5% in the dataset (compared to the planned 100 events). There were several reasons why participants did not complete the 12-month study (displayed on the participant flow diagram Figure 6.4). One of the main complaints from participants was that the conversion of their I-neb® to the Bi-neb led to the battery of the device running out more quickly. There was also a delay in setting up participants with a Bi-neb following recruitment since this required a home visit. The validation dataset was an internal one, with all participants being part of the retrospective dataset albeit at a different time point, so this may not have the diversity to fully represent the population. Ideally, a larger multi-centre dataset may eliminate this concern since model validation of an apparently accurate model may be seen to be inaccurate without appropriate datasets.[148] Second, the amount of data available for analysis was sparse. Some of this was due to sub-optimal adherence to nebulised treatments resulting in only 68% of the potential days with data actually having any breathing parameter data. The number of FEV1 readings for matching to breathing parameters was also even more limited (57% of the breathing parameter data had no FEV1 reading to match even with a ±7-day window). It had been hoped that home spirometry readings would contribute the majority of spirometry readings in the prospective dataset; however, these readings were excluded because of inaccuracy (Chapter 5). However, it should be noted that the uptake of home spirometry amongst participants was also poor with adherence of only 5.9% in the prospective study. This is in keeping with other home spirometry studies, probably due to the extra burden of carrying out additional measures.[53, 54, 134] Since the number of home readings available in this study was low (34 home readings versus 327 hospital readings), it is unlikely they would have contributed much to the overall study results other than potentially adding imprecise FEV1

readings. The challenges to obtaining home spirometry readings in this particular study were also compounded by the spirometry device not being able to automatically send results to the clinical team and not alerting the participants to carry out readings throughout the 12-months. At least five home spirometry devices stopped working during the study and several participants misplaced their device or forgot how to use it.

Beyond issues with the dataset used in the study, there are potential limitations to using I-neb® breathing parameters to predict acute changes in FEV1. The technique of using an I-neb® may vary amongst participants, thus impacting on the results. For example, a participant could take their nebulised treatments when they watch television, and every time there is an advertisement break, they may pause the dose to make a cup of tea. This could falsely increase the treatment time and rest time. Behaviours of using nebulisers may be habitual for some participants but more unplanned for others. Those without habit may have lower adherence[149] (thus reducing the amount of breathing parameter data that could be linked to each FEV1 reading) and may also have more variable technique when using the I-neb®. It was not possible to do a sensitivity analysis among those with a strong habit only, since data on habit strength were not collected during this study. It is also possible that breathing parameter readings could be affected by the state of the nebuliser filter: for example, a blocked filter due to poor cleaning practices may lead to longer treatment times.[150] The treatment time to nebulise different medications may also vary, and since the medication taken cannot be automatically distinguished from the readings this could impact the interpretation of the breathing parameters recorded. The sub-analysis explored the potential impact of Out of Angle use and found increased TT during OAA use. It is possible that the inclusion of OOA breathing parameters, alongside other real-world factors (such as breaks to make tea, use of different inhaled medications, etc.), may contribute to the relatively high false positive rates. All these confounders do occur in the real world and would be captured during the model development stage which also used real-world breathing parameter data. It is possible that the thresholds determined during the model development stage are less reliable (or lacking in internal validity) due to these real-world factors. One way to reduce false positives and increase the usefulness of the data might be to control the environment when developing the predictive model by carrying out a study similar to Miller's reported in the grey literature[82] (Chapter 3) by performing an I-neb® treatment before and after an induced decline in FEV1. This would be more difficult to do in CF than asthma since a methacholine challenge test is less likely to lead to a significant reversible drop in FEV1 in CF. It is worth considering that perhaps the I-neb® breathing parameters and FEV1 may not be comparable since using the I-neb® does not involve a forced expiratory manoeuvre and the TIM mode encourages a particular pattern of breathing. The FEV1 involves a technique that should be reproducible

and standardised unlike tidal breathing hence the two tests are different and changes in the breathing parameters may not consistently correlate with changes in lung health. Moving from a maximal standardised manoeuvre like FEV1 to other breathing parameters that are unreliable means a test is likely to become less sensitive and specific. Perhaps this theory can be most reliably tested in a controlled environment rather than a real-world setting. Nonetheless, even if FEV1 decline correlates with breathing parameters in a controlled environment, this would only have clinical application if the correlation also exists in the real-world.

The predictive model developed only identified one breathing parameter to predict an acute FEV1 decline. It may be that in fact; a model requires a combination of parameters such as including rest time which was originally postulated. The challenge is that rest time cannot be accurately determined using the TIM mode and using more parameters together in a single model may run into the problem of multicollinearity as discussed in Chapter 4.

This study only reported classification performance and discrimination of the test, not the calibration. Calibration determines whether there is agreement between the number of observed events and the estimated number of events (predicted probabilities).[151] For external validation, calibration curves typically require large sample sizes.[151] Nonetheless, it is important to determine the calibration of a predictive model especially when discrimination is moderate. Even a model with reasonable discrimination can be misleading and result in potentially harmful clinical decision-making if it is poorly calibrated.[151] For example, if the breathing parameter model was systematically under-estimating the risk of FEV1 decline irrespective of how well the model can discriminate between acute FEV1 decline vs stable FEV1, this can lead to under-treatment of the population. As it is, the discrimination of the breathing parameter model is relatively poor and it is unlikely that the model is well-calibrated.

6.5 Conclusions

This study refined and validated the predictive model developed using TT minimum to detect an acute decline in FEV1 ≥5% from baseline %predicted. Although the sensitivity of the test is low and the false positive rate is reasonably high, this test may still be of value in clinical practice because data can be obtained without additional burden for people with CF. Exacerbations are currently detected routinely on FEV1 monitoring in clinic or a measure may be triggered by the patient reporting symptoms. If the I-neb® breathing parameters are used as a routine form of monitoring, they may help to identify early FEV1 declines but there are challenges to implementing this. To better understand the test characteristics of breathing parameters, further studies are required including using a controlled environment to minimise

confounders, testing in a larger multi-centre population, and using more complex modelling techniques including calibration. It is possible that the use of the I-neb® breathing parameter in conjunction with other clinical characteristics can allow clinicians to streamline clinics before patients attend the clinic. The next chapter considers what pre-clinic information is important to the clinical team, and how this may inform clinic attendance decision-making.

CHAPTER 7: DEVELOPMENT OF A CLINIC ATTENDANCE CRITERIA

This chapter describes the process of developing a clinic attendance criteria using consensus methods.

7.1 Introduction

Standards of care in CF recommend PwCF have regular clinic reviews, but there are no clear set criteria as to when a clinic attendance is deemed necessary.[26, 42, 85, 152] As life expectancy in CF rises due to advances in medical care[153], the UK CF adult population continues to expand without a subsequent increase in resources. To meet this increased demand, new innovative ways of working are needed. CF centres with the best FEV1 outcomes target untreated infections through vigilance: by frequent monitoring and providing rescue IV antibiotics.[110, 154] It is therefore important that changes in practice ensure consistent excellence in care is still delivered.

CF clinics have often followed a conventional order of patients being reviewed by each MDT member in turn leading to at times frustratingly prolonged consultations and repetitive questioning since no prior clinic agenda has been reliably set.[155] Efforts to improve efficiency within CF clinics have previously been explored using quality improvement methodology. These have predominantly focused on improving the timely coordination of care in clinics to reduce the length of appointments.[156, 157] Over the years digital technology has advanced and in CF this has been researched and trialled for use in home monitoring, to monitor and support adherence, and in self-management.[57] Despite the potential benefits and incentives of improving the clinic process, it was not until the COVID-19 pandemic that changes to clinics to become virtual and advances using remote monitoring were rapidly implemented across the UK. The standard clinic process was disrupted due to social-distancing measures meaning in-person clinic visits were less practical. In addition, PwCF were initially thought to be vulnerable and at higher risk of serious harm if they contracted COVID-19, therefore they were shielded to protect them from infection.[158, 159] This change in care delivery coincided with the widespread introduction of Kaftrio; a potent CFTR modulator, to the majority of PwCF in the UK. This drug has improved health outcomes for many PwCF but consequently, has led to a reduction in the perceived need to take other preventative treatments and engage with CF teams for routine care.[160, 161] This sudden paradigm shift in clinical care delivery was brought about out of necessity, and due to medical advances, but it is not known whether the care quality is equivalent to the previous standard of care. It is also unclear how best to use available pre-clinic data to decide whether adult CF patients should be reviewed in clinic or if a clinic visit can be safely avoided.

The literature review in Chapter 3 identified factors that might influence clinic attendance decisions in adults with CF and considered how these may be collected remotely. CF is a useful long-term condition exemplar to study the use of pre-clinic data in avoiding some routine clinics because CF is a multiorgan condition and treatments are complex. The use of a formal consensus method can assist in complex decision-making processes, by combining existing evidence with expert clinical opinions.[162]

7.2 Aim

To develop consensus criteria using pre-clinic data that can help decide whether adult CF patients should be reviewed in clinic or if the clinic visit can be avoided.

7.3 Methods

7.3.1 Study design

The consensus exercise was conducted using the nominal group technique (NGT) with a pre-meeting online survey. An anonymised online survey was developed to identify UK adult CF clinicians' views on the role of pre-clinic data to inform clinic use. This was an efficient way of collecting basic information on how current clinic attendances are planned. When completing the survey participants were asked to agree to a statement giving consent for their data to be used as part of a consensus process. Following this the NGT was used with a panel of expert CF clinicians in order to develop a consensus clinic attendance criteria. This method seeks to obtain consensus on a problem during a face-to-face structured meeting. NGT is an iterative multi-stage process designed to combine opinion into group discussion. It aims to avoid conflict and dominating opinions, to achieve a credible solution in a short time period.[162-166] Ethical approval for the study was obtained from the Yorkshire & the Humber, South Yorkshire Research Ethics Committee, NHS Health Research Authority (15/YH/0131) and research and development approval was received from Sheffield Teaching Hospitals NHS Foundation Trust (STH18185).

7.3.2 Recruitment of participants

A face-to-face consensus meeting using the NGT requires a group of 6-12 participants.[162] With an expected recruitment rate of 30%, a purposive sample of 36 CF clinicians from 20 UK adult centres were invited to take part in the study via email since it was anticipated that not all would be able to take part due to clinical commitments. The invite included a copy of the participant information leaflet and a link to access the online survey. Participants could choose to only complete the online survey if they were unable or did not wish to attend the face-to-face meeting. Experts were asked to confirm their interest in participating in the face-to-face

meeting via email. Following an initial expression of interest they were later emailed further logistical details of the meeting.

7.3.3 Conduct of the study

Online survey

The online survey was developed following a review of factors that might influence clinic attendance decisions (Chapter 3). Where further information was required, opinion was sought from the Sheffield Adult CF MDT who were able to seek wider input from their UK CF networks. The survey contained fourteen clinical vignettes and six statements with different patient characteristics to understand how clinicians plan their clinic attendance. It also included five questions asking their views and suggestions on pre-clinic data to plan clinical contacts. One paragraph clinical vignettes described a young adult CF patient presenting in clinic for routine follow-up (see example below in Figure 7.1).

