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A Structured Airway Clearance and Exercise Program to Improve Clinical Outcomes in Cystic Fibrosis

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A STRUCTURED AIRWAY CLEARANCE AND EXERCISE PROGRAM TO IMPROVE CLINICAL OUTCOMES IN CYSTIC FIBROSIS

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Table of Contents

List of Tables

List of Figures

Abstract

Cystic fibrosis is a genetic disorder that impairs mucus clearance in the lungs, causing chronic inflammation and recurrent infections. Several airway clearance modalities are recommended to improve or preserve lung function, including chest percussion and exercise. However, there is no clinical consensus on the best treatment regimen to maximize the effect of airway clearance therapies and exercise. The purpose of this study is to determine whether a structured order of exercise and airway clearance therapy improves lung function. Using a randomized study, we will evaluate the effectiveness of a structured regimen compared to a non-structured regimen by following lung function over one year. Upon completion, we expect the structured program will result in improved lung function when compared to the non-structured program. Our results may benefit cystic fibrosis patients by informing the adoption of structured exercise and airway clearance practices to improve lung function and quality of life.

Chapter 1 – Introduction

1.1 Background

Cystic fibrosis (CF) is an autosomal recessive disease that affects 1 in every 3,000 to 4,000 live births.[1] It is estimated that over 30,000 people in the United States have CF. The disease is a result of loss of function mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene,[2] which causes decreased chloride and bicarbonate secretion and impaired fluid transport.[3] The most severe clinical impact in terms of morbidity and mortality of CF is manifested in the lungs.[4] CFTR proteins in the lungs are responsible for maintaining airway pH and fluid balance at the mucosal interface, both of which ultimately modify the viscosity of mucus.[5] Mutations in these proteins cause an impairment in mucus clearance and makes the lungs more susceptible to mucoid impaction.[6] Impaired mucociliary clearance in CF contributes to bacterial pathogen colonization and growth that causes recurrent infections and can lead to exacerbations.[7]

In addition to impaired mucus clearance, the deficiency in bicarbonate secretion causes decreased pH within the lungs.[5] This acidic environment inactivates antimicrobial peptides in the lungs and results in an impaired host defense. This, in turn, leads to "chronic non-resolving inflammation driven by continuous recruitment of immune cells."[5] The immune cells recruited into the lungs release oxidants and proteases that damage the lung tissue. Ultimately, this excessive inflammatory response leads to the development of bronchiectasis and further impairments in mucociliary clearance.

Overall, impaired mucus clearance in CF leads to chronic inflammation and tissue destruction that decreases lung function, increases morbidity, and increases mortality.[6] Progressive respiratory insufficiency is the most common cause of mortality for people with CF.[8] In fact, 85% of deaths in cystic fibrosis are due to lung disease.[9] Clinically, the

amount of air expired in the first second of forced expiration, known as FEV_1, is used to monitor disease severity and progression.[10] For example, exacerbations have been shown to directly cause a decrease in lung function and an increase in mortality.[11] Importantly, lower lung function and more frequent exacerbations also negatively impact patients' health-related quality of life.[12,13] The detrimental effects of decreased lung function and increased exacerbations on patients' overall health and quality of life underline the importance of preserving lung function and preventing exacerbations.

With the goal to increase mucus clearance, decrease exacerbations, and improve lung function,[14] patients with CF spend on average 108 minutes performing CF treatments daily.[15] In addition to medical treatments, therapies include airway clearance therapy (ACT) and exercise. ACT can be accomplished through multiple modalities, including breathing techniques, percussion, drainage, chest compression, and physical activity.[9] As studies have shown that ACT increases sputum clearance, maintains lung function, and improves quality of life, it is recommended for all patients with CF.[9] Also, aerobic exercise is recommended as an adjunct to ACT due to its benefit in lung function as well as overall physical health.

An important part of CF treatment is the use of CFTR modulators. These medications target specific molecular defects in CFTR proteins and lead to improved or restored function.[16] CFTR modulators improve lung function, decrease the risk of exacerbations, decrease the rate of lung function decline, and improve mucociliary clearance.[16] Recently available triple combination therapy significantly improved lung function with an average increase of 10% in FEV_1.[17] These results marked significant progress in advancing the treatment options for people with CF.

In summary, CF is a multiorgan, hereditary disease that adversely impacts the lungs and leads to a decline in lung function over time. It is critical to moderate this decline to prevent exacerbations, infections, and respiratory failure. Preservation of lung function is also important to maintain a higher quality of life for patients. To accomplish this, patients partake in an extensive treatment regimen with the goal of increasing mucus clearance, preventing exacerbations, and improving lung function.

1.2 Statement of the Problem

Lung function decline is a common clinical manifestation of cystic fibrosis that often progresses through adulthood. Since patients spend an extensive amount of time on treatments to moderate this decline, it would be helpful to ensure that treatments are performed beneficially. We hypothesize that integrating ACT and exercise would improve lung function and quality of life for CF patients. Exercise and ACT are both recommended in the treatment of CF, but there is limited data on a formalized combination of the two over an intervention period longer than 2-4 days.[18-21]

This study will combine ACT and exercise with the aim of maximizing the effectiveness of therapy. Importantly, this study will take place over 1 year, thus allowing us to longitudinally follow lung function as well as our secondary outcomes. A key strength of this study is that it will help understand whether the integration of ACT and exercise plays a significant role in lung function, thus allowing patients to maximize results with their treatments. The results of this study could inform future recommendations for how to most effectively perform ACT and exercise in CF.

1.3 Goals and Objectives

The primary goal of our study is to assess the effectiveness of a structured ACT and exercise program in improving lung function over 1 year. Our secondary goals are to evaluate the effect of the structured program on the frequency of exacerbations and self-reported quality of life. Our primary outcome is change in FEV_1 over 1 year. This will be measured quarterly, so changes can be trended during the course of the year. Secondary outcomes will include number of exacerbations and health-related quality of life. Exacerbations will be assessed through a medical record chart review and defined according to previously reported criteria. Quality of life will be measured through a survey given to patients at each quarterly visit.

1.4 Hypothesis

A structured program of airway clearance therapy and exercise in adults with cystic fibrosis will significantly improve baseline FEV_1 percent predicted over one year compared to a non-structured program.

1.5 Definitions

Airway Clearance Therapy (ACT): ACT is a broad term that covers a variety of techniques used to clear mucus from the lungs.[22] It includes chest physiotherapy, active breathing techniques, positive expiratory pressure therapy, vibration, and exercise. This is usually started at the time of diagnosis and is performed daily.

FEV_1: FEV_1 is the volume of air forcefully exhaled in 1 second.[23] It is measured using spirometry and used to determine the presence of airflow obstruction. It is often expressed as a percent predicted value to clinically classify the severity of the disease. The percent predicted is calculated by comparing to a healthy reference population with similar height, age, and sex.[24]

1.6 References

1. Sanders DB, Fink AK. Background and Epidemiology. *Pediatr Clin North Am.* 2016;63(4):567-584.
2. Knowles MR, Durie PR. What Is Cystic Fibrosis? *New England Journal of Medicine.* 2002;347(6):439-442.
3. Habib A-RR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. *Sci Rep.* 2019;9(1):7234-7234.
4. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. *Nature Reviews Disease Primers.* 2015;1(1):15010.
5. Cantin AM, Hartl D, Konstan MW, Chmiel JF. Inflammation in cystic fibrosis lung disease: Pathogenesis and therapy. *Journal of Cystic Fibrosis.* 2015;14(4):419-430.
6. Quinton PM. Cystic fibrosis: a disease in electrolyte transport. *Faseb j.* 1990;4(10):2709-2717.
7. Goss CH, Burns JL. Exacerbations in cystic fibrosis · 1: Epidemiology and pathogenesis. *Thorax.* 2007;62(4):360.
8. Lynch JP, 3rd, Sayah DM, Belperio JA, Weigt SS. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Semin Respir Crit Care Med.* 2015;36(2):299-320.
9. Flume PA, Robinson KA, O'Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care.* 2009;54(4):522-537.
10. Horsley A, Siddiqui S. Putting lung function and physiology into perspective: cystic fibrosis in adults. *Respirology.* 2015;20(1):33-45.
11. Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *European Respiratory Journal.* 2012;40(1):61.
12. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest.* 2002;121(1):64-72.
13. Wen Y, Wang D, Zhou M, Zhou Y, Guo Y, Chen W. Potential Effects of Lung Function Reduction on Health-Related Quality of Life. *Int J Environ Res Public Health.* 2019;16(2):260.
14. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med.* 2011;183(11):1463-1471.
15. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *J Cyst Fibros.* 2009;8(2):91-96.
16. Clancy JP, Cotton CU, Donaldson SH, et al. CFTR modulator theratyping: Current status, gaps and future directions. *Journal of Cystic Fibrosis.* 2019;18(1):22-34.
17. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with

cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet.* 2019;394(10212):1940-1948.
18. Kriemler S, Radtke T, Christen G, Kerstan-Huber M, Hebestreit H. Short-Term Effect of Different Physical Exercises and Physiotherapy Combinations on Sputum Expectoration, Oxygen Saturation, and Lung Function in Young Patients with Cystic Fibrosis. *Lung.* 2016;194(4):659-664.
19. Reix P, Aubert F, Werck-Gallois M-C, et al. Exercise with incorporated expiratory manoeuvres was as effective as breathing techniques for airway clearance in children with cystic fibrosis: a randomised crossover trial. *Journal of Physiotherapy.* 2012;58(4):241-247.
20. Baldwin DR, Hill AL, Peckham DG, Knox AJ. Effect of addition of exercise to chest physiotherapy on sputum expectoration and lung function in adults with cystic fibrosis. *Respiratory Medicine.* 1994;88(1):49-53.
21. Bilton D, Dodd ME, Abbot JV, Webb AK. The benefits of exercise combined with physiotherapy in the treatment of adults with cystic fibrosis. *Respiratory Medicine.* 1992;86(6):507-511.
22. Wilson LM, Morrison L, Robinson KA. Airway clearance techniques for cystic fibrosis: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev.* 2019;1(1):CD011231-CD011231.
23. Ranu H, Wilde M, Madden B. Pulmonary function tests. *Ulster Med J.* 2011;80(2):84-90.
24. VanDevanter DR, Konstan MW. Outcome measures for clinical trials assessing treatment of cystic fibrosis lung disease. *Clin Investig (Lond).* 2012;2(2):163-175.

Chapter 2 – Review of the Literature

2.1 Introduction

A review of the literature was performed from December 6, 2019 through June 5, 2020 using Pubmed, Ovid, Scopus, and Cochrane Medical Library. Full articles were used after reading the titles and abstracts to ensure topic relevance. The search terms used for the relationships between our independent and dependent variables included *Cystic Fibrosis, Airway Clearance Therapy, Respiratory Therapy, Physiotherapy, Exercise, Exercise Therapy, Physical Activity, Lung Function, FEV_1, Sputum Production, Sputum Expectoration, Healthy Adults, Exacerbations, Quality of Life, Adherence, and Treatment Adherence.* Key terms used for information regarding study methodology included *Cystic Fibrosis, Adherence, Age, Lung Function, Lung Function Decline, CFTR Mutation, Bacterial Colonization, Pseudomonas aeruginosa, Burkholderia cepacia, Triple Therapy, Spirometry, Spirometry Guidelines, Pulmonary Function Tests, NHANES III, FEV_1 Variability, Quality of Life, Cystic Fibrosis Questionnaire Revised, Diagnostic Criteria, Minimal Clinically Important Difference, Exercise, and Adverse Events.*

2.2 Cystic Fibrosis and Airway Clearance Therapy

ACT is used in CF to help facilitate mucus clearance. The physiological mechanism is likely a combination of multiple effects.[1] One is an increase in absolute peak expiratory flow rate that pushes mucus to the oropharynx. Another is a decrease in the mucus viscosity as a result of oscillations that leads to increased transport. Lastly, ACT increases spontaneous coughs that clear mucus through mechanical stimulation.

ACT can be delivered using different modalities. Conventional chest physiotherapy (CPT) includes postural drainage, percussion, and vibration and has been a

part of therapy for over forty years.[2] More recently, methods like high-frequency chest wall oscillation (HFCWO) and oscillating positive expiratory pressure (OPEP) have been introduced with the goal of making ACT easier to adhere to at home. HFCWO works by creating cough-like forces and vibrations to loosen mucus in the lungs, and OPEP creates positive pressure to keep airways open while creating vibrations to loosen mucus. Increasing mucus transport within the lungs is critical to help prevent infections and inflammation.[3] With multiple options for ACT, there have been numerous studies comparing the efficacy of each modality.

The Cystic Fibrosis Foundation's (CFF) Pulmonary Therapies Committee reviewed studies on ACT by focusing on sputum clearance, lung function, exacerbations, and quality of life.[4] Evidence set forth by the CFF review determined that ACT has a moderate benefit in increased sputum clearance, improved lung function, and better quality of life. Therefore, the CFF currently recommends ACT for all patients with CF. The CFF committee also determined that although all of these methods are considered to be beneficial, there is insufficient data to suggest that one modality of ACT is superior to another. Therefore, they recommended that the prescribed form of ACT should be individualized to the patient.