Figure 7.1: Example of a clinical vignette used in the online survey

You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline* FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-neb®. In the past 12 months they have required 28 days of IV antibiotics[z]. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 80% in the previous month and has remained stable. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable
B: A clinic visit would definitely still be required
C: Other comment (please specify)

Definitions:
*Best FEV1 or BMI in the past 12 months
[z]Number of IV days in the previous 12 month annual review period
[X]Community monitored FEV1, BMI, inhaled adherence
[+]I-neb® data download

In each scenario, one measurable characteristic was changed. Characteristics were classified into four categories: (1) changes in baseline lung function (FEV1), (2) acute changes in lung function (FEV1), (3) changes in objective inhaled adherence, and (4) changes in the number of intravenous antibiotics days in the past 12 months. Within these categories, the values reported in cases also varied in order to try to understand at what level a clinician might more specifically make their decision. For example within 'acute changes in lung function (FEV1)' the values included: stable, 2%, 5%, and 10% from baseline (see Table 7.1). The statements explored opinions on different baseline BMI/weight and acute changes in BMI/weight, enteral feeding, allergic bronchopulmonary aspergillus (ABPA), and CF diabetes. The use of clinical scenarios is a valid measure of a clinician's practice and has been found to reliably predict

how they treat patients in real life.[167] SurveyMonkey® was used to host the online survey which on average took fifteen minutes to complete. A copy of the full survey is provided in the Appendix 3. All data were collected and analysed in advance of the consensus meeting.

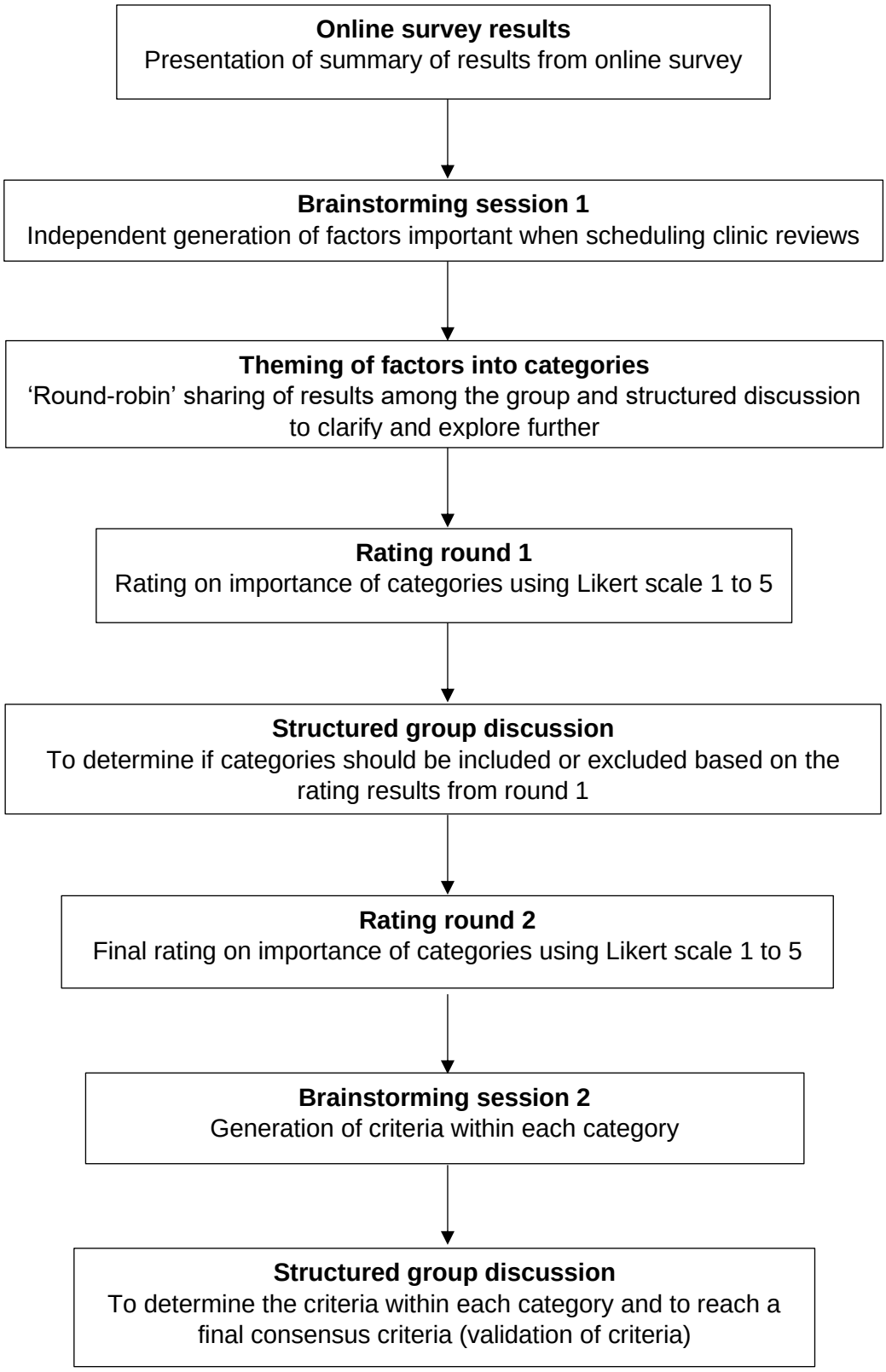
Table 7.1: Variation in factors presented in the clinical vignettes

Clinical vignette theme	Baseline clinical characteristics				Pre-clinic data available 7 days prior to clinic	
	Best FEV1 (%) in past 12 months	Best BMI/weight ($kg/m^2/kg$) in past 12 months	Average inhaled adherence in past 1 month (%)	Number of IV days in past 12 months	Acute change in FEV1 (%) from baseline	Inhaled adherence (%)
Stable FEV1, BMI, & high inhaled adherence	70	23	80	0	0	80
Change in baseline FEV1	50	23	80	0	0	80
	30	23	80	0	0	80
High IV days	70	23	80	28	0	80
Acute change in FEV1	70	23	80	0	2	80
	70	23	80	0	5	80
	70	23	80	0	10	80
Change in inhaled adherence	70	23	60	0	0	60
	70	23	40	0	0	40
	70	23	20	0	0	20
Change in inhaled adherence & IV days	70	23	60	14	0	60
	70	23	60	28	0	60
	70	23	40	14	0	40
	70	23	40	28	0	40

Consensus meeting

The consensus meeting involved a series of brainstorming sessions allowing individuals to generate ideas, independent rating rounds, and group discussions to expand and clarify aspects further (Figure 7.2 shows an overview of the consensus exercise). Written consent was obtained from all participants at the start of the meeting including agreement that the meeting would be audio-recorded and transcribed anonymously. All data for the consensus meeting was collected in May 2016, during a one-day face-to-face meeting held at the University of Sheffield. The meeting was independently facilitated by an expert in consensus work (EC) to allow each participant an equal opportunity to contribute solutions. Interactive anonymised electronic voting technology was used during rating rounds by individuals.

Figure 7.2: Overview of the consensus exercise using a nominal group technique (NGT)



Brainstorming session 1

An overview of the topic, explanation of the exercise, and anonymised results from the online survey were summarised and fed back at the beginning of the meeting. A 'brainstorming' round was then performed to allow each participant to individually record in private any factors they thought were important when scheduling clinic reviews. These were then shared with the group as a single factor at a time in a 'round robin' until all potential factors had been identified. Once all factors were displayed in public, with the assistance of the facilitator these were grouped thematically into common categories and any explanations for these were explored, clarified, and agreed upon through a structured group discussion.

Rating round 1

A preliminary rating round was performed on each category identified in the brainstorming exercise. Each participant rated the categories based on whether they thought they were important when scheduling clinic reviews using the Likert scale of 1 to 5 (1=strongly disagree, 5=strongly agree). The collective results of the ratings were displayed to the group in tables and graphically as bar charts using the electronic voting technology. This allowed a second structured group discussion on each category. Based on the scores recorded certain categories were considered further as to whether they should be included or excluded, and the reasoning behind each decision was recorded. The scoring system used in consensus exercises is described in detail in the analysis of results 7.3.4.

Rating round 2

A final rating round of the categories was performed using the same Likert scale as before. The aim of a second rating round was to elicit participants' refinement of categories following further discussion. The collated results were again displayed to the group as the consensus of categories important when scheduling clinic reviews.

Brainstorming session 2

Using the final agreed categories, a second 'brainstorming' round was performed exploring the criteria within each category that would indicate when a face-to-face clinical contact is definitely required.

Group discussion and criteria selection

A further structured group discussion was conducted regarding the criteria to allow participants to reach a consensus. Criteria with divergent or mixed responses that could not be resolved were adjudicated by a nominated health services research CF clinician expert (MJW) in the group.

7.3.4 Analysis of results

Online survey

Descriptive statistics were produced directly via SurveyMonkey® and comments from open ended text questions were themed into categories.

Consensus meeting

Following methodological reporting guidance for consensus studies[166], consensus was defined based on the proportion of scores within a range at the end of the two rating rounds using the following *a priori* criteria:

- Strong positive consensus: 70% of responses are 4 or 5
- Strong negative consensus: 70% of responses are 1 or 2
- Divergent group view: >40% 4 or 5 and >40% 1 or 2
- Medium/mixed support: All other results

All categories with a strong positive consensus were included and those with mixed responses were excluded from the final criteria. Descriptive statistics were produced for all quantitative ratings to define the consensus criteria. Group discussions were recorded and transcribed allowing simple thematic analysis to be used to identify key definitions and explanations within the final clinic attendance criteria.

7.4 Results

Online survey

Fifteen CF clinicians completed the online survey 15/36 (42%), demographics were unavailable due to the anonymised nature of the survey. Among these participants, 13/15 (87%) agreed that clinical characteristics used with pre-clinic data might allow some clinic visits to be avoided. 14/15 (93%) thought it was something that might potentially benefit their clinic. One respondent felt this would only be useful if it included respiratory microbiology sampling. Seven factors were highlighted that might influence clinic decision-making (Table 7.2). It was felt that consideration of these clinical characteristics along with pre-clinic data may allow a clinic to be avoided. 14/15 (93%) thought there were also nine exceptions or special cases where a clinic could not be avoided (Table 7.2).