For example, a crossover study evaluated HFCWO and OPEP by randomizing 29 CF patients to 4 weeks of each therapy separated by a 2-week washout period.[2] The primary outcome was spirometry and lung volumes, and the secondary outcomes were patient satisfaction and compliance. The results showed no significant differences in FEV_1 between the two therapies. Also, since there was no significant decline in lung function from baseline with either therapy, both options were considered effective. In

terms of patient opinions, reported efficacy was significantly higher for HFCWO, and reported convenience was significantly higher for OPEP. Patient preference was 50% for HCFWO, 37% for OPEP, and 13% still preferred CPT. Lastly, patient reported adherence rates were similar at 88% for HFCWO and 92% for OPEP.

These results are consistent with the CFF recommendation that no ACT modality is superior in terms of effectiveness. This study also demonstrates the variation in patient preferences between HFCWO, OPEP, and CPT. The inclusion of patient preference as an outcome is a strength of this study because it demonstrates the importance of allowing patients to choose their ACT method. The results of this study and the current recommendations both support our reasoning that patients in our study may complete their preferred method of ACT without significantly confounding our results.

Similar results were found in a non-inferiority study that compared multiple forms of ACT with FEV_1 as the primary outcome.[5] They randomized 75 patients with CF to active breathing, autogenic drainage, positive expiratory pressure (PEP), or oscillating PEP (OPEP). The frequency and duration of ACT were individualized for the participants. Lung function measurements were taken at 0, 6, and 12 months. At the end of 1 year, they found no significant difference ($P = 0.35$) in FEV_1 between all 5 modalities, but they did find a significant decline ($P = 0.02$) in FEV_1 overall. The FEV_1 percent predicted change for the whole group was -1.8%.

A strength of this study was allowing subjects to complete their individually required amount of ACT. The results show that even with varying amounts of ACT, there was no significant difference between the groups. They used this design because it is more similar to clinical practice since patients have different requirements and

preferences for ACT. Since our study timeframe is also 1 year, this approach seems the most feasible as patient requirements change over time. As a whole, these results support that if the patients in our study complete their preferred form of ACT for an individualized amount of time, it should not cause significant differences between groups.

Another important discussion point from this study is the statistically significant decline in FEV_1 over the year. The decrease of -1.8% of percent predicted FEV_1 is similar to the international average during the study time at -2.0%. Since this study lasted 1 year, the results show the progressive decline in lung function in patients with CF despite therapies. As our study uses the same time period, we may potentially see a decline in lung function in both groups, but we expect a slower decline in the intervention group. This will be reflected in our statistical analysis by using the mean absolute change in baseline FEV_1.

The studies discussed above support the recommended guidelines that ACT is beneficial, and there are no significant differences between ACT modalities. The results of these studies also demonstrate the importance of recognizing that CF patients require different amounts of ACT, and they have different preferences for ACT modalities.

2.3 Exercise

2.3.1 Exercise Benefits in Healthy Adults

It is well understood that exercise has numerous positive health effects and is frequently encouraged for most adults. For example, a crossover study evaluated the effect of exercise on lung function.[6] They included healthy adults ages 25-55 and recruited a total of 24,536 participants. Baseline lung function measures were taken, and participants were categorized to an activity level ranging from sedentary to active. They

found a significant association between FEV_1 and physical activity (measured in miles of walking or jogging) with a P value of < 0.001. The authors concluded that being sedentary was associated with lower lung function.

In addition to pulmonary health, exercise also affects quality of life. For example, a study assigned 36 subjects who did not regularly exercise to 20 minutes of aerobic exercise 3 times per week in addition to weight training.[7] They measured quality of life at baseline and every 8 weeks for 24 weeks using the Health Status Survey. They found a significant improvement in physical functioning ($P = 0.004$), bodily pain ($P = 0.005$), general health ($P = 0.009$), vitality ($P < 0.001$), and mental health scores ($P = 0.005$) compared to controls. A significant improvement was also seen in depression ($P = 0.048$) and stress ($P = 0.036$) in the intervention group compared to controls. The studies discussed above show the benefit of exercise on both physical and mental health in the general population. We will apply these concepts to adults with CF and aim to have similar effects with a structured exercise and ACT program.

2.3.2 Exercise and Cystic Fibrosis

Similar to the results shown in healthy adults, many studies have shown the benefits of exercise for patients with CF. These benefits include improved aerobic capacity, quality of life, weight gain, and lung function.[8] Multiple proposed mechanisms contribute to the benefit of exercise on lung function. This includes mechanical vibrations similar to ACT, increased ventilation, and inhibition of the sodium channel in the respiratory epithelium that results in increased water content of mucus in the lungs. [9] These mechanisms ultimately result in increased mucus clearance. Conversely, low

physical activity can cause decreased mucus clearance, thus leading to an increased risk of infections and ultimately lung function decline.[10]

The CFF Pulmonary Therapies Committee reviewed the data on the benefit of aerobic exercise in patients with CF.[4] They determined that aerobic exercise should be recommended to patients as adjunct therapy due to its moderate benefit in airway clearance, as well as a reduced risk of cardiovascular disease, osteoporosis, and depression. Despite the benefits of exercise mentioned above and to be discussed below, disease burden and adherence remain obstacles in implementation.[8] Our proposed intervention will aim to address both of these issues by creating a structured exercise program to mitigate the severity of lung function decline and improve adherence.

2.3.3 Exercise and Lung Function

Orenstein et al. conducted a 3-month supervised running program for people with CF while measuring exercise tolerance and pulmonary function.[11] It included 35 subjects who volunteered and were divided into either the exercise or the control group. All patients completed an initial evaluation including oxygen consumption and pulmonary function tests by exercising on a bicycle. The control group was instructed to maintain their usual level of activity, and the exercise group was assigned to three, 1-hour training sessions per week. The training consisted of a 5-10 minute warm-up with stretching, 10 minutes of jog-walk that increased to 30 minutes over the 3 months, a 5-minute cool-down of slow walking, and lastly recreational games. During the jog-walk, participants were to measure their heart rate by pulse palpation and maintain 70-85% of their maximum heart rate. The participants repeated the same initial tests at the end of the 3 months. They found a statistically significant ($P < 0.005$) improvement in the exercise

tolerance of the exercise group, and the exercise tolerance of the control group was slightly lower although not statistically significant. The FEV_1 of the control group was also significantly lower at the end of 3 months compared to baseline. Based on the results, they concluded that the majority of patients with CF could benefit from a similar exercise program.

This study helps justify the importance of exercise for patients with CF in improving exercise tolerance. Although they were unable to show a significant improvement in lung function, they noted no worsening in any lung function measurements in the exercise group. The lack of significant data on change in lung function may in part reflect the short, 3-month time frame of this study. The rate of lung function decline in FEV_1 varies greatly, but a separate study found the median decline in FEV_1 percent predicted to be around 2% per year in middle age.[12] Since this is not a dramatically large difference, and half of the people in the study had less than a 2% decrease, it is plausible that FEV_1 would not vary significantly over 3 months. Our proposed intervention will last for 1 year, thus providing more data points over time to measure changes in lung function.

Furthermore, our study's exercise program will be performed individually instead of as a group. As a result, our findings will be better generalizable to the CF population and more easily implemented into each individual's daily schedule. Lastly, this study did not follow the number of exacerbations or quality of life as an outcome. As exacerbations are closely connected to lung function, disease progression, and quality of life, our study will use these as important secondary outcomes.

Another study on exercise and lung function in Swiss CF centers randomized 42 participants to strength training, aerobic training, or no exercise.[9] The intervention groups participated in 30-45 minutes of exercise 3 times per week for the first 6 months. For the first 6 months, participants received phone calls once a month to discuss adherence. For the following 6 months, participants were encouraged to continue with their assigned training without phone calls. At 3, 6, 12, and 24 months, participants returned to their health centers to measure outcomes including FEV_1, body composition, and physical activity. To measure compliance, the strength-training group filled out cards at the gym, and the aerobic training group wore heart rate monitors. They noted that 80% of all the participants performed their 3 days of exercise per week, and all participants completed at least 65% of all training sessions. This data shows that participants were generally adherent to their assigned exercise program over the 6 months.

The results of this study showed a significant ($P < 0.05$) improvement in the FEV_1 of patients in both of the training groups compared to control at 3, 6, and 12 months. These differences were noted to range from 8-10% at the 6-month time point. They also found a significant ($P < 0.05$) improvement in hyperinflation and aerobic performance in the training groups compared to the control at 6 months. Unlike the Orenstein et al. study, this study found a significant change in FEV_1 with exercise. The longer study period of a total of 12 months, with 6 months of intervention, is likely contributory to this result. Our study will have 1 year of intervention with quarterly measurements to ensure adequate time to measure changes in lung function. This study used monthly phone calls during the first 6 months to encourage adherence to the assigned program, and they noted the improved effects they saw at 6 months began to taper down at the end of 1 year. They

suggest that for training to be effective, it must be continuously supervised for long-term results. Our study will use this recommendation in our design to increase adherence to the assigned interventions. Lastly, similar to the Orenstein et al. study, this study did not measure exacerbations or quality of life of the participants.

2.3.4 Exercise and Sputum Expectoration

Sputum expectoration is a commonly used outcome in CF. A study by Dwyer et al. measured sputum production in patients immediately after exercise on a treadmill and a bicycle compared to resting breathing.[13] The study was a 3-day crossover design that involved fourteen adults with CF in Australia. The participants were assigned to 20 minutes of resting breathing, cycle exercise, or treadmill exercise, during which ventilation and respiratory flow were measured. Ease of expectoration and sputum properties were measured before, immediately after, and twenty minutes after resting. They found no significant differences in the ease of expectoration when comparing before and after both the treadmill and cycle interventions, but they did see a trend ($P = 0.096$) in improved ease in the treadmill group compared to control and a significant ($P = 0.034$) improvement in ease in the cycling group compared to control. They measured ventilation and respiratory flow in terms of minute ventilation, peak inspiratory flow, and peak expiratory flow, and all were significantly higher with treadmill exercise and cycling compared to controls. Overall, this study showed improved ventilation and thus ease of sputum expectoration with exercise compared to the control group.

This study did not measure our primary outcome of FEV_1 and instead focused on sputum expectoration as its primary outcome. It can be suggested that increased sputum expectoration leads to decreased infections and exacerbations, thus improving or better

preserving lung function over time. However, measuring sputum production may not correlate as well with clinical outcomes as FEV_1. In CF, patients range from low-sputum producers to high-sputum producers, thus resulting in a high degree of variability.[14] This is due to many factors, including the willingness to expectorate, swallowing of sputum, and differences in cough that alter the mobilization of sputum. Furthermore, individual production varies depending on day and time. For example, production is usually higher in the morning. Lastly, it can be difficult to determine if the increase in sputum is due to increased production or increased clearance. For these reasons, we will measure lung function over time instead of sputum expectoration.

2.3.5 Exercise and Quality of Life

In addition to lung function and sputum expectoration, exercise has also been shown to improve the ability to complete activities of daily life (ADLs), and thus leads to an increased quality of life.[10] A study assigned 10 CF patients to a home exercise program with the primary outcome of the degree of limitation in completing ADLs. The study started with 8 weeks of a control period during which participants were to maintain their normal routines, followed by a 12-week cycling program. The daily cycling program consisted of 3 minutes of warm-up, 15 minutes of training, and 3 minutes of cool-down and was supervised by a physiotherapist 2 days per week. They measured exercise tolerance and pulmonary function testing at the start of the 8 weeks, the end of the 8 weeks, and every 4 weeks during the cycling program. Participants were then instructed to continue their home program for 4 more weeks, and exercise and pulmonary testing was measured at completion. They measured ADLs with a survey of 11 activities that participants filled out at the start and end of the intervention period. The survey

included activities like eating, dressing, bathing, working, traveling, housework, and walking.[15]

They found a significant increase (P = 0.004) in maximal exercise capacity and maximal oxygen uptake (P = 0.008) between the start and end of the 12-week training period, but there was no significant change in pulmonary function.[10] The lack of a significant change may again be the result of a short intervention period of 12 weeks. Although this was adequate time to see changes in exercise capacity, the measures of lung function likely need a longer period of time to show changes.

This study found a significant improvement in limitations of ADLs over the training period.[10] Since we can suggest an increased ability to complete daily activities leads to an improved quality of life, this result helps justify our hypothesis that our structured exercise program will result in an improved quality of life. Also of importance was that, during the follow-up period, 7 patients continued cycling at home and were able to maintain or improve their training effects and performance level. This indicates a high level of adherence even when patients were not supervised closely. The researchers attributed this result to a combination of the prior supervised period and the ages of the patients (all > 15 years of age). We hope to have a similar rate of adherence in our study since our participants will be of older age, and we will design our intervention to encourage adherence through close follow-up during the intervention period. Overall, engagement in an exercise program is critical in CF, as evidence shows that poor adherence can lead to worsening respiratory disease and increased infections.

The studies above show the benefits of exercising to improve exercise tolerance, lung function, sputum expectoration, and quality of life. The most notable gap in research

of these studies is the short length of intervention and follow-up periods. Secondly, many of these studies did not measure the frequency of exacerbations or quality of life as secondary outcomes. We believe that these are important markers that are directly related to each other, as are patient satisfaction and adherence. Our goal is to create a structured exercise and ACT program that improves CF clinical outcomes while being realistic for the daily lives of patients with CF.