Table 7.2: Factors that may be important in clinic attendance decision-making

Clinical characteristics and pre-clinic data that may allow a clinic to be avoided	Exceptions or special cases where clinic could not be avoided
• Importance of reliable objective pre-clinic data – FEV1, BMI, adherence • Patient preference not be seen if clinic if not required • Availability of subjective symptom screening pre-clinic • Baseline disease severity i.e. if mild or stable disease • Relationship with multidisciplinary team i.e. if reliable engagement • If no need for tests/changes to treatment/face-to-face discussions • Respiratory microbiology sampling still required even if not seen in clinic (i.e. postal microbiology sampling)	• If complex/multiple comorbidities • If receiving intensive treatment i.e. non-tuberculous mycobacterium • Patient preference to be seen in clinic • Poor adherence/self-management • Need for other specialties input i.e. CF diabetes and liver disease (joint clinics) • If within 1 year of transition • Mental health issues/psychological support impacting on CF • Lack of engagement with the process of data collection/remote monitoring (pre-clinic data) or insufficient data • If need to assess/discuss issues face-to-face +/- with family. Including transplant, fertility, adherence, physiotherapy technique review including non-invasive ventilation, etc.

Based on the clinical vignettes there was agreement amongst 12/15 (80%) that a routine clinic may potentially be avoidable if the baseline clinical characteristics (FEV1, BMI, inhaled adherence) were high and remained stable. The lower the baseline FEV1 the less likely it was that a clinic may be avoidable. If there was an acute decline in FEV1 of 2% from baseline with all other characteristics remaining stable 9/15 (60%) thought a routine clinic may still be avoidable but any decline >2% meant that this was less likely. Similarly when objective inhaled adherence was deemed to be suboptimal (<80%) and IV antibiotic days exceeded 14 days per year most thought a routine clinic review was still required in particular so a patient could be supported to self-manage and to optimise their treatment (Figure 7.3). Results from the clinical statements (see Table 7.3) showed that 12/15 (80%) thought all those enterally fed should be seen by a dietitian at every routine clinic. Otherwise, views were mixed regarding other associated co-morbidities and changes in BMI/weight. In patients with obesity, it was noted that although this may be less of a worry in CF than those underweight it was still thought reviews would be needed to give weight loss advice. It was also felt that decision-making would depend on what methods to optimise BMI/weight were being used outside of a clinic by dietitians. Within CF diabetes it was felt that even if blood sugar control was stable if the HbA1c was high a review of treatment and self-management would still be beneficial. Regarding quiescent ABPA there were some concerns as to whether pre-clinic data would be sensitive enough to detect any relapse and hence the importance of blood monitoring. For most of the statements even with simplification of key information provided there were very few circumstances where it was thought that a routine clinic may be avoidable.

Figure 7.3: Clinician responses to clinical vignettes: proportion of responses where a clinic may be potentially avoidable

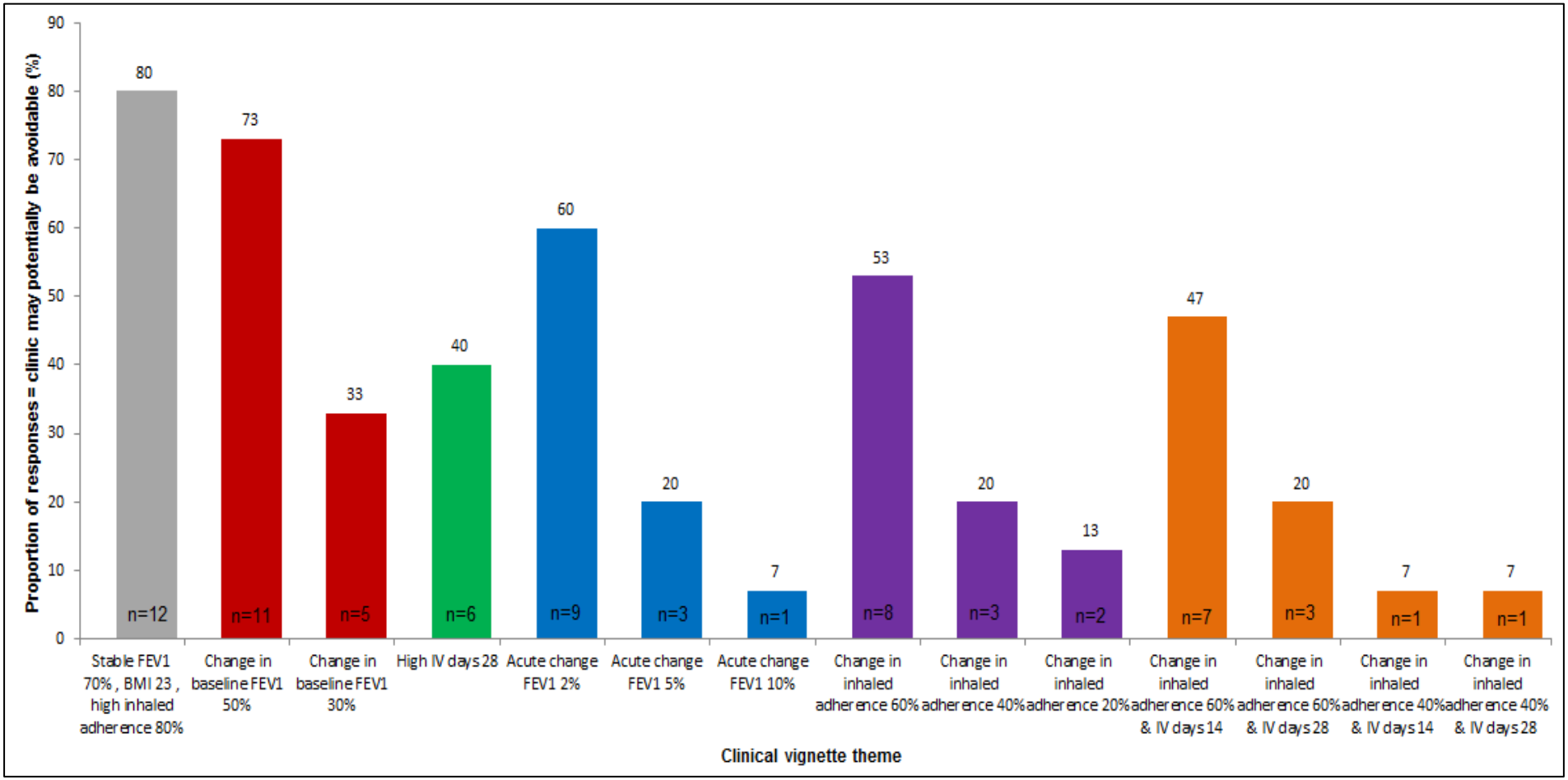


Table 7.3: Variation in clinical statements and clinicians' responses

Theme	**Clinical Statement**	**Proportion of responses = agree with statement n (%)**
Change in BMI/weight ($kg/m^2/kg$) *Recommended BMI for female with CF 22kg/m² & male 23kg/m²* [42]	CF patients using enteral feeding should be seen by a dietitian in all routine clinics	12 (80)
	CF patients not enterally fed should be seen by a dietitian in all routine clinics if: BMI <19, or BMI 19-21.9/22.9 with a 5% weight loss in the last 12 weeks, or BMI >22/23 with 5% weight loss in last 12 weeks	11 (73)
	CF patients not enterally fed should be seen by a dietitian every 6 months if: BMI 19-21.9/22.9 & weight stable This includes those with pancreatic insufficiency as long as no other clinical indictors (e.g. steatorrhoea, or recent change to enzyme dosing, or newly diagnosed pancreatic insufficiency)	7 (47)
	CF patients not enterally fed should be seen by a dietitian every 12 months if: BMI >22/23 & weight stable This includes those with pancreatic insufficiency as long as no other clinical indictors (e.g. steatorrhoea, or recent change to enzyme dosing, or newly diagnosed pancreatic insufficiency)	6 (40)
CF diabetes (CFD)	CF patients with CFD should be seen in routine clinic (alongside their CFD specialist clinic visits which should be a minimum of once a year if stable) if: There has been a preceding change in insulin or if their HbA1c within the past 3 months has increased to >70 or decreased to <60 compared to the previous 3-month result However, if their HbA1c has remained stable and they are well a routine clinic visit may be avoidable	7 (47)
Allergic bronchopulmonary aspergillus (ABPA) *Definitions based on 2003 CFF guidance for ABPA*[168]	CF patients with active ABPA requiring monitoring and/or treatment will be seen in all routine clinics. However, in those with quiescent ABPA it is expected that the decision to see in routine clinic can be guided by the change in other measures i.e. FEV1, BMI, and adherence	10 (67)

Consensus meeting

Eight adult CF clinicians attended the consensus meeting from five specialist adult CF centres. Participants consisted of 4 (50%) females with median 6 years 7 months (IQR 1 year 8 months to 10 years 10 months) of experience as a CF consultant. The initial brainstorming round identified 105 individual factors deemed important in scheduling clinic reviews. These were themed into 17 categories and within these further sub-categories were developed. Provisional explanations and definitions were described where necessary (see Table 7.4). In rating round 1 there was mixed opinion on four categories (severe CF liver disease, post-transplant, enteral feeding, and geographic location and social deprivation) which prompted further discussion. This highlighted some variation in practice across UK adult CF centres in terms of post-transplant management and the different strategies dietitians use to manage patients outside of clinics. It also started to allow the group to consider in more detail how terms such as 'severe' would be defined in the context of CF liver disease. After more consideration the group started to decide that geographic location and social deprivation could actually be considered separately. Following the second rating round strong consensus was agreed on 14 categories and a total of 29 sub-categories (see Table 7.5). It was then decided to re-categorise mental health/psychological status under the overarching theme 'non-CF vulnerability' and within this to include social deprivation. In the second 'brainstorming' exercise and subsequent group discussion it became apparent that developing the criteria for each category was more difficult. For some categories the group were unable to agree objective criteria within the timeframe available. This included what baseline measures of FEV1, and BMI/weight would deem a clinic could be considered avoidable. For FEV1 it was felt each patient case had to be considered in context, and for BMI/weight there were two different criteria with mixed consensus. The co-morbidities as noted in the online survey were increasingly challenging to clarify further and set criteria. This again involved issues such as to how to deal with terms such as 'severe'. Therefore, where possible the criteria for each category/sub-category were defined to produce a consensus criteria indicating a face-to-face clinical contact is definitely required (see Table 7.6). In other words, a face-to-face contact may only be avoided if the clinical parameters (FEV1, BMI/weight, objective inhaled adherence) are satisfactory and in the absence of other complications e.g. co-morbidity that requires complex care or planning. The group defined baseline measures (FEV1 and BMI/weight) as the best measure obtained in the previous 12 months. Adherence to inhaled therapies was to be calculated as 'normative adherence', which involves numerator adjustment (capping daily maximum nebuliser use at 100%, and accounting for dose spacing of inhaled antibiotics & irregular lifestyle) and denominator adjustment (to define the minimum effective treatment regimen according to a person's *Pseudomonas aeruginosa* status and exacerbation history) as previously described.[169]

Table 7.4: Categories deemed important in scheduling clinic review (Brainstorming round)

Category	Subcategory	Explanation
FEV1	Baseline FEV1	Baseline FEV1 = best FEV1 in past 12 months Review if baseline FEV1 low even if stable (indicating severe disease)
	Acute change in FEV1	Review if acute change from baseline
	Trend in FEV1	Review if declining trend
Adherence (Objective)	Baseline adherence	Baseline adherence = average normative adherence over at least 3 consecutive months Review if adherence low
	Acute change in adherence	Review if acute decline in adherence from baseline
	Adherence trend	Review if declining trend
BMI/weight	Baseline BMI/weight	Baseline BMI/weight = best BMI/weight in past 12 months Review if baseline at either extreme even if stable
	Acute change in BMI/weight	Review if acute change from baseline
	BMI/weight trend	Review if declining or increasing trend
Acute symptoms/unwell	Patient concern	Based on reported symptoms
	Clinician concern	
Relationship with multidisciplinary team		Review if psychosocial factors, poor contact with team if relationship building, if needs multi-disciplinary team review
Palliative care/end of life		Review if palliative or end of life
Mental health/psychological status		Review if there are mental health/psychological issues impacting on CF
Face-to-face processes of care	Need for diagnostic test	Review if requires hospital only tests including annual review
	Need for MDT input – specific intervention or discussion	Review if needs physiotherapy technique review, fertility discussion, to start or titrate treatment, prescription issues, end of IV review, pre-holiday review, pre-surgical procedure review etc.
Co-morbidity	ABPA & other fungal	Review if monitoring or treating co-morbidity Complex infection includes non-tuberculous mycobacterium
	Pregnancy	
	CF Diabetes	
	Severe CF related liver disease	
	Intensive management of complex infection	
Patient awareness or ability to report symptoms and use remote technology		Review if unable to remotely monitor or report symptoms
Transplant	Pre-transplant	Review if under-going transplant assessment
	Post-transplant	Review if post-transplant
Patient preference or request to be seen		Review if patient requests or prefers
Enteral feeding		Review if using enteral feeding
Recent transition or new late diagnosis of CF		Review if recently transitioned to adult services or new late diagnosis of CF
Pulmonary exacerbations	Number IV days per year	Review if high IV use, high oral use, or high hospital admissions
	IV trend per year	
	Number of hospital days per year	
	Number of oral antibiotic courses per year	
Geographic location and social deprivation		Socioeconomic and demographic factors

Table 7.5: Categories included/excluded after each rating round

Category	Subcategory	Round 1		Round 2	
		Scores*	Consensus	Scores*	Consensus
FEV1	Baseline FEV1	5, 5 (4-5)	Include	4.5, 4&5 (4-5)	Include
	Acute change in FEV1	5, 5, (5-5)	Include	5, 5 (5-5)	Include
	Trend in FEV1	5, 5 (4-5)	Include	5, 5 (4-5)	Include
Adherence (Objective)	Baseline adherence	4, 4 (4-5)	Include	4.5, 5 (3-5)	Include
	Acute change in adherence	5, 5 (3-5)	Include	5, 5 (4-5)	Include
	Adherence trend	4.5, 5 (3-5)	Include	4.5, 5 (3-5)	Include
BMI/weight	Baseline BMI/weight	4.5, 5 (3-5)	Include	4.5, 4&5 (4-5)	Include
	Acute change in BMI/weight	5, 5 (4-5)	Include	5, 5 (4-5)	Include
	BMI/weight trend	4.5, 5 (3-5)	Include	5, 5 (3-5)	Include
Acute symptoms/unwell	Patient concern	5, 5 (4-5)	Include	5, 5 (4-5)	Include
	Clinician concern	5, 5 (4-5)	Include	5, 5 (4-5)	Include
Relationship with multidisciplinary team		4, 4&5 (2-5)	Include	4, 4 (3-5)	Include
Palliative care/end of life		5, 5 (2-5)	Include	5, 5 (4-5)	Include
Mental health/psychological status		4.5, 5 (3-5)	Include	4, 4 (4-5)	Include
Face-to-face processes of care	Need for diagnostic test	4.5, 5 (2-5)	Include	4.5, 5 (3-5)	Include
	Need for MDT input – specific intervention or discussion	5, 5 (4-5)	Include	5, 5 (4-5)	Include
Co-morbidity	ABPA & other fungal	4, 4 (3-5)	Include	4, 4 (4-5)	Include
	Pregnancy	4.5, 4&5 (4-5)	Include	4.5, 4&5 (4-5)	Include
	CF diabetes	4, 4 (3-5)	Include	4, 4 (4-5)	Include
	Severe CF related liver disease	4, 4 (3-4)	Mixed	4.5, 4&5 (4-5)	Include
	Intensive management of complex infection	5, 5 (4-5)	Include	5, 5 (4-5)	Include
Patient awareness or ability to report symptoms and use remote technology		5, 5 (3-5)	Include	4.5, 5 (2-5)	Include
Transplant	Pre-transplant	5, 5 (3-5)	Include	4, 4 (4-5)	Include
	Post-transplant	3, 3 (3-5)	Mixed	2.5, 3 (1-3)	Mixed
Patient preference or request to be seen		5, 5 (4-5)	Include	4.5, 5 (3-5)	Include
Enteral feeding		3.5, 3 (2-5)	Mixed	3, 3 (1-4)	Mixed
Recent transition or new late diagnosis of CF		5, 5 (2-5)	Include	5, 5 (3-5)	Include
Pulmonary exacerbations	Number IV days per year	5, 5 (3-5)	Include	4, 4 (3-5)	Include
	IV trend per year	4, 4 (4-5)	Include	4, 4 (4-5)	Include
	Number of hospital days per year	4.5, 5 (2-5)	Include	4, 4 (3-5)	Include
	Number of oral antibiotic courses per year	4.5, 5 (3-5)	Include	4, 4 (2-5)	Include
Geographic location and social deprivation		3.5, 3 (3-5)	Mixed	2.5, 2 (2-5)	Mixed

*Median, mode, range of scores presented retrospectively Score: 1=strongly disagree, 2=disagree, 3=neural, 4=agree, 5=strongly agree

Table 7.6: Consensus criteria indicating a face-to-face clinical contact is definitely required

Category	Sub-category	Criteria indicating clinical contact required
FEV1 % predicted	Baseline FEV1 =best FEV1 in past 12 months	No set criteria – each case considered in context rather than FEV1 alone
	Acute change in FEV1	>2% decline in FEV1 from baseline
	FEV1 trend	Sustained 2% decline in FEV1 over 3 visits
Adherence (objective) %	Baseline adherence =average normative adherence over at least 3 consecutive months	<80% objective adherence
	Acute change in adherence	>20% decline in adherence
	Adherence trend	>20% decline in adherence over 3 months
BMI/weight Kg/m^2/kg	Baseline BMI =best BMI in past 12 months	Mixed consensus: Group 1 – Male<21, Female<20 Group 2 – Male<19, Female<18
	Acute change in BMI	Decline of 2-3kg or 5% change from baseline (Assuming BMI within limits Male<26, Female<25)
	BMI trend	Sustained 2-3kg or 5% change over 3 visits (Assuming BMI within limits Male<26, Female<25)
Exacerbations	No. IV days/year	>14 days or >1 course/year
	IV trend/year	>14 days or >1 course/year
	No. hospital days/year	>1 admission (for more than 24hrs)/year for the same problem excluding admission for IV antibiotics
	No. PO antibiotic courses/year	>2 courses/year
Acute symptoms/unwell	Patient concern	
	Clinician concern	
Relationship with MDT		If high 'Did not attend' (DNA) rate/unreliable
Palliative/end of life care		
Non-CF related vulnerability		Includes mental health/psychological status /social deprivation
Face-to-face processes of care	Need for diagnostic test	Includes annual review
	Need for MDT member discussion of specific intervention/issue	Includes discussions about fertility, transplant, assessment of physio technique, etc.
Co-morbidity	ABPA and other fungal	If unstable/on active treatment
	Pregnancy	
	CF diabetes	No specific criteria obtained
	Severe CF related liver disease	No specific criteria to define severity obtained
	Intensive management of complex infection	Includes mycobacterium abscessus
Patient awareness and ability to report symptoms/use remote technology		If unable/unreliable reporting of symptoms & use of remote technology to obtain pre-clinic data
Pre-transplant work-up status		If undergoing pre-transplant assessment
Patient preference/requests		If wishes to be seen
Recent transition/new late diagnosis of CF		Within 1 year

7.5 Discussion

This consensus exercise developed a clinic attendance criteria using an online survey (CF clinician response rate 15/36) and iterative, multi-stage nominal group technique to integrate opinions from eight experienced CF clinicians across the UK. Most of the survey respondents (13/15) agreed that certain clinical characteristics combined with pre-clinic data may allow some clinic visits to be avoided and that this could potentially benefit their clinic. The survey identified seven factors that might influence clinic decision-making and nine exceptions or special cases when a clinic could not be avoided. Accordingly, clinic may only be avoided if important clinical parameters such as FEV1, BMI/weight, and objective inhaled adherence were satisfactory and there were no complicating factors such as complex co-morbidity or the need for advanced care planning. The face-to-face meeting reached a consensus on 14 categories deemed important to clinic attendance decision-making. Where necessary categories were defined and sub-divided. Within these categories, specific criteria were generated by discussion until a consensus was reached.

The final clinic attendance criteria included acute changes in clinical measures (FEV1, BMI/weight, and objective inhaled adherence) from baseline, as well as highlighted the importance of declining trends in measures over time. Consensus suggested those with an acute FEV1 decline of >2% from baseline %predicted should be seen in clinic face-to-face. An acute change in BMI/weight of 2-3kg or 5% change from baseline was seen as another trigger for a clinic review. Objective inhaled adherence was identified as an important category with consensus being reached that normative adherence <80% consistently (over at least 3 consecutive months) should lead to a clinic review. The majority of the categories (10/14) did not have specific criteria attached at the end of the consensus meeting but were broadly clarified further.

Development of a clinic attendance criteria is important since Standards of care in CF recommend regular reviews yet there are resource implications for providers as the CF population continues to grow. In addition, many PwCF are keen to avoid routine clinic reviews unless they are symptomatically unwell or wish to address a particular aspect of their condition. This may be due to finding clinic burdensome[170] and certainly, the introduction of Kaftrio has resulted in a perceived reduced necessity to be seen due to improved health outcomes.[160, 161] Using a structured consensus method to develop a set of criteria is of value since ad hoc strategies or strategies that are not systematically developed may even be detrimental to outcomes in PwCF.[51]

This study highlights some of the complexity in clinic attendance decision-making in CF probably in part due to the multi-organ nature of the condition hence the large number of variables to consider. Another important issue is the insensitivity of the tests available to detect a deterioration in clinical condition. For example, negative sputum microbiology does not necessarily exclude a pulmonary exacerbation. People can also be non-specifically unwell but their FEV1 may still be reasonably stable. It can therefore often be easier to pick up subtle signs of deterioration in a face-to-face interaction.[171] In order to operationalise a clinic attendance criteria pre-clinic data needs to be available to provide continuous reassurance that preventative treatment is optimised. However, the complexity of obtaining robust pre-clinic data to support decision making is challenging and should be carefully considered as demonstrated in Chapter 5 in relation to home spirometry. The first point to consider is that any additional measures or remote monitoring adds extra burden which patients may not engage with. The second point is that any results obtained may be unreliable such as home spirometry as discussed in Chapter 5. Another example is with home sputum collection where there can be issues with postal sputum sample quality due to delays in samples being received in time to be accurately analysed.[172] It is also uncertain how much pre-clinic data is enough and what is the maximum suitable time frame from the data recording to make a decision. For example, if a home spirometry reading is done 10 days before a clinic review is planned it is uncertain if this result can be used to infer current lung health and allow a clinic attendance decision to be made. Having easy access to retrospective recorded data such as co-morbidities, IV antibiotic days, and baseline measures is important to inform a clinic attendance criteria. An electronic healthcare record provides an advantage here, yet these are not available in all UK CF centres.[173]

The online survey in this study used clinical vignettes to gather information similar to that drawn from standardised patients and medical records. Clinical vignettes have been used in other chronic conditions including CF as they examine variations in practice and can identify factors relevant to medical knowledge, diagnosis, decision-making, and determining treatment approaches.[174, 175] The advantage of this is they can describe ‘real world’ patients and be sent electronically to CF clinicians to be completed at a suitable time.