2.4 Airway Clearance Therapy vs. Exercise

ACT and exercise both improve mucociliary clearance to minimize infections and lung function decline.[10] Dwyer et al. compared the effects of exercise versus positive expiratory pressure (PEP) on anatomical regions of sputum expectoration.[16] In this crossover study, 15 adults were randomized to one intervention per visit that included constant-load treadmill exercise, PEP, or resting breathing. Participants had an initial visit for baseline lung function and exercise capacity measurements, and the following 3 visits were at least 48 hours apart over 2 weeks. The interventions were performed for 20 minutes, and measurements were taken before, immediately after, and within 60 minutes after. They measured mucus clearance at each time point using a mucus clearance scan of the right lung, and they counted the number of coughs during the time periods.

They found that treadmill exercise had a significant ($P < 0.001$) increase in mucus clearance compared to resting breathing in the intermediate and peripheral regions of the right lung, but the central region was not significantly different. A trend towards more spontaneous coughs during treadmill exercise compared to resting breathing was also noted. PEP therapy led to a significant ($P < 0.001$) increase in mucus clearance of all regions of the right lung (central, intermediate, and peripheral) compared to resting

breathing, and there was a significant increase in coughs during PEP compared to resting breathing. In comparing treadmill exercise and PEP, treadmill exercise was associated with significantly lower mucus clearance in the central region ($P < 0.001$), but they found no significant difference between the intermediate or peripheral regions. They concluded that treadmill exercise was significantly better for mucus clearance than resting breathing, but PEP was more effective in all lung regions than treadmill exercise.

A limitation of this study is that the PEP therapy included forced expiratory technique (FET, which is relaxed breathing and huffing), while the treadmill exercise did not. Researchers noted a significant increase in coughing during PEP compared to treadmill exercise, and they attribute this to the FET component.[16] Since the resting breathing group was not designed as a control group for number of coughs, they were unable to determine if the difference in the central region clearance was due to PEP or FET. They concluded that PEP therapy (including FET) should be included with exercise to increase clearance of the central region. The results of this study show the potential benefit of combining exercise and ACT on mucus clearance as opposed to a single therapy. Our study is using this concept to create a structured program of both therapies, although our primary outcome is FEV_1 and not mucus clearance. Also, the short length of this study would not have allowed for longitudinal measurements of changes in lung function as it was only 2 weeks.

2.5 Combined Exercise and Airway Clearance Therapy

Several studies, similar to our proposed intervention, have evaluated the effect of combining exercise and ACT. A crossover study looked at the acute effect of 60 minutes of exercise before physiotherapy (PT) by measuring sputum weight.[17] Eight patients

participated in 2, non-consecutive days of exercise plus PT and PT alone. Exercise consisted of 40 minutes of brisk walking, stretching, cycling, step-ups, jumping, rowing, and jogging, and PT included postural drainage, percussion, deep breathing, vibrations, and FET. They measured sputum weight during the 40 minutes of exercise and 20 minutes of rest after (or rest on the PT alone day) and during the 60 minutes of PT plus 30 minutes after completion. Lung function was also measured at baseline, after exercise or rest, after PT, and 30 minutes after PT.

They found a significant (P = 0.023) difference in total mean sputum weight of 14g with ACT only and 21.5g with ACT plus exercise. The mean sputum weight from the rest period on the PT alone day was 2.6g compared to 7g during the exercise period on the exercise plus PT day, although the difference was just outside of significant (P = 0.053). They did find a significant (P = 0.007) difference in mean sputum weight between the PT period on the PT alone day (11.4g) versus the PT period on the PT plus exercise day (14.5g). Lastly, they did not find a significant difference in lung function between the groups. The authors attribute this to the short study period as opposed to long-term follow-up. These results show an added benefit of combining exercise and PT on sputum weight, but a longer study would be needed to determine the effect on lung function.

This study is useful in helping us plan our exercise program. They allowed subjects to determine the maximum workload that was comfortably tolerated in contrast to measuring a particular goal heart rate or oxygen consumption level. This decision was made because they felt it was more similar to clinical practice. We agree that measuring outcomes like oxygen consumption is not feasible for a one-year intervention performed at home. However, asking subjects to measure their heart rate during exercise would be a

more practical approach to ensure the exercise intensity is adequate. Another important outcome of this study is that all patients preferred the day of combined exercise and PT compared to PT alone. This result is encouraging for the design of our study, as our subjects will be asked to perform combined sessions.

A similar study compared the amount of sputum expectoration between exercise, PT, and a combination of both.[18] Eighteen subjects were assigned to a random order of 20 minutes of PT, 20 minutes of cycling, 10 minutes of cycling followed by 10 minutes of PT, and 10 minutes of PT followed by 10 minutes of cycling. They chose the 20-minute treatment period because they felt it was representative of how long clinically stable patients needed to clear secretions. The treatments were performed over 4 days, and each was performed twice daily. They weighed expectorated sputum during the 20-minute sessions as well as for 30 minutes following and throughout the rest of the day. Expiratory flow volumes were also measured before treatment, after treatment, and 30 minutes post-treatment.

They found a significantly ($P < 0.01$) higher amount of sputum production in both PT alone or PT plus exercise than with exercise alone. This trend was found in both high and low sputum producers in the study. Lung function measures (FEV_1 and FVC) were not different 30 minutes post-therapy compared to baseline values. However, they did find a significant ($P < 0.05$) increase in the immediate measures of FEV_1 after 20 minutes of exercise, although it returned to baseline after 30 minutes. In terms of patient preference, the study also found that patients preferred exercise followed by PT ($P < 0.001$). This was because patients felt that it was the most effective, and researches hypothesized that PT after exercise was more relaxing.

The results of this study show the importance of including ACT in a daily regimen to improve mucus expectoration and begin to show a potential added benefit of combination with exercise. Our study will continue with this idea over a long-term period as opposed to 4 days. Perhaps the most helpful result of this study in creating our structured program is the patient preferences. As we are hoping to improve patient experience and quality of life, we will use this information in the order of our ACT and exercise with the hope of ultimately increasing adherence. A weakness of this study lies in its short intervention period, as well as a lack of a washout period between interventions. In their discussion, the authors concluded that patients could be recommended to perform a combination of exercise and PT for a daily regimen.

A study by Salh et al. instructed 19 adult patients to use an at-home cycle and perform 10 minutes 5 days per week.[19] The patients were to increase their work rate as tolerated, and sputum production and lung function were measured at the beginning of the study and after 2 months. Additionally, they had a smaller sample of 10 patients in the hospital who were instructed to undergo either 15 minutes of PT or 15 minutes of cycling followed by a 2-hour period of sputum measurement. They would then perform the other therapy, either PT or exercise. Sputum was measured during and after the interventions, and this was continued for 2 days. The regimen was then switched to the opposite order of PT and exercise for 2 more days. In the larger study, they found a significant increase in work capacity, oxygen consumption, and minute ventilation after 2 months of exercise. There was not a significant change in FEV_1 or sputum weight, although they noted a trend in increased sputum production after the intervention period. In the smaller study,

PT produced significantly ($P < 0.01$) more sputum than exercise, and there were no significant differences between the order or PT and exercise.

The larger study showed the benefit of exercise on the outcomes of work capacity ($P = 0.003$), oxygen consumption ($P < 0.001$), and minute ventilation ($P = 0.004$), thus showing an increase in exercise tolerance. The study had a short intervention period of 2 months, making it difficult to measure changes in FEV_1 longitudinally. The smaller study showed similar results to studies mentioned in previous sections with a greater sputum production with PT compared to exercise. In regards to the order of PT and exercise, they found no difference in their outcomes. A weakness of this study is that they did not address patient preference with the order of PT and exercise. Based on these results, researchers stated recommending exercise is reasonable as it may prevent a decline in lung function due to infected sputum retention. Overall, they believe PT and exercise should be complementary therapies.

In another study on sputum expectoration by Kriemler et al. in Switzerland, 12 patients were randomized to 3 non-consecutive days of cycling, trampoline, or billiards (sham group) followed by PT.[20] They participated in 30 minutes of the assigned exercise followed by 30 minutes of PT that consisted of 10 minutes of an oscillator device and 20 minutes of deep maximal inspiration and slow exhalation. After each treatment, researchers measured sputum expectoration and FEV_1. They found a significantly higher amount of sputum expectoration after the trampoline compared to billiards ($P = 0.021$) and a trend of increased sputum expectoration after cycling compared to billiards ($P = 0.074$). Additionally, they found a similar amount of sputum expectoration after all PT

sessions regardless of the exercise modality used. However, they did not find a difference in the FEV_1 between any of the groups.

This study is similar to our proposed study in terms of the combined exercise and PT program but differs in its crossover design and short study period. The short study period likely contributes to the findings of no significant difference in FEV_1. Again, we expect that a longer treatment period is required to see significant changes in lung function.

In a crossover study by Reix et al., 34 pediatric CF patients participated both in one session of 20 minutes of ACT (control) and one session of 20 minutes of combined exercise and forced expiratory techniques (intervention).[21] These sessions were performed on non-consecutive days. They found a significant improvement in FEV_1 after the intervention session compared to the control session. The relative improvement after the intervention was 2.7% with a significant mean difference of 3.2% (95% CI 0.5 to 6.0) compared to the control. Patients also reported a significantly higher satisfaction score with the intervention group compared to control.

The results of this study show that there may be even an immediate effect on lung function by combining ACT and exercise as opposed to ACT alone. Although the researchers note the lower end (0.5%) of the confidence interval is not clinically important, the upper end (6%) is a clinically important difference. The largest limitation of this study is the design of only 1 intervention session because it does not provide data on how long the changes are sustained. Our study utilizes the same concept of combined ACT and exercise, but it will be performed regularly over 1 year to gather longitudinal results. The higher satisfaction scores with the inclusion of exercise are also encouraging

for our study intervention. With improved patient satisfaction comes an improved quality of life and treatment adherence, both of which are goals with our study.

2.6 FEV_1 and Secondary Outcomes (Exacerbations and Quality of Life)

Since FEV_1 decline marks disease progression in CF, it is closely related to exacerbations and quality of life. As the number of exacerbations increases, FEV_1 tends to decrease.[22] Using information from the CF Patient Registry, the relationship between increasing exacerbation rate and decreasing lung function is linear.[23] This means that patients with a higher FEV_1, indicating better lung function, have a decreased incidence of exacerbations. One study followed patients over 3 years and found that those with less than 1 exacerbation per year had a mean FEV_1 change of -4.85%, while those with 1-2 exacerbations had a change of -5.44%, and patients with more than 2 exacerbations had a change of -6.49%.[22] They also found that patients with more than 2 exacerbations per year had a lower baseline FEV_1 as well as a more severe progression in FEV_1 decline compared to those with fewer exacerbations. Additionally, these patients had a significantly increased risk of death within 3 years. This information demonstrates the importance of preserving lung function and limiting the number of exacerbations per year.

Multiple studies have also looked at the impact of cystic fibrosis on quality of life. Exacerbations are associated with significant decreases in the physical well-being and psychosocial quality of life of CF subjects.[24] Bradley et al. compared quality of life between people with CF with no pulmonary exacerbation, mild exacerbation, and severe exacerbation.[25] They found that the more severe the exacerbation, the lower the quality of

life in multiple aspects like physical function, role limitations, emotional functioning, and social functioning.

A systematic review of CF and quality of life looked at studies that used the Cystic Fibrosis Questionnaire – Revised (CFQ-R).[26] After evaluating 28 articles, they concluded that a lower FEV_1 has a correlation with physical functioning, respiratory symptoms, and treatment burden. They also found a significant association between exacerbations and lower CFQ-R scores. They concluded that since FEV_1 and pulmonary exacerbations have the strongest impact on the health-related quality of life for those with CF, these are aspects that must be addressed clinically. In our study, we will be looking at these outcomes to determine the benefit of a structured exercise and ACT program. Our goal is to ultimately improve lung function and decrease exacerbations to improve quality of life for people with CF.

2.7 Adherence to Therapy

Adherence can be defined as an "active, voluntary, collaborative involvement of the patient in a mutually acceptable course of behavior to produce a desired preventative or therapeutic result." [27]Adherence to therapy is challenging with CF because as lung function deteriorates over time, the complexity of the therapy increases. Patients are also living longer, and as a result, they face added social and professional responsibilities in their daily lives. This has made gathering information on treatment adherence even more important.

In general, studies have shown that adherence declines with increasing treatment time and complexity.[27] The treatment regimen for CF is time-consuming and includes oral or inhaled antibiotics, pancreatic enzymes, mucolytic agents, vitamin supplements,

and physiotherapy treatments. One study found the most common reason reported for non-adherence was forgetfulness followed by the time and effort commitment.[28] Although it can be difficult to measure adherence due to reporting, studies have found that in CF, antibiotic adherence is around 80-95%, nebulized medication and pancreatic enzyme adherence is 65-80%, and adherence to vitamins, diet, exercise, and physiotherapy is 40-55%.[27] These numbers show that the components of our intervention, including exercise and physiotherapy, have the lowest adherence rates. This information is important for us to account for when designing our structured program. Our goal is to create a program that can be implemented into the daily lives of people with CF without significantly increasing their treatment burden. We will encourage adherence during the intervention period with close follow-up that could be reproducible outside of the study through CF clinics.

To address adherence, we will implement a similar concept to a study by Schneiderman-Walker et al.[29] This study had 72 participants who were randomized either to an exercise group or the control group. The exercise group was instructed to partake in aerobic activity for 20 minutes at least 3 times weekly over 3 years. They had participants fill out a daily journal that was collected at each 3-month visit. The pages listed the date, type of activity, duration in minutes, and the intensity of the exercise. They also had phone calls with the participants every 4-6 weeks. Over 3 years, the study found that the mean scores in exercise compliance did not vary, and the exercise group had consistently higher amounts of activity compared to control. These results show that the methods used were effective, as they did not find a decline in adherence over the 3 years.