There were a number of limitations to the study approach taken to develop a clinic attendance criteria. This study involved a relatively small number of CF experts. Although the number of participants was appropriate for the NGT, ideally a broader consensus should be sought involving a wider audience and other MDT members. This would then allow the criteria to evolve and be refined further. The developed clinic attendance criteria however are suitable

for testing and start to address a gap in current methods for changing the way clinical care is delivered. Another limitation was conducting the NGT consensus meeting face-to-face. This is the standard way a NGT meeting is usually carried out which has some advantages but, in this study, due to the complexity of the topic, it meant there were time constraints on reaching a consensus, and some criteria were not well defined. Given more time the criteria may have become further refined. Several clinicians who completed the online survey had been keen to attend the meeting but due to the scheduled time and geographic location, it meant it was not possible for them to coordinate being away from their busy clinical duties. One way to address this limitation would have been to carry out the meeting online virtually although at the time of the study virtual meetings were much less available than post COVID-19. Another way would have been to carry this consensus out over a series of email exchanges. This approach has been used in a study to develop a criteria to define chronic pseudomonas in adults with CF.[176] During the consensus meeting it became apparent that clinician opinions varied in certain areas due to the availability of local resources, for example, different CF centres manage post-transplant care compared to others that have less involvement in these patients, and some centres have joint clinics with other specialists to manage CF complications such as diabetes and liver disease.

Objective inhaled adherence is one of the categories identified as important in clinic attendance decision-making. It was agreed that normative adherence consistently <80% would indicate that a patient should be reviewed face-to-face. Based on this category alone few PwCF would be able to avoid clinic since adherence in chronic conditions is suboptimal.[177] Retrospective I-neb® data from the Sheffield adult CF centre in 2014 suggests that if this category was used where adherence was known only 19% (18/97) of patients would have been able to avoid a clinic visit. It is likely that adherence to inhaled therapy has declined even further now since the introduction of Kaftrio. It is also important to consider that not everyone will need such high levels of adherence to maintain clinical stability.[178, 179] This criterion may therefore be unsuitable when attempting to operationalise a clinic attendance criteria for clinic streaming.

This study was conducted before the COVID-19 pandemic and the introduction of Kaftrio. It is therefore important to recognise that the clinic attendance consensus cannot change current practice without further research because CF care has changed. A useful immediate piece of future work would be to test the clinic attendance criteria in a single CF centre over 6 to 12 months. This would allow practical limitations with the criteria to be identified so that the criteria can be iterated before testing in multiple centres. It may also be possible that the clinic attendance criteria can be further refined. For example, instead of making a binary decision

(attend clinic or not), more complex decision-making such as streamlining into different clinics ('Green stream' – express slot or no clinic required, 'Red stream' – action required; diagnostic or adherence support slot) can be undertaken in advance. The concept of using pre-clinic data has previously been used to streamline clinic visits in other long-term conditions.[180]

7.6 Conclusions

Consensus methods have been used to identify criteria that can be used in clinic attendance decision-making. Deciding if a clinic may be avoided is challenging with multiple complex factors being considered. However, using a pragmatic approach it is possible to reach a consensus on an initial set of criteria that can be investigated further. It should be noted that obtaining a sufficient amount of high-quality pre-clinic data will be integral for the successful implementation of any clinic criteria. Consideration should be also given to the data collection process to ensure it is realistic and not too burdensome for patients. In the discussion and conclusions chapter (Chapter 8), the impact of remote data collection is further considered.

CHAPTER 8: DISCUSSION AND CONCLUSIONS

This chapter summarises the overall findings of the thesis, explains the context of the findings in relation to other research, discusses the relevant learning points, and provides suggestions for the future.

8.1 Summary of the findings

This thesis had two main aims: To explore whether the breathing parameters automatically recorded by the I-neb® correlate with acute changes in lung function allowing the early detection of pulmonary exacerbations, and to develop a clinic attendance criteria using pre-clinic data to optimise clinic use.

The importance of detecting acute changes in FEV1 and maintaining lung health was highlighted in Chapter 1. The I-neb® was identified as a potential solution since it automatically records breathing parameters with each treatment which was hypothesised to correlate with acute changes in FEV1, and thus could be used to remotely infer lung health. The chapter also discussed the problem of limited additional resources being available to manage an ever-growing CF population. Therefore, there is a need to find new innovative ways of delivering care ideally involving remote telemonitoring without imposing too much extra burden for patients. Research questions and aims were clearly defined in Chapter 2 to address these issues.

The literature review in Chapter 3 identified some evidence that forced expiratory mid-flows mirror FEV1 but with poorer repeatability and reliability. Only the grey literature attempted to demonstrate absolute changes in tidal breathing measures compared to FEV1. Since there was no literature directly comparing the I-neb® breathing parameters with changes in FEV1, the thesis set out to address this evidence gap. This chapter also reviewed current UK adult CF guidelines to identify factors that might influence clinicians' clinic attendance decisions. A summary of the routine measures required for monitoring and how these could potentially be collected remotely was produced. It was apparent that although there are recommended key areas for review, there are no specific criteria on what outcome results should prompt a review. Without a structured clinic attendance criteria already in place, the thesis set out to develop one using consensus methods.

A retrospective observational analysis of breathing parameter data from the I-neb® and hospital FEV1 readings within a ±3-day window was used to develop a predictive model for an acute FEV1 decline in Chapter 4. This included data from 61 adults in Sheffield over a 7-

year period. The study determined estimated threshold values ("normal" or "abnormal") for each breathing parameter by calculating the 25th and 75th centiles. These values varied with baseline FEV1 and the I-neb® mode used (TIM or TBM). Logistic regression results were used alongside clinical judgment to identify the minimum Treatment Time (TT) value as the most promising breathing parameter to detect an acute FEV1 decline of ≥5% from baseline. When the TT minimum reading was >75th centile of the group threshold, the test was considered 'positive' indicating a potential decline in FEV1. Using TT minimum as a predictive test for acute FEV1 decline ≥5% it was found to have a low sensitivity (~10% TIM, ~20% TIM) and high specificity (~90% TIM, ~70% TBM). Since there were limited hospital FEV1 readings for analysis, it was initially planned that more FEV1 readings from home monitoring could add value to the prospective validation dataset. Before including the home FEV1 readings, its accuracy was explored in Chapter 5.

A cross-sectional observational study was conducted using unsupervised home spirometry readings collected in the Lung Health prospective study in Chapter 5. These results were paired with hospital FEV1 readings using a ±3-day window. The Lung Health prospective study (Chapter 6) included 34 participants with a 1-year follow-up. Only 43 home FEV1 readings were obtained from the participants. With 17 home spirometry readings per person per year considered as 'complete data', the median data completeness was 5.9% (IQR 0 to 11.8%). Home spirometry data from 17/34 participants was analysed since the majority did not submit readings within ±3 days of the clinic. Using a Bland-Altman plot a mean difference of 111ml (95% limits of agreement -299ml to 76ml) was found, with the home spirometer tending to under-read compared to the hospital spirometer. The intra-individual discrepancy was higher (>150ml) for some participants suggesting that home spirometry readings are clinically unreliable particularly when performed unsupervised. Based on results indicating a lack of accuracy and the sparsity of data, home spirometry readings were excluded from the validation dataset in Chapter 6.

The predictive model developed in Chapter 4 was refined and validated in Chapter 6 with an internal prospective observational dataset. Fifty adults in Sheffield were recruited to use a Bi-neb for up to 12 months which allowed breathing parameter data to be sent via Bluetooth to the clinical team. The model was refined based on results from the development phase and on clinical grounds. A ±7-day window was used instead of a ±3-day window, and breathing parameters from both I-neb® modes (TIM and TBM) were used in the same dataset to detect acute FEV1 decline ≥5%. Only 34/50 participants completed the 1-year follow-up and were included in the full data analysis. The study found a predictive model using TT minimum to have a similar sensitivity (~31%) and false positive rate (~32%). Exploratory analysis

suggested that using shorter FEV1 detection windows (±3-day window and even using only breathing parameter on the same day as FEV1 readings) did not significantly reduce the false positive rate but may reduce the sensitivity. Further analysis also indicated that Out of Angle use (using the Bineb in a non-horizontal orientation) appears to affect the TT minimum breathing parameter results. Despite some of the limitations and relatively high false positive rate, it was felt that using the I-neb® breathing parameters to continually monitor lung health may still have a clinical role since this has the advantage of potentially detecting more events of acute FEV1 decline compared to usual care yet imposed no extra remote monitoring burden.

In Chapter 7 a set of clinic attendance criteria was developed using consensus methods. This combined results from an online survey of clinical vignettes (CF clinician response rate of 15/36), with opinions from eight experienced CF clinicians sought in a face-to-face meeting using the nominal group technique. The final clinic attendance criteria identified 14 categories deemed important to clinic attendance decision-making. Where necessary, categories were defined and sub-divided, for example, FEV1 %predicted: baseline FEV1, acute change in FEV1, and FEV1 trend. Within these categories, specific criteria were generated including acute changes in clinical measures (e.g. acute FEV1 decline >2% from baseline) and declining trends over time (e.g. trend of declining weight over 3 visits).

Overall, the findings from this thesis highlight the difficulties of predicting an acute FEV1 decline using breathing parameters from the I-neb® in part due to potential confounders, and the challenges of identifying a clinic attendance criteria due to CF being a multi-organ condition and involving a number of complex factors. It also demonstrates the importance of obtaining sufficient high-quality remote measures in a way that is least burdensome for patients to monitor their health and inform clinical decision-making.