Another way we are designing this study to increase adherence and generalizability is by allowing participants to make some decisions in their intervention. One study measured change in lung function over 3 years between those who exercise regularly and those who do not.[30] They allowed the intervention group to choose their method of exercise, which included the gym, dance, and jogging. Their justification for the decision was because patient adherence improves when patient preference is considered in the treatment plans. Despite this, they still found a significant difference between the two groups in FEV_1. In the exercise group, annual FEV_1% decline was 0.4% compared to 1.6% in the control group. Unfortunately, they do not specifically describe the parameters of the length and frequency of "regular exercise," but they do mention that the exercise was mostly all aerobic and at least 3 times weekly.

Using the information from this study, it seems feasible for participants to choose their method of exercise from a list of acceptable modalities. An additional consideration is the decision between supervised, partially supervised, and unsupervised participation in ACT and exercise. Again in line with creating a feasible regimen, supervised exercise and ACT would greatly increase the costs and personnel time required for a study, as well as impair generalizability because regularly supervised exercise and ACT is not practical in the daily lives of those with CF. Another study of 2 years allowed the exercise group to choose their methods as long as they increased their activity by three 60-minute sessions per week.[31] They continued to have their appointments every 3 months. The study was able to conclude that a partially supervised and individual-based home exercise program may be sufficient in changing activity levels for patients. They concluded that the type of activity likely does not matter in regards to the positive effects. Although less supervision

may reduce the compliance of participants, we plan to mitigate this through the measures discussed above including allowing individual preferences, monthly phone calls, and daily journals.

2.8 Possible Confounders

Lung function is a variable measurement depending on many factors in people with CF. One possible confounding factor on lung function is age.[32] In general, patients with CF see a decline in FEV_1 percent predicted by 2% annually.[22] One study followed lung function in people with CF for 10 years.[32] Overall, they found an 8.8% decline in FEV_1%. Another study measured FEV_1 over 5 years and found an average total decline of 11.9%. [33] These studies demonstrate a decline in lung function with increasing age, which is important to be aware of in our study. As our participants will have a wide age range, we should expect a wide range of baseline FEV_1 measurements.

Also of note, the decline in lung function seems to plateau after reaching a certain age.[12] One study showed the steepest decline to be during childhood and early adulthood and became a modest decline until the age of 30 when it became more stable. This will play a role in our study since our study population is adults. For participants over the age of 30, their natural lung function decline will be less than those under 30. In our study, this means that those who are older will likely have smaller sizes of effect from our intervention compared to those who are younger.[34] To address this, we will match subjects by age and baseline FEV_1 during analysis.

Along with age, lung function varies based on the type of CF-causing mutation.[35] In CF, these mutations are categorized based on the amount of CFTR protein created and its functional ability at the cell surface.[36] The most common CF-causing mutation is

Phe508del, a class II mutation.[37] In subjects harboring this mutation, CFTR protein is synthesized, but it is misfolded and degraded by proteases before reaching the cell surface, resulting in minimal to no *CFTR* function. Those with class I or II *CFTR* mutations on both *CFTR* alleles have significantly lower FEV_1 compared to those with at least one III, IV, or V mutation (milder CF-causing mutations with residual CFTR function).[38] These patients also had a more significant decline in their lung function during follow-up. Additionally, those with class I or II mutations on both alleles had a significantly higher rate of Pseudomonas colonization.

Another possible confounder with lung function is the patients' status of bacterial colonization. The most common organism in CF is *Pseudomonas aeruginosa*.[39] Once a person with CF is colonized with *P. aeruginosa*, it marks a progressive decline in lung function.[40] For example, a study found a significant ($P < 0.0001$) decline in FEV_1 in patients who were colonized *with P. aeruginosa*.[41] On average, these patients had a 13% lower FEV_1 than those who were not infected. The other opportunistic organism frequently associated with CF is *Burkholderia cepacia*.[42] A study followed the lung function of patients with CF who were either colonized with Burkholderia and Pseudomonas, Pseudomonas alone, or neither for 8 years.[40] They found that those who were not colonized with either had significantly higher FEV_1% compared to both of the other groups. They also found a significant difference in the FEV_1 decline between those with both organisms (-5.4%) versus Pseudomonas alone (-3.9%). This study overall showed that additional infection with Burkholderia led to an accelerated decline in lung function compared to those with Pseudomonas alone. We must be aware of this during our study because if our participants become infected with either organism during the

study, we can expect to see a greater decline in their lung function. In order to address this potential confounder, we will match subjects according to sputum microbiology whenever possible in our analysis.

Lastly and perhaps most importantly, we considered the potential impact of novel triple-combination CFTR modulator therapies in our study. A treatment combining CFTR modulators (Elexacaftor, Tezacaftor, and Ivacaftor), known commercially as Trikafta, became available in 2019.[43] Phase 3 trials in patients with the *f508del* mutation showed a significant improvement in FEV_1 predicted with a mean increase of 10% after 4 weeks.[44] There was also a significant improvement in CFQ-R scores with a mean increase of 16 points (4 points is set as the minimal clinically important difference). As 90% of people with CF are either homozygous or heterozygous for the *f508de*l mutation,[45] the majority of patients have the potential to experience substantial improvements in lung function and quality of life. As a result, those starting triple therapy will see great increases in their lung function, thus creating a possible confounder in our study.

The phase 3 trial for Trikafta had a duration of 4 weeks, which was noted to be shorter than previous phase 3 studies for CFTR modulators that used 24 weeks.[44] However, this was chosen because previous studies of other CFTR modulators, including Tezacaftor-Ivacaftor,[46] Lumacaftor-Ivacaftor,[47] and Ivacaftor,[48] all showed that the greatest changes in FEV_1 occurred within the first 4 weeks of treatment and were then sustained.[44] Therefore, we will assume those who have been on triple combination therapy for longer than 4 weeks have already seen the largest improvement in their FEV_1, and the medication should no longer be a confounder. Of note, a benefit of the introduction of triple combination therapy is that a greater amount of patients will have a

higher lung function that allows them to partake in exercise. This will increase the number of patients that are medically stable to participate in our study.

2.9 Review of Relevant Methodology

2.9.1 Measuring FEV_1

All of the reviewed studies that measured lung function used spirometry. Spirometry is a form of pulmonary function testing (PFT) that measures volume against time.[49] PFTs are regularly used in medicine to determine the presence of airflow obstruction to help make a diagnosis. The patient is instructed to take a full inhalation and then a forceful expiration for as long and as quickly as they are able. Along with several other measures, this results in the FEV_1, the volume of air exhaled in the first second of forceful expiration. FEV_1 is used to monitor disease progression and treatment response of CF,[50] therefore, it is an ideal measurement to follow as a primary outcome.

FEV_1 is often expressed as a percent predicted to standardize the results across different ages, heights, sex, and ethnicities.[50] There are several equations used to calculate the percent predicted. One study used the percentage of the FEV_1 of the vital capacity,[11] one used Sherril,[9] another used Tammeling,[10] and one used Quanjer[20] for their calculations. The Yale Adult CF Program uses the third National Health and Nutrition Examination Survey (NHANES III) equation. This equation comes from a survey that collected spirometry data from a sample size of 7,429 people in the United States.[51] The data was used to create reference equations for pulmonary function for Caucasians, African-Americans, and Mexican-Americans based on age, sex, and height. This study has multiple strengths, including that it was conducted nationwide and had a diverse

sample population. As a result, the equations produced are likely to be representative of the population.

The difficulty in following FEV_1 lies in its variability. There are variations seen when FEV_1 is followed over time due to 3 reasons: variability between patients, within a patient, and due to measurement.[50] This shows why some of the short-term studies may not have provided enough data points to ensure that changes, or a lack of change, were not due to this variability. Since our study intervention period is 1 year, we will have more data points to look at overall trends, and thus each individual may serve as his/her own reference, which will ensure this variability will not have as large of an impact on our results. To address this issue, one study had each subject perform 3 rounds of spirometry, and they used the highest results in their data.[17] This sounds like a reasonable way to decrease measurement errors, although if the source of the error is the person assisting with performing spirometry, then this method may not help. Therefore, most of the reviewed studies also had the same person assisting the patients with their spirometry to minimize variability between users.

According to the American Thoracic Society Standardization Guidelines for Spirometry, the spirometry maneuver should be performed at least 3 times and a maximum of 8 times.[52] The additional maneuvers should be performed if the FEV_1 values are not repeatable between the first 3; this is defined as the difference between the 2 largest FEV_1 measurements must be less than or equal to 0.150L. These guidelines are important to follow so that all spirometry measurements are performed the same, thus decreasing the amount of variability in our results.

2.9.2 Survey to Measure Quality of Life

There are many surveys to measure quality of life. One example is the Cystic Fibrosis Questionnaire-Revised (CFQ-R) designed for patients with CF who are 14 years or older.[53] This survey is ideal for measuring health-related quality of life for several reasons. The first is that the CFQ-R is specifically designed for people with CF. The second reason is that the CFQ-R is the most accepted survey to measure quality of life in patients with CF.[26] For example, multiple clinical trials for new CF medications, including the phase 3 trial of Trikafta,[44] used the CFQ-R.[53] It is also the survey used at our primary study location at The Yale Adult CF Program, and patients already fill the CFQ-R out at each quarterly CF appointment.

2.9.3 Inclusion and Exclusion Criteria

Most studies reviewed and discussed above excluded participants with previous lung transplant and those who were not deemed clinically stable by their CF provider. Several of the studies excluded those colonized with *B. cepacia*. One study excluded those with non-CF related chronic conditions that would pose a risk with exercising.[9] This included esophageal varices, pulmonary bullae, a drop in arterial oxygen saturation below 80%, or signs of pulmonary hypertension on EKG. These criteria are all reasonable measures to ensure the safety of the participants in undertaking an exercise program. Another important parameter for participation is baseline FEV_1 values. The studies reviewed with an FEV_1 cutoff used either greater than or equal to 35% predicted or 40% predicted. Since these values mark severely declined lung function, it is more likely that the subject would not be able to safely tolerate an increase in physical activity.

Other inclusion criteria for all studies included a diagnosis of CF, however, the definition of diagnosis varied between studies. Studies that listed specific criteria for diagnosis included abnormal sweat test, typical pulmonary or digestive symptoms, family history of CF, and genetic testing. These criteria are similar to the diagnosis criteria outlined on DynaMed for CF, which is made by at least 1 of the 3 following criteria: 1) Elevated sweat chloride concentration, 2) 2 disease defining mutations in *CFTR* gene, or 3) Organ dysfunction such as lung or gastrointestinal. As our study participants are subjects with a confirmed diagnosis of CF recruited from the Yale Adult CF Program Clinic, we will adopt their definition of a CF diagnosis, which is also similar. This includes a clinical presentation consistent with CF and *CFTR* sequencing that shows CF causing mutations in both *CFTR* alleles.

2.9.4 Recruitment

All but one of the studies reviewed recruited study participants from either one or multiple CF centers based on their own willingness. One study also used advertisements in a CF newsletter.[16] CF patients attend their clinic every 3 months, so these frequent visits pose a feasible method for recruitment within the centers. Although not mentioned in any reviewed studies, another option to increase the number of participants would be to work with the Cystic Fibrosis Therapeutics Development Network (CF TDN). The TDN was established by the Cystic Fibrosis Foundation to create access to a larger patient population for therapeutic trials.[54] The CF TDN consists of 91 accredited CF care centers around the US.[55] If more subjects were needed for our research, we could contact the TDN Coordinating Center to present our study and request that they notify sites that may be interested in joining. The design of our study would be easily implemented in any

CF clinic because it utilizes the routinely used FEV_1 and health-related quality of life measurements already applied during routine clinic visits. Therefore, other locations that may participate in the study would not need additional equipment or measurements.

2.9.5 Sample Size

Although FEV_1 is a frequently used outcome measure in CF trials, it is difficult to determine a minimal clinically important difference (MCID) for the population.[56] Instead, it is argued that the MCID should be based on each individual as lung function varies greatly with CF. Since this is difficult to standardize, a statistically significant difference between the intervention and control groups is usually considered a successful trial as opposed to reaching a specific MCID. This concept is reasonable, but it does pose additional difficulty in calculating a sample size based on an effect size. Therefore, we must use the results of previous studies to calculate our sample size as opposed to an MCID. Of the reviewed studies that combined ACT and exercise, the sample sizes ranged from 8[17] to 34.[21] Although these sample sizes are all small, the studies found statistical significance in some or all of their outcomes.

2.9.6 Intervention

In the reviewed studies with an intervention of both exercise and ACT, the specifications of the regimen varied. The interventions consisted of either: 40 minutes of exercise prior to 25-40 minutes of ACT,[17] 30 minutes of exercise followed by 30 minutes of ACT,[20] 10 minutes of exercise and 10 minutes of ACT compared to the reverse order of 10 minutes of ACT and 10 minutes of exercise,[18] or 3 periods of 5 minutes of aerobic exercise spaced by 1.5 minutes of ACT.[21] Although all of these studies had a primary

outcome of sputum expectoration instead of lung function, they all produced significant results.