8.2 How the research work presented in the thesis relates to other research work in CF

This research links to wider CF studies that have also attempted to remotely monitor PwCF to detect pulmonary exacerbations early and use remote telemonitoring to change the way clinical care is delivered. Both the eICE[53] and HomeCF[54] studies used home spirometry as part of remote monitoring to identify early FEV1 decline in adults with CF. One of the common challenges was getting PwCF to carry out the home spirometry due to the extra burden of additional measures. Chapter 5 (data from the Lung Health prospective study) highlighted the same problem with a median adherence to home spirometry of only 5.9%. This was lower than eICE (mean adherence 19%) likely due to the spirometry device not being able to automatically send results to the clinical team and not provide reminders alerting the

participants to carry out readings over the 12-month period. Simplifying the burden of treatment in CF was one of the top 10 priorities set by the CF community in 2018 as part of the James Lind Alliance consultation[181] therefore it should be a key consideration when attempting to implement remote telemonitoring to change clinical care. The Lung Health study actively seeks to do this since the breathing parameters automatically recorded by the I-neb® are a by-product from using the device to take treatment, hence I-neb® has the potential to infer lung health without the need for extra remote measures.

SmartCareCF (NCT02416375) is a multi-centre observational study set up in 2015 to explore the use of remote monitoring in adult CF patients to reduce pulmonary exacerbations. This required participants to carry out daily measures including pulse rate, oxygen saturation, wellness and cough scores, spirometry, physical activity, temperature, weight, sleep quantity and quality, and collect sputum samples. Data was collected via Bluetooth-enabled devices and transmitted to a website. This study enrolled 148 participants and was completed in 2019 though the results have yet to be published.[55] SmartCareCF was then renamed 'Project Breathe', which aimed to use remote monitoring to create a tool for PwCF to self-manage, assist CF centres with clinical decision-making, and to validate and refine predictive algorithms. Having investigated the feasibility and acceptability of using Blue-toothed devices for home monitoring this allowed clinic consultations via virtual link when needed to minimise the disruption of routine clinic visits.[182] This study has now been further extended and is using artificial intelligence and machine learning to predict exacerbations up to 10 days in advance (ACE-CF: Artificial Intelligence to Control Exacerbations in adult CF).[182] It is unclear what conceptual framework is being used to develop the interventions and models used and to date, little of the actual results from all this work have been published except for CLIMB-CF. CLIMB-CF is a "paediatric version" of SmartCareCF with results demonstrating that even children with rigorous parents struggle to comply with the remote monitoring requirements.[134] Much like the Lung Health study what has become increasingly recognised is the need to use novel remote monitoring devices to improve the frequency and quality of data. In particular, replacing burdensome monitoring such as spirometry with more passive devices such as smartwatches. The challenge is finding the effortless measures to infer health states that can be continually monitored and to encompass all aspects of this multi-faceted chronic condition. Even though using the I-neb® to monitor lung health imposes no extra burden, the number of breathing parameters available for monitoring is still limited by low adherence to nebulised treatments.[112]

For at least forty years, there has been interest in using telemedicine to remotely manage and replace face-to-face CF clinics.[57] This probably stems from the high frequency of reviews,

the long distances PwCF have to travel to CF centres, and the infection control issues leading to segregation. Despite numerous research studies and systematic reviews, it was not until the COVID-19 pandemic that things rapidly changed. This happened at a time when it was more apparent that standards of care were becoming unsustainable due to a rise in life expectancy leading to an increasing CF population. It also coincided with the introduction of highly efficacious CFTR modulators for >90% of PwCF. This change in care delivery out of necessity has resulted in more publications outlining how different centres attempted to monitor their patients over this time period and what learning is now being taken forward. Dixon et al. summarise some of the key issues post-pandemic including that telemedicine approaches are not a 'one-size-fits-all', the importance of building a rapport face-to-face, and recommends that widespread adoption of the pandemic changes should not continue without critical focus on areas that could be improved or evidenced to support them.[183] They also raise the issues post Kaftrio introduction of sputum less likely to be expectorated and spirometry being poorly sensitive in early lung disease hence the need to explore different ways to monitor lung health. For example, sputum induction can be performed with good yields[184] although this can be time-consuming and require input from physiotherapists, and imaging can help detect early lung changes but requires a hospital visit. Taking these factors into account, not all face-to-face visits can be replaced. Otherwise, changes in health outcomes such as pulmonary exacerbations may go undetected in a timely manner, or important investigations could not be carried out leading to poorer future outcomes. The clinic attendance criteria developed in this study may therefore offer a structured approach that can be further refined to deliver clinics using telemedicine and eventually streamline these based on a pre-defined need or agenda set by the clinical team in partnership with the patient. The systematic approach taken to develop the clinic attendance criteria using consensus methods may also offer a viable and pragmatic approach for other centres to develop their own clinic streaming strategy.

It is worth considering the strengths and limitations of the research studies reported in this thesis in the context of other research work in CF. Strengths of the predictive model for acute FEV1 decline (Lung Health study) were the use of routinely available data for the model and the real-world setting of the study. Other CF studies required additional data capture (which can be burdensome) for the remote monitoring of lung health. Limitations were the limited sample size, small numbers of breathing parameters and FEV1 readings, and the use of relatively unsophisticated statistical analysis. Hence it is possible that a stronger relationship between breathing parameter and FEV1 decline may have been missed. A strength of the clinic attendance criteria study was the systematic approach using a recognised consensus method. It appears that this is the first study in CF to design a set of clinic attendance criteria

using such an approach. However, limitation were the lack of further evaluation of clinic attendance criteria and the criteria were set in the pre-Kaftrio era, hence further adaptations may well be required before the criteria are suitable for current clinical application.

8.3 Highlights and discussion points

The limitations of the research studies reported in this thesis meant that neither the predictive model using breathing parameters from I-neb®, nor the set of clinic attendance criteria are suitable for clinical use without further research. Whilst the research may not necessarily change the present clinical practice, some insights generated during the course of the research merit further discussion.

Providing useful tools requiring minimal burden that can remotely detect changes in lung health and inform clinic attendance decisions is an important part of CF management. The Lung Health study describes a proof of concept since it is the first to explore the use of the I-neb® breathing parameters to detect acute changes in FEV1 in adults with CF. This study identified threshold values (25^{th} and 75^{th} centile) for each breathing parameter which allowed the measures to be operationalised as a predictive model taking into account different baseline lung functions and I-neb® mode used. The main advantage of using this approach to continually monitor lung health and detect acute exacerbations is that it requires no extra active involvement for patients. However, since the false positive rate was found to be reasonably high this does mean that some patients would need to be reviewed unnecessarily with spirometry when they are well. The true clinical value of the test therefore needs to be assessed[120] and since this study has a number of limitations, more robustly designed studies are needed to determine if this test could be of use in clinical practice. One challenge to consider is the limitations in data availability. Adherence to medication is a problem in chronic conditions and in CF this has become more of an issue following the introduction of Kaftrio since increasingly PwCF do not see the necessity to take other preventative treatments.[177, 185] The study CF STORM (ISRCTN14081521) is attempting to establish whether nebulised treatment can be rationalised in adults on Kaftrio without impacting lung function. This followed the paediatric study SIMPLIFY which suggested that lung function remained relatively well preserved when daily nebulised hypertonic saline or dornase alfa was discontinued for 6 weeks.[186] Stopping proven preventative treatments is difficult since Kaftrio has only been in clinical use for a relatively short time, so the long-term effects are yet to be seen. With Ivacaftor, the first highly effective CFTR modulator, real-world data suggests the loss of effectiveness after around 5 years following an initial improvement in health outcomes. Therefore it may be too early to determine whether other preventative treatments can be reduced whilst on Kaftrio, especially since all preventative treatments were continued

during the landmark Kaftrio RCTs.[39,187-189] What is certain is that PwCF will experiment by stopping treatments if they feel well, therefore, any studies to evidence this need to be robustly designed to ensure they are adequately powered, objectively measure adherence, and consider what might be an acceptable clinically relevant decline in FEV1 if nebulised therapy is stopped. Without this, the CF community cannot be fully informed of the true outcomes. A potential study that may provide some answers is NEEMO (National Efficacy-Effectiveness CFTR Modulator Optimisation).[190] This is a 5-year prospective observational study that is nested within the CFHealthHub digital learning health system.[191] It uses real-world objective data to determine the effect of co-adherence to inhaled therapies on FEV1 decline among adults prescribed Kaftrio, and the difference in co-adherence before and after the initiation of Kaftrio.[190]

As the CF population continues to grow and patient expectations have changed, standard care has become inefficient. A disadvantage of intermittent monitoring in a chronic condition is that declines in health can be missed or delayed and at other times patients can be seen in good health when this may not be necessary. Using telemedicine and remote monitoring is one way to overcome this by continual monitoring but it does not work for all patients.[192] For those who readily 'monitor' their condition, this approach may be appropriate but for those who are 'blunters' engaging with monitoring becomes more difficult.[193] 'Blunters' often struggle to adhere, self-manage, and engage with healthcare providers yet this group usually requires the most rescue treatment and can be the hardest to reach.[193] It is therefore important to tailor care to ensure the 'blunters' are not under-served and are supported in the same way as those who have high self-efficacy and regularly engage.

Detecting exacerbations has become more difficult as many PwCF on Kaftrio no longer have typical symptoms and the amount of sputum produced has reduced such that most people are no longer productive. As a result, they aren't always alerted to seek medical attention, and if a decline in FEV1 is incidentally found they may be more reluctant to agree to treatments if they feel well or have less severe symptoms. A previous study suggests that people with CF were less willing to accept a recommendation for intravenous antibiotics if they were less symptomatic.[111] This means that even if an exacerbation is identified early through remote monitoring it does not necessarily translate into the desired outcome of appropriate treatments to reverse the FEV1 decline. This has been demonstrated in a number of remote monitoring studies where although more exacerbations were identified patients chose not to accept IV antibiotics but instead agreed to oral antibiotics which may not be as effective.[53, 54, 194, 195] The ideal scenario would be to predict who is at risk of the greatest FEV1 decline or identify the onset of an exacerbation before the decline in FEV1. Since once the FEV1 decline

has occurred it is easy to detect but perhaps not as easy to resolve. It is also difficult to know if the FEV1 decline seen in an individual patient from baseline is an acute decline or more gradual only revealed at the time of an exacerbation. To date, there is sparse literature exploring the factors associated with the degree of acute FEV1 decline during exacerbations.[196, 197]

The findings in this thesis have raised many more questions but the results produced add to the current literature and ongoing research studies. The most readily available non-burden monitoring tool, the I-neb® has been explored and this study has systematically developed a set of criteria for an alternative clinic process. Finding ways to use both of these alongside targeted medications should be a step towards providing the right care and treatments personalised to the right patients at the right time and in the right context. Therefore, though the research findings may not alter current clinical practice, the insights generated may be worthy of future research.

8.4 Future directions

Following the recent transformations in CF care it is ever more important to identify ways to effectively monitor PwCF at a distance and tailor clinical care. The results presented in this thesis have identified a need for further work to generate robust evidence using systematic approaches.