In the studies that focused only on the longitudinal effects of exercise and not ACT, the regimen again varied. The interventions consisted of: 1 hour of training (stretching, walking/jogging, and recreational activities) 3 times weekly,[11] 30-45 minutes of activity 3 times weekly,[9] and 21 minutes of cycling daily.[10] Two of the studies showed significant improvements in exercise tolerance with the intervention, [10,11] and one study showed a significant improvement in FEV_1 with the intervention. [9] Based on these results, all of these exercise interventions could have a significant impact on the lung function of patients with CF.

Several of these studies implemented measures to ensure a specific intensity of exercise. One study had patients palpate their pulse and encouraged a heart rate of 70-85% of their maximal heart rate,[11] another used 70% of maximum heart rate,[10] and one targeted a heart rate of 140-160 beats per minute.[20] Five of the studies used VO_2 levels of 65%,[9] 60%,[13,16,18] and 50%[19] of the patients' peak oxygen capacity to measure exercise capacity. Of note, 2 of the 3 studies that lasted at least 3 months used heart rate as opposed to VO_2 levels to quantify the exercise,[10,11] and the study that used VO_2 used watches that measured heart rate to correlate to their target VO_2.[9] Perhaps this suggests that for longer-term studies, heart rate is a more feasible target to follow, especially for patients at home, as opposed to VO_2. One study addressed this issue by allowing patients to subjectively work at a level they could tolerate.[17] They chose this method because it better represented a clinical situation, and they were still able to find a significant improvement in sputum expectoration with exercise before ACT.

2.9.7 Adverse Events

Although exercise is generally recommended as a therapy for CF, no physical activity comes without risks of possible harm to the body. One study, to identify adverse events from exercise in those with CF, sent out questionnaires to patients regarding this issue.[57] The survey included pneumothorax, loss of consciousness, and acute dyspnea and cough (asthma attack) after exercise. They were also able to write in their own adverse events. The patient survey was completed by 256 patients with a mean weekly average of 3.6 hours of exercise. 67% of the patients had experienced no adverse events, 22% had an asthma attack, 6% had an injury, 4% had a pneumothorax, and 1% had a loss of consciousness. Of the answers written in by patients, 4% had worsening arthritis with exercise, 3% had hemoptysis, and 1% had hypoglycemia with exercise. In summary, this study found low incidences of adverse events related to exercise in those with CF.

Of the studies discussed that mentioned adverse events, most had none to report.[9,11,16,18] These studies specifically mentioned the absence of cardiac and orthopedic complications, injuries, pneumothorax, asthma attacks, hypoglycemia, heart rate, and oxygen saturation. One study had 5 participants with adverse events, which were not statistically significant between the intervention and control group.[21] This included fatigue, breathlessness, and oxygen desaturation below 92%, and these resolved quickly with rest. Overall, the risk of any of these possible adverse events is low; however, they remain important to monitor during our study to ensure the safety of the participants.

2.10 Conclusion

Based on the studies discussed in this section, the individual benefits of ACT and exercise as treatment modalities in CF are clear. However, there is limited data on the

long-term effects of a combined regimen. Available studies combining ACT and exercise are short-term and often focused on sputum production as opposed to lung function. These studies, however, have demonstrated the benefit of ACT in preventing exacerbations in order to better preserve lung function and quality of life. As we note above, sputum production is a frequently measured outcome, but is fraught by variability and technical difficulties. More importantly, measurements of sputum clearance may not directly reflect the clinical impact of exercise and ACT on lung function and quality of life. Therefore, we concentrate on clinically relevant measurements of FEV_1 and quality of life throughout our study.

2.11 References

1. McCarren B, Alison JA. Physiological effects of vibration in subjects with cystic fibrosis. *European Respiratory Journal.* 2006;27(6):1204.
2. Oermann CM, Sockrider MM, Giles D, Sontag MK, Accurso FJ, Castile RG. Comparison of high-frequency chest wall oscillation and oscillating positive expiratory pressure in the home management of cystic fibrosis: A pilot study*. *Pediatric Pulmonology.* 2001;32(5):372-377.
3. Morrison L, Innes S. Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database Syst Rev.* 2017;5(5):CD006842-CD006842.
4. Flume PA, Robinson KA, O'Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care.* 2009;54(4):522-537.
5. Pryor JA, Tannenbaum E, Scott SF, et al. Beyond postural drainage and percussion: Airway clearance in people with cystic fibrosis. *Journal of Cystic Fibrosis.* 2010;9(3):187-192.
6. Cheng YJ, Macera CA, Addy CL, Sy FS, Wieland D, Blair SN. Effects of physical activity on exercise tests and respiratory function. *British Journal of Sports Medicine.* 2003;37(6):521.
7. Atlantis E, Chow C-M, Kirby A, Fiatarone Singh M. An effective exercise-based intervention for improving mental health and quality of life measures: a randomized controlled trial. *Preventive Medicine.* 2004;39(2):424-434.
8. Schneiderman JE, Wilkes DL, Atenafu EG, et al. Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. *European Respiratory Journal.* 2014;43(3):817.
9. Kriemler S, Kieser S, Junge S, et al. Effect of supervised training on FEV1 in cystic fibrosis: a randomised controlled trial. *J Cyst Fibros.* 2013;12(6):714-720.
10. De Jong W, Grevink RG, Roorda RJ, Kaptein AA, Van Der Schans CP. Effect of a Home Exercise Training Program in Patients With Cystic Fibrosis. *Chest.* 1994;105(2):463-468.
11. Orenstein DM, Franklin BA, Doershuk CF, et al. Exercise Conditioning and Cardiopulmonary Fitness in Cystic Fibrosis: The Effects of a Three-month Supervised Running Program. *Chest.* 1981;80(4):392-398.
12. Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. *J Cyst Fibros.* 2010;9(4):250-256.
13. Dwyer TJ, Alison JA, McKeough ZJ, Daviskas E, Bye PTP. Effects of exercise on respiratory flow and sputum properties in patients with cystic fibrosis. *Chest.* 2011;139(4):870-877.
14. Rubin BK. Designing clinical trials to evaluate mucus clearance therapy. *Respir Care.* 2007;52(10):1348-1358; discussion 1358-1361.
15. Schrien AC, Dekker FW, Kaptein AA, Dijkman JH. Quality of Life in Elderly Patients with Chronic Nonspecific Lung Disease Seen in Family Practice. *Chest.* 1990;98(4):894-899.
16. Dwyer TJ, Daviskas E, Zainuldin R, et al. Effects of exercise and airway clearance (positive expiratory pressure) on mucus clearance in cystic fibrosis: a randomised crossover trial. *European Respiratory Journal.* 2019;53(4):1801793.

17. Baldwin DR, Hill AL, Peckham DG, Knox AJ. Effect of addition of exercise to chest physiotherapy on sputum expectoration and lung function in adults with cystic fibrosis. *Respiratory Medicine.* 1994;88(1):49-53.
18. Bilton D, Dodd ME, Abbot JV, Webb AK. The benefits of exercise combined with physiotherapy in the treatment of adults with cystic fibrosis. *Respiratory Medicine.* 1992;86(6):507-511.
19. Salh W, Bilton D, Dodd M, Webb AK. Effect of exercise and physiotherapy in aiding sputum expectoration in adults with cystic fibrosis. *Thorax.* 1989;44(12):1006-1008.
20. Kriemler S, Radtke T, Christen G, Kerstan-Huber M, Hebestreit H. Short-Term Effect of Different Physical Exercises and Physiotherapy Combinations on Sputum Expectoration, Oxygen Saturation, and Lung Function in Young Patients with Cystic Fibrosis. *Lung.* 2016;194(4):659-664.
21. Reix P, Aubert F, Werck-Gallois M-C, et al. Exercise with incorporated expiratory manoeuvres was as effective as breathing techniques for airway clearance in children with cystic fibrosis: a randomised crossover trial. *Journal of Physiotherapy.* 2012;58(4):241-247.
22. de Boer K, Vandemheen KL, Tullis E, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. *Thorax.* 2011;66(8):680-685.
23. Goss CH, Burns JL. Exacerbations in cystic fibrosis · 1: Epidemiology and pathogenesis. *Thorax.* 2007;62(4):360.
24. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest.* 2002;121(1):64-72.
25. Bradley JM, Blume SW, Balp M-M, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *European Respiratory Journal.* 2013;41(3):571.
26. Habib A-RR, Manji J, Wilcox PG, Javer AR, Buxton JA, Quon BS. A Systematic Review of Factors Associated with Health-Related Quality of Life in Adolescents and Adults with Cystic Fibrosis. *Annals of the American Thoracic Society.* 2015;12(3):420-428.
27. Kettler LJ, Sawyer SM, Winefield HR, Greville HW. Determinants of adherence in adults with cystic fibrosis. *Thorax.* 2002;57(5):459.
28. Conway SP, Pond MN, Hamnett T, Watson A. Compliance with treatment in adult patients with cystic fibrosis. *Thorax.* 1996;51(1):29-33.
29. Schneiderman-Walker J, Pollock SL, Corey M, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. *The Journal of Pediatrics.* 2000;136(3):304-310.
30. Elce A, Nigro E, Gelzo M, et al. Supervised physical exercise improves clinical, anthropometric and biochemical parameters in adult cystic fibrosis patients: A 2-year evaluation. *The Clinical Respiratory Journal.* 2018;12(7):2228-2234.
31. Hebestreit H, Kieser S, Junge S, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. *European Respiratory Journal.* 2010;35(3):578.

32. Abbott J, Hurley MA, Morton AM, Conway SP. Longitudinal association between lung function and health-related quality of life in cystic fibrosis. *Thorax.* 2013;68(2):149.
33. Gojšina BZ, Rodić M, Višekruna J, Trajković GZ, Sovtić AD, Minić PB. Pulmonary exacerbations as a risk factor for lung function decline - experiences of the National Cystic Fibrosis Center. *Egzacerbacije plućne bolesti kao faktor rizika od sniženja funkcije pluća - iskustva Nacionalnog centra za cističnu fibrozu.* 2019;76(11):1110-1114.
34. Konstan MW, Morgan WJ, Butler SM, et al. Risk Factors For Rate of Decline in Forced Expiratory Volume in One Second in Children and Adolescents with Cystic Fibrosis. *The Journal of Pediatrics.* 2007;151(2):134-139.e131.
35. Schaedel C, De Monestrol I, Hjelte L, et al. Predictors of deterioration of lung function in cystic fibrosis. *Pediatric Pulmonology.* 2002;33(6):483-491.
36. Elborn JS. Cystic fibrosis. *The Lancet.* 2016;388(10059):2519-2531.
37. Grasemann H. CFTR Modulator Therapy for Cystic Fibrosis. *New England Journal of Medicine.* 2017;377(21):2085-2088.
38. de Gracia J, Mata F, Alvarez A, et al. Genotype-phenotype correlation for pulmonary function in cystic fibrosis. *Thorax.* 2005;60(7):558-563.
39. Ren CL, Konstan MW, Yegin A, et al. Multiple antibiotic-resistant Pseudomonas aeruginosa and lung function decline in patients with cystic fibrosis. *J Cyst Fibros.* 2012;11(4):293-299.
40. McCloskey M, McCaughan J, Redmond AOB, Elborn JS. Clinical outcome after acquisition ofBurkholderia cepacia in patients with cystic fibrosis. *Irish Journal of Medical Science.* 2001;170(1):28.
41. Kerem E, Viviani L, Zolin A, et al. Factors associated with FEV₁ decline in cystic fibrosis: analysis of the ECFS Patient Registry. *European Respiratory Journal.* 2014;43(1):125.
42. Courtney JM, Dunbar KEA, McDowell A, et al. Clinical outcome of Burkholderia cepacia complex infection in cystic fibrosis adults. *Journal of Cystic Fibrosis.* 2004;3(2):93-98.
43. Mahase E. Cystic fibrosis: triple therapy shows promising results. *BMJ.* 2019;367:l6347.
44. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet.* 2019;394(10212):1940-1948.
45. Davies JC, Moskowitz SM, Brown C, et al. VX-659–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *New England Journal of Medicine.* 2018;379(17):1599-1611.
46. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England Journal of Medicine.* 2017;377(21):2013-2023.
47. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *New England Journal of Medicine.* 2015;373(3):220-231.

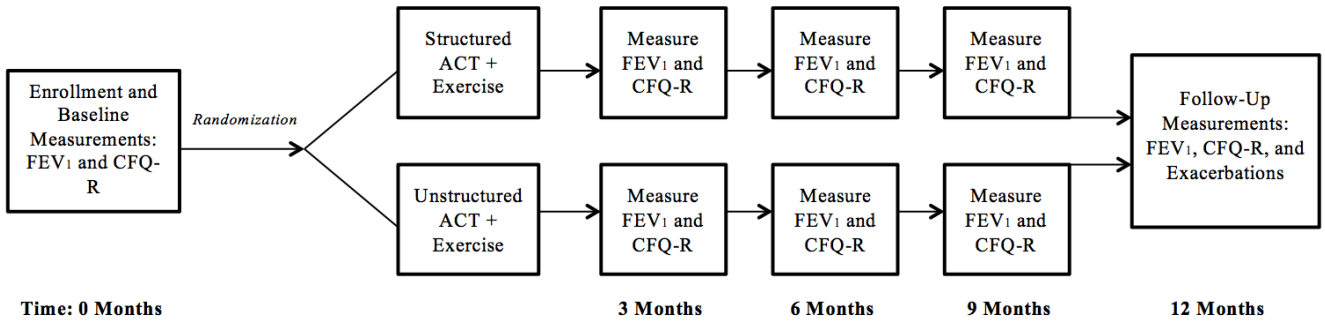
48. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *New England Journal of Medicine.* 2011;365(18):1663-1672.
49. Ranu H, Wilde M, Madden B. Pulmonary function tests. *Ulster Med J.* 2011;80(2):84-90.
50. Szczesniak R, Heltshe SL, Stanojevic S, Mayer-Hamblett N. Use of FEV(1) in cystic fibrosis epidemiologic studies and clinical trials: A statistical perspective for the clinical researcher. *J Cyst Fibros.* 2017;16(3):318-326.
51. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric Reference Values from a Sample of the General U.S. Population. *American Journal of Respiratory and Critical Care Medicine.* 1999;159(1):179-187.
52. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American Journal of Respiratory and Critical Care Medicine.* 2019;200(8):e70-e88.
53. Solé A, Olveira C, Pérez I, et al. Development and electronic validation of the revised Cystic Fibrosis Questionnaire (CFQ-R Teen/Adult): New tool for monitoring psychosocial health in CF. *Journal of Cystic Fibrosis.* 2018;17(5):672-679.
54. Goss CH, Mayer-Hamblett N, Kronmal RA, Ramsey BW. The cystic fibrosis therapeutics development network (CF TDN): a paradigm of a clinical trials network for genetic and orphan diseases. *Advanced Drug Delivery Reviews.* 2002;54(11):1505-1528.
55. Why Work With the TDN. Cystic Fibrosis Foundation. https://www.cff.org/Research/Researcher-Resources/Therapeutics-Development-Network/Working-with-the-TDN/Why-Work-With-the-TDN/. Accessed 06/02/20, 2020.
56. Stanojevic S, Ratjen F. Physiologic endpoints for clinical studies for cystic fibrosis. *Journal of Cystic Fibrosis.* 2016;15(4):416-423.
57. Ruf K, Winkler B, Hebestreit A, Gruber W, Hebestreit H. Risks associated with exercise testing and sports participation in cystic fibrosis. *Journal of Cystic Fibrosis.* 2010;9(5):339-345.

Chapter 3 – Study Methods

3.1 Study Design

Our study will be a prospective randomized controlled trial. Patients will be randomized to either structured ACT and exercise or unstructured ACT and exercise. The CF providers and respiratory therapists performing spirometry will be blinded to the intervention. The intervention period will last 1 year, and subjects will not crossover to the other intervention. Outcome measurements will occur at 0, 3, 6, 9, and 12 months. At the end of the study, participants are free to alter their exercise regimens as desired.

Figure 1: Proposed Study Design



3.2 Study Population and Sampling

The study population will be adult patients (≥18 years of age) with a confirmed diagnosis of CF from The Yale Adult CF Program within the Yale CF Care Center. Providers at the clinic will be approached to discuss the study, and they will be asked to recruit patients that fit our eligibility criteria. This sampling method will aim to ensure that the subjects recruited regularly attend their CF appointments. This is important for several reasons; the first is that those who regularly go to their appointments will have more contact with their providers, thus making it easier for the provider to deem the patient is safe to participate. Second, it will target patients who are motivated and actively

participate in their own care. Since this study is evaluating an at-home program, it is likely that those who would participate outside the study would also only be those who are more motivated. Lastly, if patients attended their previous appointments, it is more likely they will attend future appointments at which study measurements will take place. Also, those who attend appointments regularly will have closer follow-up to adjust their other treatments as needed, which is important for their safety.

3.3 Inclusion

Inclusion criteria will be given to the providers at the CF clinic to screen for eligible patients – Patients must be 18 years of age and older and deemed stable by their CF provider to exercise and participate in the study. Also, patients must already use a form of ACT before starting the study. Women will not be excluded if already pregnant or if they become pregnant during the study. Patients will be recruited regardless of race to best represent the population of those with CF, although it should be noted the disease is more prevalent in Caucasians. Patients who already exercise and those who do not may be included, as they will be randomized to the intervention.

3.4 Exclusion

Patients with an $FEV_1 < 40\%$ will be excluded from the study. Those who are post lung transplant will also be excluded. Patients who have comorbidities other than CF that inhibit their ability to exercise or affect their lung function will be excluded. This includes diagnoses of pulmonary hypertension, heart failure, and other advanced lung diseases like COPD, asthma, and idiopathic pulmonary fibrosis. Lastly, those who have started taking any CFTR modulator medications within the last 4 weeks will be excluded (those who have been on a stable dose for longer than 4 weeks will be eligible). These

exclusion criteria are primarily for the safety of the patients participating in the study to decrease the chance of any adverse events with exercise. The criteria will also increase the likelihood that changes in lung function are a result of the intervention as opposed to other causes. Children are not included in this study because they have different patterns of lung function decline compared to adults, and the CFQ-R is designed for 14 years of age and older.

3.5 Subject Protection and Confidentiality

Before the initiation of this study, we will first gain approval by the Yale University Institutional Review Board (IRB). All participants in the study must complete and sign our informed consent form. The form will cover important information for the patient and will be reviewed with study recruitment staff. The consent form will describe the procedures of the study and the potential risks and benefits. A description of patient confidentiality and privacy will be included to explain the handling of patient information during the study. Lastly, the patient will be able to ask any questions regarding the study, and they may take time to consider joining before signing the form. A sample of the consent form can be found in Appendix A. The study protocol and patient confidentiality will comply with the Health Insurance Portability and Accountability Act (HIPAA) regulations. Patient information will be de-identified and kept confidential. Participation in the study is entirely voluntary, and participants may withdraw from the study at any time without affecting the care they receive at the CF clinic. A description on how to withdraw from the study is included in the consent form.

3.6 Recruitment

Recruitment will take place over 1 year at The Yale Adult CF Program within The Yale CF Care Center. Since patients attend the CF clinic every 3 months, this will provide a large number of potential participants. The providers at the CF clinic will be provided with study details and inclusion/exclusion criteria and asked to recruit eligible patients. Flyers will also be sent to the patients of the clinic with information regarding the study and information on how to enroll. A sample flyer can be found in Appendix B. Additionally, if more participants are needed, we may recruit from the Adult Cystic Fibrosis Clinic at Hartford Hospital. This would create a larger pool of patients to sample from while keeping in proximity to our primary site. Lastly, the study may be presented to the Cystic Fibrosis Therapeutics Development Network to further recruit participants from CF clinics around the United States.

3.7 Study Variables and Measures

The independent variable of this study is the regimen of exercise and ACT. The subjects will be separated into 2 groups: Either structured exercise and ACT (intervention) or non-structured exercise and ACT (control). The main outcome and dependent variable of this study is FEV_1 percent predicted. This will be measured at baseline as well as at each quarterly visit during the year. FEV_1 will be measured with spirometry using the most up-to-date American Thoracic Society guidelines and expressed as percent predicted using the NHANES III equation. Respiratory therapists within the CF clinic will perform spirometry.

Secondary outcomes will include exacerbation frequency and quality of life. Exacerbations will be assessed using medical records through an Epic chart review upon completion of the intervention. An exacerbation will be defined using criteria by Fuchs et

al.: “A patient treated with parenteral antibiotics for any 4 of the following 12 signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38 °C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary infection.”[1] Quality of life will be measured using the Cystic Fibrosis Questionnaire-Revised (CFQ-R). A copy of the survey can be found in Appendix C. The survey will be completed at baseline and each 3-month clinic visit during the year.

Table 1. Primary and Secondary Outcomes

Outcome	**Primary or Secondary Outcome**	**Timeframe**	**Measurement**	**Importance**
Change in FEV_1 % Predicted	Primary	Baseline, Every 3 months for 1 year	Standard Spirometry, NHANES III Equation	Measure changes in lung function
Change in Frequency of Exacerbations	Secondary	During intervention period (1 year)	Chart Review	Show frequency of exacerbations
Change in Quality of Life Score	Secondary	Baseline, Every 3 months for 1 year	Cystic Fibrosis Questionnaire - Revised	Quantify the health-related quality of life of patients

3.8 Methodology Considerations

3.8.1 Experimental Protocol

The study will consist of a 1-year intervention period. Before starting the intervention, study-recruiting personnel will discuss exercise parameters with the subjects. They will be instructed to choose their preferred type of exercise from the provided list (Appendix D). To ensure subjects are exercising at a high intensity, they

will be instructed to record their heart rate in their journal before starting exercise, at 15 minutes of exercise, and upon completing 30 minutes of exercise. Study personnel will demonstrate how to calculate heart rate by counting the heart rate for 15 seconds and multiplying that number by 4. Subjects will be provided their target heart rate and asked to increase their intensity if their heart rate is below target when checked at the 15-minute point. Instructions will also be written in the journal, which can be found in Appendix E. Calculations for target heart rate can be found in Appendix F.

Subjects randomized to structured ACT and exercise will perform 30 minutes of exercise immediately followed by ACT 3 times weekly. The length and modality of ACT will be performed according to the CF provider's recommendations. If the subject performs more than 1 session of ACT in a day, they may choose which session to combine with exercise. Upon completing each session, the participant will fill out their journal entry for the day. The journal should be filled out every day whether they exercised or not. For those assigned to the non-structured program, they will also be instructed to exercise 3 times weekly, but it should be separated by at least 2 hours from an ACT session. ACT should be performed according to the provider's recommendations.

Figure 2. Sample Weekly Schedule of ACT and Exercise

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
30 Minutes of Exercise + ACT	ACT	30 Minutes of Exercise + ACT	ACT	ACT	30 Minutes of Exercise + ACT	ACT

3.8.2 Blinding of Intervention

Blinding of the intervention to the study subjects is not feasible given their active participation in the intervention. The assignment of the intervention will be blinded to the

respiratory therapist performing spirometry measurements. Providers will also be blinded to the intervention. Subjects will be asked to keep their intervention confidential from their providers.

3.8.3 Blinding of Outcome

The subjects will not be blinded to the outcomes of FEV_1% or exacerbation frequencies. As the study is longitudinal, they should be aware of their lung function during the year, and they will already be aware of their exacerbations. Subjects will be blinded to their CFQ-R scores. Providers will not be blinded to any of the outcome measures for the safety of the participants. This will allow providers to modify treatment regimens, if needed, due to unexpected changes in lung function or clinical condition.

3.8.4 Assignment of Intervention

Intervention will be assigned using randomizeR software.

3.8.5 Adherence

Adherence will be monitored throughout the study. At home, patients will use a daily journal to log modality and time spent on exercise and ACT. These logs are to be brought to every appointment to be reviewed and discussed. During the months the patient does not have an appointment, they will receive a monthly phone call from study personnel to discuss adherence and answer any questions.

3.8.6 Monitoring of Adverse Events

Before beginning the study, patients will be made aware of the very low risk of possible adverse events such as physical injury, an increase in dyspnea or coughing, hypoglycemia, loss of consciousness, worsening of arthritis, and pneumothorax. At each office appointment, in addition to spirometry, vitals (blood pressure, heart rate, and

oxygen saturation) will be measured and compared to previous vitals. Patients will also be asked if they have noticed any changes in their health or if they have any concerns at every visit and during every phone call, and they will be encouraged to document these in their logs. Patients will be instructed to immediately discontinue exercise if they feel that they are unable to complete a session. The phone number to their CF provider will be given to all patients to call if they have any questions or concerns.

3.9 Data Collection

Data collection will take place for 1 year. During this time, participants will continue to have quarterly appointments. At each of these appointments, all participants will perform spirometry with a respiratory therapist to measure FEV_1. They will also complete the CFQ-R to evaluate their health-related quality of life. Data collection on exacerbations will take place at the end of the study based on chart review for the year of the intervention period.

3.10 Sample Size Calculation

The previous studies that combined exercise and ACT used a short-term outcome follow-up, and did not find significant differences in FEV_1 to inform our sample size calculations for a 1 year intervention design. Therefore, we used a study with a similar exercise intervention and a longer follow-up period to calculate our sample size. Our sample size calculation is based on change in FEV_1 percent predicted over 6 months in adults with CF from a study by Kriemler et al.[2] The exercise intervention is similar with 30 minutes of exercise 3 times weekly, and subjects received monthly phone calls in addition to quarterly appointments. The exercise group had an increase in FEV_1 of 5.76±3.7% over 6 months, and the control group had a decrease in FEV_1 of -4.42±14.7%.

Using these numbers, and assuming an alpha of 0.05 and power of 90% with a two-tailed hypothesis, we calculated a sample size of 50. As this study does not directly include ACT as part of the intervention, and it compares an exercise group to a control group without specific exercise instructions, in addition to increasing power to 90%, we will add 10 more subjects to each arm to account for this difference in study design. Also, to accommodate for a 10% dropout rate, we aim to recruit a total of 77 participants. The sample size calculation can be found in Appendix G.