Development and validation of the Lung Health predictive model could have used different methods which may have given a better understanding of the breathing parameters. Instead of dichotomising the data a restricted cubic spline regression[198] or even machine learning methods e.g. generalised boosted regression models[199] could be performed since the variables are continuous and this would not assume there is a linear relationship. Using a data-driven approach would be more complex but could be carried out with the right expertise. This study is essentially an effectiveness study however, conducting an efficacy study would be of value to determine if there is a true correlation between changes in breathing parameters and changes in FEV1 in an ideal (or laboratory) condition.

The clinic attendance criteria can be prospectively evaluated in a single centre to identify any practical limitations, then iterated further with the use of quality improvement methods (PDSA-Plan-Do-Study-Act cycles)[200] before further testing in a multi-centre setting. This approach may also allow the set of criteria to be personalised according to the availability of resources and subtle differences in care delivery of different CF centres.

A plan is in place to publish the results of this thesis. The publication plan includes the Lung Health study using the I-neb® as a tool to potentially monitor lung health and to describe in more detail the full clinic attendance set of criteria developed so that this can hopefully stimulate further future research.

8.5 Concluding remarks

The fight for as normal a life as possible has meant CF has always been at the forefront of revolutionary medical advances and improvements in care quality. Over the years as life expectancy has dramatically increased this has brought with it new challenges and problems to address. The introduction of the highly efficacious CFTR drug modulators has been another major milestone and the unexpected COVID-19 pandemic has started to transform CF care further into a more remote digital world.

This thesis has explored the novel use of I-neb® breathing parameters to function as a predictive model to detect acute changes in FEV1 and has developed a set of clinic attendance criteria as a stepping stone to streamlining clinics in the future. The thesis found it was difficult to develop an accurate statistical model to predict FEV1 decline using the breathing parameters from the I-neb® and it was challenging to identify a set of clinic attendance criteria. It is hoped that some of the insights in this thesis may stimulate future research. It may be that the breathing parameters can eventually play a role as a passive sensor in a machine-learning process and be applied to a set of more refined clinic attendance criteria allowing tailored patient care.

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Last updated October 2022

Appendix 2: sensitivity and specificity with clustered data

Prof Michael J Campbell February 2020

Method

One test per person

Consider two binary variables, Truth and Test. Truth takes the value 1 if a participant has a condition/disease and zero otherwise and Test takes the value 1 if the test for the condition is positive and zero otherwise.

They are usually summarised in the following 2x2 table

Table 1 Sensitivity and specificity in a two by two table

		Truth (D)		Total
		1 = +ve	0 = -ve	
Test (T)	1 = +ve	a	b	a+b
	0 = -ve	c	d	c+d
Total		a+c	b+d	n

Then the *sensitivity* of the test is the probability that a person has a positive result *given* they have the disease which is a/(a+c) and the *specificity* of the test is the probability that the test is negative *given* the person does not have the disease namely d/(b+d).

If the disease is present the chance of a positive test is P(+|D+)= a/(a+c) and if the disease is absent it is P(T+|D-)=b/(b+d). The positive likelihood ratio is the ratio of the probability of a positive test given the condition is present to the probability of a positive test given the disease is absent which is {a/(a+c)}/{b/(b+d)}. This can be seen as LR(+) =sensitivity/(1-speciificity).

The negative likelihood ratio is the ratio of the probability of a negative test given disease is present to the probability of a negative test given the disease is absent. This can be shown to be LR(-)={c/(a+c)}/{d/(b+d)}=(1-sensitivity)/specificity.

We can write this as a log-linear model. Suppose T and D are binary 0/1 variables indicating +/-ve test and present/absence of disease respectively.

The model is Log(E(T))=α+βD (1) where E(T) is the expected value of T=P(T+)

When D=1 log P(T+|D+)=α+β

When D=0 log P(T+|D-)=α.

Thus β= log P(T+|D+)- log P(T+|D-) and so LR(+)=exp(β)

Similarly if we model T'=1-T in model (1) we get LR(-)=exp(β)

If we assume that P(T+) is binomially distributed, then we can fit this model as a log-linear model using any statistical package.

If we restrict the data to D=1, we get Log P(T+|D+)=α =sensitivity

If we restrict the data to D=0, log(T'|D-)=α=specificity

Extension to multiple tests on the same person.

In this case, we assume that for each person, the individual tests are independent but that each person. i. has an additional but different fixed probability of a positive test, independent of whether they had the disease or not.

The model is now

Log(T)=$\alpha+\tau_i+\beta D$ (2) where τ_i are i.i.d random variables, usually assumed N(0, σ^2).

We can fit model 2 using a random effects model, or using generalised estimating equations with an exchangeable correlation and the cluster variable is the id number of the individual.

All modelling used the GLM module in Stata(13)

Example from Cystic Fibrosis

Two data sets on a Test and FEV decline (condition)

The large data set comprises 703 observations on 61 individuals. The smaller data set comprises 94 observations on 13 individuals

Unadjusted for subject analysis

Sensitivity

Stata code: binreg Test if FEV1d5==1, rr

```
------------------------------------------------------------------------------
             |                 EIM
        Test | Risk Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .0911271    .014093   -15.49   0.000     .0672987    .1233923
------------------------------------------------------------------------------
```

i.e. the sensitivity is 0.091 (95%CI 0.067 to 0.123)

Specificity

```
Stata code binreg Testm1 if FEV1d5==0, rr
------------------------------------------------------------------------------
             |                 EIM
       Testm1| Risk Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .9020979   .0175728    -5.29   0.000     .8683051    .9372058
------------------------------------------------------------------------------
```

i.e. sensitivity =0.902 (95%CI(0.868 to 0.937)

Positive Likelihood ratio

```
binreg Test FEV1d5, rr
------------------------------------------------------------------------------
             |                 EIM
        Test | Risk Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      FEV1d5 |   .9307982   .2205323    -0.30   0.762     .5850352    1.480912
       _cons |   .0979021   .0175727   -12.95   0.000     .0688665    .1391798
------------------------------------------------------------------------------
```

i.e LR(+)=0.93 95% CI (0.59 to 1.48)

Negative likelihood ratio

binreg TT FEV1d5 , rr

```
------------------------------------------------------------------------------
             |                 EIM
      Testm1 | Risk Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      FEV1d5 |    1.00751   .0250849     0.30   0.764     .9595251    1.057895
       _cons |   .9020979   .0175728    -5.29   0.000     .8683051    .9372058
------------------------------------------------------------------------------
```

i.e. LR(-)= 1.01 (95% CI 0.96 to 1.06)

Large data set, allowing for clustering within individuals

Table 2 shows the number of measurements per individual

Table 2

ID	Freq.	Percent	Cum.
1	4	0.57	0.57
2	22	3.13	3.70
3	12	1.71	5.41
4	35	4.98	10.38
5	27	3.84	14.22
6	4	0.57	14.79
7	18	2.56	17.35
8	8	1.14	18.49
9	10	1.42	19.91
10	12	1.71	21.62
11	48	6.83	28.45
12	28	3.98	32.43
13	14	1.99	34.42
14	7	1.00	35.42
15	23	3.27	38.69
16	3	0.43	39.12
17	12	1.71	40.83
18	1	0.14	40.97
19	2	0.28	41.25
20	11	1.56	42.82
21	5	0.71	43.53
22	2	0.28	43.81
23	19	2.70	46.51
24	22	3.13	49.64
25	19	2.70	52.35
26	9	1.28	53.63
27	15	2.13	55.76
28	7	1.00	56.76
29	5	0.71	57.47
31	2	0.28	57.75
32	2	0.28	58.04
33	18	2.56	60.60

34	2	0.28	60.88
35	5	0.71	61.59
36	3	0.43	62.02
37	17	2.42	64.44
38	8	1.14	65.58
39	6	0.85	66.43
40	3	0.43	66.86
41	29	4.13	70.98
42	5	0.71	71.69
43	9	1.28	72.97
44	8	1.14	74.11
46	15	2.13	76.24
47	22	3.13	79.37
48	10	1.42	80.80
49	2	0.28	81.08
50	18	2.56	83.64
51	8	1.14	84.78
52	18	2.56	87.34
53	3	0.43	87.77
54	25	3.56	91.32
55	24	3.41	94.74
57	6	0.85	95.59
59	18	2.56	98.15
60	12	1.71	99.86
61	1	0.14	100.00
Total	703	100.00	

Sensitivity

Stata code . xtgee Test if FEV1d5==1, family(binomial 1) link(log) corr(exchangeable) eform

```
GEE population-averaged model                   Number of obs      =       417
Group variable:                           ID    Number of groups   =        52
Link:                                    log    Obs per group: min =         1
Family:                             binomial                   avg =       8.0
Correlation:                   exchangeable                   max =        38
                                               Wald chi2(0)       =         .
Scale parameter:                          1    Prob > chi2        =         .

------------------------------------------------------------------------------
        Test |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .0965855   .0220685   -10.23   0.000     .0617197    .1511471
```

Specificity

. xtgee Testm1 if FEV1d5==0, family(binomial 1) link(log) corr(exchangeable) eform

```
GEE population-averaged model                   Number of obs      =       286
Group variable:                           ID    Number of groups   =        54
Link:                                    log    Obs per group: min =         1
Family:                             binomial                   avg =       5.3
Correlation:                   exchangeable                   max =        17
                                               Wald chi2(0)       =         .
Scale parameter:                          1    Prob > chi2        =         .

------------------------------------------------------------------------------
      Testm1 |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .8957537   .0236277    -4.17   0.000      .850621    .9432811
```

Positive Likelihood Ratio

```
. xtgee TTm1 FEV1d5, family(binomial 1) link(log) corr(exchangeable) eform

GEE population-averaged model                   Number of obs      =       703
Group variable:                           ID    Number of groups   =        57
Link:                                    log    Obs per group: min =         1
Family:                             binomial                   avg =      12.3
Correlation:                   exchangeable                   max =        48
                                               Wald chi2(1)       =      0.86
Scale parameter:                          1    Prob > chi2        =    0.3550

------------------------------------------------------------------------------
        TTm1 |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      FEV1d5 |   .8132361   .1817707    -0.92   0.355     .5247592    1.260298
       _cons |   .1194522   .0250905   -10.12   0.000     .0791411    .1802961
------------------------------------------------------------------------------
```

Negative likelihood ratio

```
. xtgee TT FEV1d5, family(binomial 1) link(log) corr(exchangeable) eform

GEE population-averaged model                   Number of obs      =       703
Group variable:                           ID    Number of groups   =        57
Link:                                    log    Obs per group: min =         1
Family:                             binomial                   avg =      12.3
Correlation:                   exchangeable                   max =        48
                                               Wald chi2(1)       =      0.84
Scale parameter:                          1    Prob > chi2        =    0.3605

------------------------------------------------------------------------------
          TT |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      FEV1d5 |   1.025336   .0280578     0.91   0.361     .9717922    1.081829
       _cons |   .8805478   .0250905    -4.46   0.000     .8327193    .9311235
------------------------------------------------------------------------------
```

Small data set

Sensitivity

```
. binreg Test if FEV1D51==1, rr
```

		EIM				
Test	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_cons	.2647059	.0535005	-6.58	0.000	.1781249	.3933711