3.11 Analysis

The study population will be characterized using descriptive statistics for parameters including age, sex, race, baseline FEV_1, and baseline CFQ-R score (Table 2). This will utilize both unpaired Student's t-tests for continuous variables and Chi-squared tests for categorical variables. All analyses will be performed using the intention to treat principle, and statistical significance will be designated as $P < 0.05$. The outcomes of FEV_1 % predicted, exacerbation frequency, and QOL scores are all continuous variables and will be described as means with standard deviations. Unpaired Student's t-tests will be used to compare the change in FEV_1, change in CFQ-R score, and the difference in exacerbation frequency between the 2 groups. Paired Student's t-tests will be used to compare the change in FEV_1 CFQ-R score within the same subjects from baseline. If data is not normally distributed, then paired and unpaired Wilcoxon's rank-sum tests will be used instead. As FEV_1 and CFQ-R scores will be measured quarterly, those time points will be compared using unpaired Student's t-tests. To look at the effect of the intervention in specific groups, results will also be stratified by *CFTR* genotype,

colonization with *Pseudomonas aeruginosa*, colonization with *Burkholderia cepacia*, and type of CFTR modulator medication used.

Table 2. Sample Table of Baseline Characteristics of Subjects

Characteristic	Structured	Non-Structured	P value
Sample Size (n)			
Gender (% F, %M, % Other)			
Age (Years)			
Race (White, African American, Hispanic, Other)			
FEV_1 (% Predicted)			
CFQ-R Score (Points)			

3.12 Timeline and Resources

Before recruitment begins, the Human Investigation Committee (HIC) process is estimated to take 2-3 months. The recruitment phase and intervention phase will be a total of 2 years. Upon completion of the intervention period, data analysis is estimated to take 2-3 months.

Figure 3. Proposed Study Phases

The personnel required to complete this study includes the CF team who the patient normally sees every 3 months, including the physician and the respiratory therapist to perform the spirometry, and a research assistant for recruitment assistance and data entry. The principal investigator will also perform recruitment assistance as well as conduct the monthly phone calls. As the study is utilizing the patients' already scheduled 3-month visits, additional office space for appointments will not be needed.

3.13 References

1. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of Aerosolized Recombinant Human DNase on Exacerbations of Respiratory Symptoms and on Pulmonary Function in Patients with Cystic Fibrosis. *New England Journal of Medicine.* 1994;331(10):637-642.
2. Kriemler S, Kieser S, Junge S, et al. Effect of supervised training on FEV1 in cystic fibrosis: a randomised controlled trial. *J Cyst Fibros.* 2013;12(6):714-720.

Chapter 4 – Conclusion

4.1 Advantages and Disadvantages

Our proposed study has several advantages over previous studies that investigated the relationships between lung function, exercise, and ACT in patients with CF. First, our intervention period of 1 year is longer than most studies and will provide a longitudinal look at FEV_1 measurements to ensure sustained results. As a result, our findings will give greater insight into the long-term benefits of ACT and exercise as opposed to their immediate effects. Additionally, our study takes advantage of the already scheduled appointments that patients with CF have quarterly, thus decreasing the time burden of appointments for our participants.

Another strength of this study is that we are aiming to create an exercise and ACT regimen that could feasibly be implemented into the lives of those with CF. In contrast to studies that have directly supervised or closely monitored exercise sessions, our exercise regimen will be performed individually. Also, ACT will be performed with the participants' modality of choice and for the amount of time instructed by their providers. Overall, we believe this makes the intervention more generalizable to those with CF because it does not require additional resources like trainers or new ACT modalities.

An important limitation of our study design is that a less-regulated structure allows for variability in the intensity of the exercise performed by the participants, and we must rely on self-reported adherence. This also means that participants will be completing different forms of ACT for different time periods. However, the different forms of ACT should not cause a significant difference in change in lung function, as

previous studies have shown no significant differences between the modalities. Furthermore, since this study takes place over 1 year and subjects have varying lung function status, it would pose a risk to the subjects if they were instructed to perform the same length and frequency of ACT.

Another limitation of our study design as an at-home program is that it requires a certain level of motivation from the patients to fully participate. Yet, we believe this is an acceptable limitation because outside of the study, those who would implement the regimen into their lifestyle would need to have some level of motivation as well. Regardless, the results of this study are not as generalizable to those who either do not desire or do not have the ability to exercise regularly.

4.2 Clinical and Public Health Significance

The addition of CF treatments to other personal responsibilities for adults with CF can be burdensome. Therefore, the treatments that patients perform should be beneficial to their health to maximize their use of time. Both exercise and ACT are recommended therapies, but a program that combines both may provide even greater effects on lung function. Preservation of lung function in patients with CF is extremely important in preventing health decline and further sequelae of the disease. The proposed study will start to examine this relationship between the timing and integration of exercise and ACT on lung function longitudinally.

If an integrated exercise and ACT program is found to improve lung function, then CF providers will have a specific regimen to provide to their patients. Importantly, the regimen still allows for personal adjustments and preferences, so it can be individually tailored for each subject. Hopefully, the integrated program will also

increase patient adherence to exercise and ACT both as a result of improved lung function as well as the feasibility of implementation into daily life. In addition to improved lung function, if the intervention decreases exacerbation frequency, this will also drastically affect the daily lives of patients. Fewer exacerbations would better preserve lung function and lessen the need for antibiotics and hospitalizations. These results could ultimately lead to an improved quality of life for patients with CF.

If the proposed integrated program does not have a significant effect on lung function in the study, then perhaps the order and timing of ACT and exercise are not as important as long as they are completed. If this is the case, ACT and exercise should continue to be recommended to patients, but it could be argued that the combination does not maximize benefits. The results of the secondary outcomes must also be considered in this situation because it could be possible that the intervention does not significantly affect lung function, but it may decrease exacerbations or improve quality of life, both of which are likely valued by patients with CF. Either way, the results of this study will provide greater insight into the best methods for patients to perform exercise and ACT. Additionally, the details of the intervention (time and frequency of exercising, monitoring of exercise, ACT session length and frequency, etc.) could be adjusted for future studies to determine the most effective regimen to improve lung function.

In conclusion, the integration of ACT and exercise in patients with CF has an encouraging potential to improve lung function over time. The proposed study will allow CF providers to make recommendations for ACT and exercise to their patients based on long-term results of lung function and exacerbation frequency. Overall, this study has the potential to greatly improve the quality of life for those living with CF.

Appendices

Appendix A. Sample Consent Form

Written with the 200 FR.1 HIC Consent Template

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 1 (2016-2)
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE NEW HAVEN HOSPITAL

Study Title: A Structured Airway Clearance and Exercise Program to Improve Clinical Outcomes in Cystic Fibrosis
Principal Investigator: Rachel Rose, PA-SII
Co-Principal Investigator: Clemente Britto-Leon, MD

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to evaluate the effectiveness of an integrated exercise and airway clearance therapy on lung function in adults with cystic fibrosis. You have been asked to participate because you have been diagnosed with cystic fibrosis and you are older than 18 years. Approximately 77 people will participate in this study.

Before you decide if you want to partake in this research study, it is important that you are aware of the risks and benefits in order to make an informed decision. This consent form will present you with information regarding the study, and this will be discussed with a research team member. The details to be discussed include the purpose, procedures to be performed, possible risks and benefits, and possible alternative treatments. Upon reading this form, you will be asked to sign this form if you wish to participate.

Description of Procedures

If you choose to participate in this study, you will be randomly assigned to either the intervention group or the control group. In the intervention group, you will be asked to perform an integrated program of exercise and airway clearance therapy (ACT). This will entail performing 30 minutes of exercise prior to an ACT session three times per week. You may choose your type of exercise from a list of accepted forms, and you will be asked to measure your heart rate before, once during, and after the 30 minutes of exercise. You will receive instructions on how to measure your heart rate prior to starting the study.

In the control group, you will be asked to perform 30 minutes of exercise from a list of accepted forms three times weekly. The exercise sessions must be separated by any ACT sessions by at least 2 hours. You will be asked to measure your heart rate before, once during, and after exercise, and you will receive instruction on how to measure your heart rate prior to starting the study.

In both groups, you will be asked to continue your CF appointments at the adult CF clinic every three months where you will perform spirometry and fill out a questionnaire on quality of life. You will also receive a phone call on the months that you do not have an appointment to discuss any questions. Additionally, you will be asked to fill out a daily

journal to record activity levels. The journal will include type of exercise performed, type of ACT performed, length of ACT performed, any side effects noticed, and heart rate measurements. This study will last for a time period of one year.
During the study, you may continue any other treatments you are receiving. You will not be standardized to a specific amount or method of ACT, and you should continue this as prescribed by your provider.
As required by U.S. Law, a description of this study can be found on http://www.ClinicalTrials.gov. This is a database that is used for people to see what studies are being done and what studies have been completed. The website will not include any information that can identify you, and will, at most, show a summary of the results. You may search this website at any time.
You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate. If research results are published, your name and other personal information will not be given.

Risks and Inconveniences
Both exercise and airway clearance therapy have been studied in many clinical trials, and they are recommended in the treatment of cystic fibrosis. The incidence of side effects in previous similar studies is rare, but they can occur.
Exercising carries certain risks or bodily harm that includes: physical injury (strain, fracture, etc.), acute dyspnea and cough, hypoglycemia, worsening of arthritis, cardiac arrhythmias, pneumothorax, and loss of consciousness. Some people may also experience soreness or stiffness after exercise. We will minimize these risks by encouraging you to wear proper clothing and shoes for exercise. We also ask that you discontinue exercising if you experience any side effects and either call the number listed on your daily journal or record the event in your daily journal.
Other risks from participating in the study include the breach of confidentiality about your health status and participation in the study. This is very unlikely to occur, as all study investigators are trained and certified in research privacy.
In the case of injury during the study, Yale School of Medicine and Yale New Haven Hospital will not cover the costs of a research-related injury. If you are injured, treatment will be provided, but you or your insurance carrier will be expected to pay for the treatment costs. There is no additional monetary compensation if you are injured.

Benefits
The results from this study may provide greater insight into the most effective integration of both exercise and ACT as CF therapies. The potential benefits of this study include improved lung function, decreased exacerbations, and improved health-related quality of life.

Economic Considerations
There are no costs associated with your participation in the study.

Treatment Alternatives/Alternatives
If you decide not to participate in this study, the alternative treatment is to continue your current regimen of exercise and ACT as recommended by your provider.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Data will be stored on a HIPAA compliant and encrypted device that is password protected. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

We understand that information about your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies your personal health information. This may include information that might directly identify you, such as his or her name and address, telephone number, and email address, or mobile phone number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you and your coded information, and this link will be kept secure and available only to the principal investigator or selected members of the research team. Any information that can identify you will remain confidential. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 5 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- Results of lung function testing and health-related quality of life survey answers
- Records about the monthly phone calls made as part of this research
- Records in medical chart regarding exacerbations during study period

Information about your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of your child's information.

If you choose to participate in this study, the investigators will check your electronic medical record at Yale (EPIC) to make sure you qualify. Any access to your electronic medical record will be done consistent with HIPAA regulations.
Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.
You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation
You are free to choose not to participate in this study. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not agree to participate. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study
If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.
The researchers may withdraw you from participating in the research if necessary. This includes, but is not limited to, non-compliance (i.e. not attending appointments) or in the cases of serious side effects.
If you choose not to participate or if you withdraw it will not harm your relationship with your own doctors or with the Yale School of Medicine and Yale New-Haven Hospital. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

You do not give up any of your legal rights by signing this form.

Questions
As this form contains detailed information and technical terms, please feel free to ask any questions regarding the study. You may take as much time as you need to consider joining this study before you make a final decision.

Authorization
I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____
Signature:_____
Relationship:_____
Date:_____

_____ _____
Signature of Principal Investigator Date
or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project, or if you have a research-related problem, you may contact the Principal Investigator, Rachel Rose PA-SII (***) ***- **** or the Co-Principal Investigator, Clemente Britto-Leon, MD (***) *** -****.
If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix B. Sample Recruitment Flyer

Volunteers Needed for a Cystic Fibrosis Research Study

We are looking for participants in a study to determine if combining exercise with airway clearance therapy improves lung function, decreases exacerbations, and improves quality of life in people with cystic fibrosis.

You May Be Eligible If:

- You have been diagnosed with cystic fibrosis
- You are at least 18 years of age
- You are able to participate in exercise
- You are currently performing some form of airway clearance therapy

What Will You Have to Do?

- Complete 30 minutes of exercise three times per week
- Fill out a daily journal
    - Record the amount of time and type of exercise and airway clearance therapy performed
    - Record your heart rate before, during, and after exercise
- Continue attending quarterly CF appointments for spirometry and to fill out a quality of life questionnaire

If you are interested in participating, or if you have any questions, please contact:

Rachel Rose, Principal Investigator: (***)***-**** or at ********@yale.edu

You may also discuss this with your CF provider at your next visit!

Appendix C. Sample CFQ-R Survey

CFQ-R **Adolescents and Adults** (Patients 14 Years Old and Older)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have cystic fibrosis. Thank you for your willingness to complete this form.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Section I. Demographics

Please fill-in the information or check the box indicating your answer.

A. What is your date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Mo Day Year

B. What is your gender?

☐ Male ☐ Female

C. During the **past two weeks**, have you been on vacation or out of school or work for reasons **NOT** related to your health?

☐ Yes ☐ No

D. What is your current marital status?

- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

E. Which of the following best describes your racial background?

- ☐ Caucasian
- ☐ African American
- ☐ Hispanic
- ☐ Asian/Oriental or Pacific Islander
- ☐ Native American or Native Alaskan
- ☐ Other (please describe) _____
- ☐ Prefer not to answer this question

F. What is the highest grade of school you have completed?

- ☐ Some high school or less
- ☐ High school diploma/GED
- ☐ Vocational school
- ☐ Some college
- ☐ College degree
- ☐ Professional or graduate degree

G. Which of the following best describes your current work or school status?

- ☐ Attending school outside the home
- ☐ Taking educational courses at home
- ☐ Seeking work
- ☐ Working full or part time (either outside the home or at a home-based business)
- ☐ Full time homemaker
- ☐ Not attending school or working due to my health
- ☐ Not working for other reasons

CFQ-R **Adolescents and Adults** (Patients 14 Years Old and Older)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Section II. Quality of Life

Please check the box indicating your answer.