Specificity

```
. binreg TT1 if FEV1D51==0, rr
```

		EIM				
TT1	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_cons	.6153846	.0954111	-3.13	0.002	.4541232	.8339107

Positive likelihood ratio

```
. binreg Test  FEV1D51, rr
```

		EIM				
Test	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
FEV1D51	.6882353	.2202225	-1.17	0.243	.3675938	1.288563
_cons	.3846154	.0954113	-3.85	0.000	.2365209	.6254373

Negative likelihood ratio

```
. binreg TT1  FEV1D51, rr
```

TT1	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
FEV1D51	1.194853	.2046392	1.04	0.299	.8541448	1.671465
_cons	.6153846	.0954111	-3.13	0.002	.4541232	.8339107

Small data set, allowing for clustering within individuals

Table 3 shows the distribution of measurements per individual

Table 3 Number of observations per individual

ID1	Freq.	Percent	Cum.
1	4	4.26	4.26
2	1	1.06	5.32
3	5	5.32	10.64
10	2	2.13	12.77
26	7	7.45	20.21
28	1	1.06	21.28
29	7	7.45	28.72
33	3	3.19	31.91
34	42	44.68	76.60
37	4	4.26	80.85
46	11	11.70	92.55
51	5	5.32	97.87
54	2	2.13	100.00
Total	94	100.00	

Sensitivity

. xtgee Test if FEV1D51==1, family(binomial 1) link(log) corr(exchangeable) eform

```
GEE population-averaged model                   Number of obs      =         68
Group variable:                         ID1     Number of groups   =         11
Link:                                   log     Obs per group: min =          1
Family:                            binomial                    avg =        6.2
Correlation:                   exchangeable                    max =         37
                                               Wald chi2(0)       =          .
Scale parameter:                           1   Prob > chi2        =          .

------------------------------------------------------------------------------
       Test  |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .1465409   .0749745    -3.75   0.000     .0537601    .3994457
------------------------------------------------------------------------------
```

Specificity

. xtgee TT1 if FEV1D51==0, family(binomial 1) link(log) corr(exchangeable) eform

```
GEE population-averaged model                   Number of obs      =         26
Group variable:                         ID1     Number of groups   =         12
Link:                                   log     Obs per group: min =          1
Family:                            binomial                    avg =        2.2
Correlation:                   exchangeable                    max =          5
                                               Wald chi2(0)       =          .
Scale parameter:                           1   Prob > chi2        =          .

------------------------------------------------------------------------------
         TT1 |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .7249825   .1268295    -1.84   0.066     .5145375    1.021499
------------------------------------------------------------------------------
```

Positive likelihood ratio

. xtgee Test FEV1D51, family(binomial 1) link(log) corr(exchangeable) eform

```
GEE population-averaged model                   Number of obs      =         94
Group variable:                         ID1     Number of groups   =         13
Link:                                   log     Obs per group: min =          1
Family:                            binomial                    avg =        7.2
Correlation:                   exchangeable                    max =         42
                                               Wald chi2(1)       =       5.11
Scale parameter:                           1   Prob > chi2        =     0.0237

------------------------------------------------------------------------------
       Test  |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     FEV1D51 |   .3390223   .1621742    -2.26   0.024     .1327543    .8657806
       _cons |   .3325356   .1151324    -3.18   0.001     .1687059      .65546
------------------------------------------------------------------------------
```

Negative likelihood ratio

```
. xtgee TT1 FEV1D51, family(binomial 1) link(log) corr(exchangeable) eform

GEE population-averaged model                   Number of obs      =         94
Group variable:                         ID1     Number of groups   =         13
Link:                                   log     Obs per group: min =          1
Family:                            binomial                    avg =        7.2
Correlation:                   exchangeable                    max =         42
                                               Wald chi2(1)       =       4.54
Scale parameter:                           1   Prob > chi2        =     0.0331

------------------------------------------------------------------------------
         TT1 |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     FEV1D51 |   1.329304   .1775515     2.13   0.033     1.023132    1.727098
       _cons |   .6674644   .1151324    -2.34   0.019     .4759951    .9359524
------------------------------------------------------------------------------
```

Appendix 3 - Adult CF Clinic Attendance Criteria: Pre-consensus meeting questionnaire

Please answer the following questions:

1a. Do you think that certain patient characteristics combined with pre-clinic data[X] may allow adult CF patients to avoid some routine clinic visits?

A: Yes

B: No

C: Other comment (please specify) _____

1b. Do you think this is something that may potentially benefit your CF clinic?

A: Yes

B: No

C: Other comment (please specify) _____

1c. What do you think the important characteristics and pre-clinic data[X] are that would allow you to decide if a clinic could be avoided?

_____

1d. Do you think there are any exceptions or special cases where a clinic could not be avoided?

A: Yes

B: No

C: Other comment (please specify) _____

1e. What do you think the exceptions or special cases are?

_____

Stable lung function, BMI & high inhaled adherence

2a. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline[*] FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 80% in the previous month and has remained stable. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

2b. Would your decision have been different if their baseline* FEV1 is 50%?

A: Yes

B: No

C: Other comment (please specify) _____

2c. Would your decision have been different if their baseline* FEV1 is 30%?

A: Yes

B: No

C: Other comment (please specify) _____

Stable lung function, BMI, high inhaled adherence & high IV days

3. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline* FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. In the past 12 months they have required 28 days of IV antibioticsᶻ. Pre-clinic dataˣ in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence⁺ is 80% in the previous month and has remained stable. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

Change in lung function

4. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline* FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. Pre-clinic dataˣ in the 7 days prior to clinic shows the FEV1 has decreased by 2% from baseline. The BMI has remained stable and the inhaled adherence⁺ is 80% in the previous month and has remained stable. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

5. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline* FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 has decreased by 5% from baseline. The BMI has remained stable and the inhaled adherence+ is 80% in the previous month and has remained stable. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

6. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline* FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 has decreased by 10% from baseline. The BMI has remained stable and the inhaled adherence+ is 80% in the previous month and has remained stable. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

Change in inhaled adherence

7. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline* FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence+ is 60% in the previous month. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

8. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline[*] FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 40% in the previous month. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

9. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline[*] FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 20% in the previous month. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

Change in inhaled adherence & IV days

10. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline[*] FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. In the past 12 months they have required 14 days of IV antibiotics[z]. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 60% in the previous month. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

11. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline[*] FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. In the past 12 months they have required 28 days of IV antibiotics[z]. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 60% in the previous month. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

12. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline[*] FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. In the past 12 months they have required 14 days of IV antibiotics[z]. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 40% in the previous month. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

13. You are reviewing a 19 year old patient with CF at a regular scheduled clinic visit. They are chronically colonised with *Pseudomonas aeruginosa*. Their baseline[*] FEV1 is 70% and their BMI is 23. They take daily promixin bd and Dnase od via an I-Neb. In the past 12 months they have required 28 days of IV antibiotics[z]. Pre-clinic data[X] in the 7 days prior to clinic shows the FEV1 and BMI have remained stable at baseline. The inhaled adherence[+] is 40% in the previous month. The patient has identified no issues that they wish to discuss in clinic. At this point if the preceding information had been available pre-clinic do you think?

A: A clinic visit is likely to be unnecessary and potentially avoidable

B: A clinic visit would definitely still be required

C: Other comment (please specify) _____

Change in weight/BMI

14. For CF patients using enteral feeding it is expected that they will need to be seen by a dietitian in all routine clinics.

A: Agree

B: Disagree

C: Other comment _____

15. For CF patients not enterally fed it is expected that they will need to be seen by a dietitian in all routine clinics if their BMI is <19, or if there BMI is 19 – 21.9/22.9 with a 5% weight loss in the last 12 weeks, or if their BMI is >22/23 with a 5% weight loss in the last 12 weeks.

A: Agree

B: Disagree

C: Other comment _____

16. For CF patients not enterally fed it is expected that if the BMI is 19 – 21.9/22.9 and their weight has remained stable that they will need to be seen by a dietitian every 6 months. This is the same for those with pancreatic insufficiency as long as there are no other clinical indicators (e.g. steatorrhoea, or recent change to enzyme dosing, or newly diagnosed pancreatic insufficiency).

A: Agree

B: Disagree

C: Other comment _____

17. For CF patients not enterally fed it is expected that if the BMI is >22/23 and their weight has remained stable that they will need to be seen by a dietitian every 12 months. This is the same for those with pancreatic insufficiency as long as there are no other clinical indicators (e.g. steatorrhoea, or recent change to enzyme dosing, or newly diagnosed pancreatic insufficiency).

A: Agree

B: Disagree

C: Other comment _____

CFRD

18. In patients with CFRD it is expected that they will need to be seen in routine clinic (alongside their CFRD specialist clinic visits which should be a minimum of once a year if stable) if there has been a preceding change in insulin or if their HbA1c within the past 3 months has increased to >70 or decreased to <60 compared to the previous 3 month result. If however their HbA1c has remained stable and they are well a routine clinic visit may be avoidable.

A: Agree

B: Disagree

C: Other comment _____

ABPA

19. For CF patients with active ABPA requiring monitoring and/or treatment[1] it is expected that they will need to be seen in all routine clinics. However in those with quiescent ABPA it is expected that the decision to see in a routine clinic can be guided by the change in other measures i.e. FEV1, BMI, and adherence.

A: Agree

B: Disagree

C: Other comment _____

[1] As per the 2003 CFF Consensus Conference Guidance for ABPA in CF

Table 9. Treatment recommendations for allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF).

Total serum IgE, IU/mL	Pulmonary symptoms and/or worsening PFT results	New infiltrates on CR or CT	Positive serology[a]	Treatment recommendation(s)
>1000 or >2-fold rise from baseline	Yes	Yes	Yes	Treat for ABPA
>1000 or >2-fold rise from baseline	No	No	Yes	No treatment; monitor IgE, CR, PFT
>1000 or >2-fold rise from baseline	No	Yes	Yes	Treat for CF-related infection; consider treatment for ABPA if no response
>1000 or >2-fold rise from baseline	Yes	No	Yes	Consider treatment for ABPA, CF-related infection, and/or asthma
>500 in the past; no change from baseline	Yes	Yes	Yes	Treat for CF-related infection; consider treatment for ABPA or asthma if no response
500–1000	Yes	Yes	Yes	Treat for ABPA

NOTE. CR, chest radiography; PFT, pulmonary function testing.

[a] Aspergillus-specific IgG or IgE or presence of precipitins to *Aspergillus fumigatus*. Because these test results may not be available quickly, they are not required for initiation of therapy but should be obtained.

Stevens DA et al. Allergic Bronchopulmonary Aspergillus in Cystic Fibrosis-State of the Art: Cystic Fibrosis Foundation Consensus Conference. CID 2003:37 (Suppl 3). S253.

Thank you for your time

Definitions:

[X]Community monitored FEV1, BMI, inhaled adherence

[*] Best FEV1 or BMI in the past 12 months

[+]I-Neb data download

[z]Number of IV days in the previous 12 month annual review period