During the past two weeks, to what extent have you had difficulty:	A lot of difficulty	Some difficulty	A little difficulty	No difficulty
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, groceries, or school bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐

During the past two weeks, *indicate how often:*	Always	Often	Sometimes	Never
6. You felt well	☐	☐	☐	☐
7. You felt worried	☐	☐	☐	☐
8. You felt useless	☐	☐	☐	☐
9. You felt tired	☐	☐	☐	☐
10. You felt energetic	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

Thinking about the state of your health over the last two weeks:

13. To what extent do you have difficulty walking?
1. You can walk a long time without getting tired
2. You can walk a long time but you get tired
3. You cannot walk a long time because you get tired quickly
4. You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
1. Just thinking about food makes you feel sick
2. You never enjoy eating
3. You are sometimes able to enjoy eating
4. You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
1. Not at all
2. A little
3. Moderately
4. A lot

16. How much time do you currently spend each day on your treatments?
1. A lot
2. Some
3. A little
4. Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

18. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

Thinking about your health during the past two weeks, indicate the extent to which each sentence is true or false for you.	Very true	Somewhat true	Somewhat false	Very false
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐
29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, advancing in a job, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

Section III. School, Work, or Daily Activities

Questions 35 through 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?
1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptom Difficulties

Please select a box indicating your answer.

Indicate how you have been feeling during the past two weeks.	A great deal	Somewhat	A little	Not at all
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?	☐	☐	☐	☐
41. Have you been coughing during the day?	☐	☐	☐	☐
42. Have you had to cough up mucus?	☐	☐	☐	☐ Go to Question 44

43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

How often during the past two weeks:	Always	Often	Sometimes	Never
44. Have you been wheezing?	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?	☐	☐	☐	☐
47. Have you had problems with gas?	☐	☐	☐	☐
48. Have you had diarrhea?	☐	☐	☐	☐
49. Have you had abdominal pain?	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

Appendix D. List of Exercise Options

You may choose any form of exercise listed below to complete your 30 minutes of exercise 3 times per week:

- Running
- Fast Walking
- Biking
- Hiking
- Aerobics Class
- Jumping (Jump Rope, Trampoline, etc.)
- Kickboxing
- Boxing
- Swimming
- Circuit Training
- Dancing
- Rowing
- High-intensity Interval Training
- Elliptical
- Stair Machine
- Cross-country Skiing
- Basketball
- Soccer

If you have any other preferred exercises, please contact our research team at (***)***-**** to see if it qualifies for this study.

Appendix E: Sample Exercise and ACT Daily Log

Directions: Please fill out one row of the table below every day. Under "Exercise Minutes" and "ACT Minutes," record the number of minutes spent on each therapy, and under "Exercise Activity" and "ACT Method," write what type of exercise you completed and which type of ACT you used. On days you do not exercise or do ACT, record 0 minutes and leave the activity or method box blank. The "Side Effects" column is for you to record any side effects you notice while completing the exercise and ACT. If you do not experience any side effects, leave the box blank.

On the three days per week that you exercise, record your heart rate before exercise (#1), once in the middle of exercise (around 15 minutes, #2), and after completing exercise (#3). Please calculate your heart rate as demonstrated by our research team at your first appointment. Also, use the target heart rate you have been provided with as a goal—If your heart rate is lower than the target in the middle of exercise, then increase the intensity of exercise as tolerated.

Please bring this log with you to all of your appointments at your CF clinic over the next year. If you have any questions, contact our research team at (***) *** - ****.

Date	Exercise Activity	Exercise Minutes	ACT Method	ACT Minutes	Heart Rate #1	Heart Rate #2	Heart Rate #3	Side Effects

Appendix F. Calculations for Target Heart Rate

1. Maximum heart rate will be calculated according to CDC guidelines[1]:

220 – Age (In Years)

2. Target heart rate will be in the range of 70-85% of maximum heart rate:

.70 (Maximum HR) to 0.85 (Maximum HR)

Example: For a person 25 years of age…

Maximum Heart Rate: 220 - 25 = 195

0.70 (195) = 136.5

0.85 (195) = 165.75

Target Heart Rate Range: 137 – 166 beats per minute

Appendix G. Sample Size Calculation

Sample size calculation based on:

Alpha (α, level of significance) = 0.050

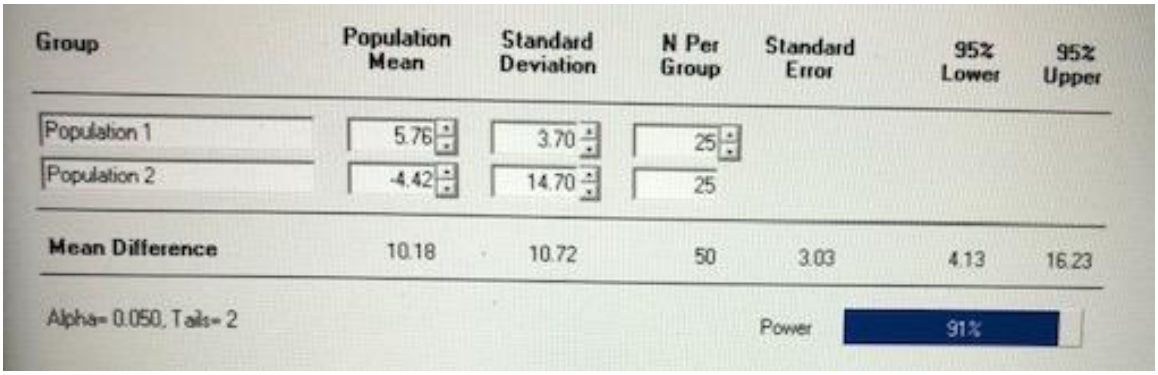
B (β, type II error) = 0.10, Power of 90%

$\mu_1 = 5.76\% \pm 3.70$

$\mu_2 = -4.42\% \pm 14.70$

n = 25 per group

Adding an additional 10 subjects to each arm plus a 10% dropout rate results in a total sample size of n = 77



Group	Population Mean	Standard Deviation	N Per Group	Standard Error	95% Lower	95% Upper
Population 1	5.76	3.70	25			
Population 2	-4.42	14.70	25			
Mean Difference	10.18	10.72	50	3.03	4.13	16.23

Alpha= 0.050, Tails= 2 Power 91%

Calculated using Power and Precision. Version 4.0. Biostat, Inc. Englewood, New Jersey.

References

1. Target Heart Rate and Estimated Maximum Heart Rate. Center for Disease Control and Prevention. https://www.cdc.gov/physicalactivity/basics/measuring/heartrate.htm. Updated 4/10/2020. Accessed.

Complete Bibliography

Why Work With the TDN. Cystic Fibrosis Foundation. https://www.cff.org/Research/Researcher-Resources/Therapeutics-Development-Network/Working-with-the-TDN/Why-Work-With-the-TDN/. Accessed 06/02/20, 2020.

Target Heart Rate and Estimated Maximum Heart Rate. Center for Disease Control and Prevention. https://www.cdc.gov/physicalactivity/basics/measuring/heartrate.htm. Updated 4/10/2020. Accessed.

Abbott J, Hurley MA, Morton AM, Conway SP. Longitudinal association between lung function and health-related quality of life in cystic fibrosis. *Thorax.* 2013;68(2):149.

Atlantis E, Chow C-M, Kirby A, Fiatarone Singh M. An effective exercise-based intervention for improving mental health and quality of life measures: a randomized controlled trial. *Preventive Medicine.* 2004;39(2):424-434.

Baldwin DR, Hill AL, Peckham DG, Knox AJ. Effect of addition of exercise to chest physiotherapy on sputum expectoration and lung function in adults with cystic fibrosis. *Respiratory Medicine.* 1994;88(1):49-53.

Bilton D, Dodd ME, Abbot JV, Webb AK. The benefits of exercise combined with physiotherapy in the treatment of adults with cystic fibrosis. *Respiratory Medicine.* 1992;86(6):507-511.

Bradley JM, Blume SW, Balp M-M, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *European Respiratory Journal.* 2013;41(3):571.

Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest.* 2002;121(1):64-72.

Cantin AM, Hartl D, Konstan MW, Chmiel JF. Inflammation in cystic fibrosis lung disease: Pathogenesis and therapy. *Journal of Cystic Fibrosis.* 2015;14(4):419-430.

Cheng YJ, Macera CA, Addy CL, Sy FS, Wieland D, Blair SN. Effects of physical activity on exercise tests and respiratory function. *British Journal of Sports Medicine.* 2003;37(6):521.

Clancy JP, Cotton CU, Donaldson SH, et al. CFTR modulator theratyping: Current status, gaps and future directions. *Journal of Cystic Fibrosis.* 2019;18(1):22-34.

Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med.* 2011;183(11):1463-1471.

Conway SP, Pond MN, Hamnett T, Watson A. Compliance with treatment in adult patients with cystic fibrosis. *Thorax.* 1996;51(1):29-33.

Courtney JM, Dunbar KEA, McDowell A, et al. Clinical outcome of Burkholderia cepacia complex infection in cystic fibrosis adults. *Journal of Cystic Fibrosis.* 2004;3(2):93-98.

Davies JC, Moskowitz SM, Brown C, et al. VX-659–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *New England Journal of Medicine.* 2018;379(17):1599-1611.

De Boer K, Vandemheen KL, Tullis E, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. *Thorax.* 2011;66(8):680-685.

De Gracia J, Mata F, Alvarez A, et al. Genotype-phenotype correlation for pulmonary function in cystic fibrosis. *Thorax.* 2005;60(7):558-563.

De Jong W, Grevink RG, Roorda RJ, Kaptein AA, Van Der Schans CP. Effect of a Home Exercise Training Program in Patients With Cystic Fibrosis. *Chest.* 1994;105(2):463-468.

Dwyer TJ, Alison JA, McKeough ZJ, Daviskas E, Bye PTP. Effects of exercise on respiratory flow and sputum properties in patients with cystic fibrosis. *Chest.* 2011;139(4):870-877.

Dwyer TJ, Daviskas E, Zainuldin R, et al. Effects of exercise and airway clearance (positive expiratory pressure) on mucus clearance in cystic fibrosis: a randomised crossover trial. *European Respiratory Journal.* 2019;53(4):1801793.

Elborn JS. Cystic fibrosis. *The Lancet.* 2016;388(10059):2519-2531.

Elce A, Nigro E, Gelzo M, et al. Supervised physical exercise improves clinical, anthropometric and biochemical parameters in adult cystic fibrosis patients: A 2-year evaluation. *The Clinical Respiratory Journal.* 2018;12(7):2228-2234.

Flume PA, Robinson KA, O'Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care.* 2009;54(4):522-537.

Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of Aerosolized Recombinant Human DNase on Exacerbations of Respiratory Symptoms and on Pulmonary Function in Patients with Cystic Fibrosis. *New England Journal of Medicine.* 1994;331(10):637-642.

Gojšina BZ, Rodić M, Višekruna J, Trajković GZ, Sovtić AD, Minić PB. Pulmonary exacerbations as a risk factor for lung function decline - experiences of the National Cystic Fibrosis Center. *Egzacerbacije plućne bolesti kao faktor rizika od sniženja funkcije pluća - iskustva Nacionalnog centra za cističnu fibrozu.* 2019;76(11):1110-1114.

Goss CH, Burns JL. Exacerbations in cystic fibrosis · 1: Epidemiology and pathogenesis. *Thorax.* 2007;62(4):360.

Goss CH, Mayer-Hamblett N, Kronmal RA, Ramsey BW. The cystic fibrosis therapeutics development network (CF TDN): a paradigm of a clinical trials network for genetic and orphan diseases. *Advanced Drug Delivery Reviews.* 2002;54(11):1505-1528.

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American Journal of Respiratory and Critical Care Medicine.* 2019;200(8):e70-e88.

Grasemann H. CFTR Modulator Therapy for Cystic Fibrosis. *New England Journal of Medicine.* 2017;377(21):2085-2088.

Habib A-RR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. *Sci Rep.* 2019;9(1):7234-7234.

Habib A-RR, Manji J, Wilcox PG, Javer AR, Buxton JA, Quon BS. A Systematic Review of Factors Associated with Health-Related Quality of Life in Adolescents and Adults with Cystic Fibrosis. *Annals of the American Thoracic Society.* 2015;12(3):420-428.

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric Reference Values from a Sample of the General U.S. Population. *American Journal of Respiratory and Critical Care Medicine.* 1999;159(1):179-187.

Hebestreit H, Kieser S, Junge S, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. *European Respiratory Journal.* 2010;35(3):578.

Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the

F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet.* 2019;394(10212):1940-1948.

Horsley A, Siddiqui S. Putting lung function and physiology into perspective: cystic fibrosis in adults. *Respirology.* 2015;20(1):33-45.

Kerem E, Viviani L, Zolin A, et al. Factors associated with FEV₁ decline in cystic fibrosis: analysis of the ECFS Patient Registry. *European Respiratory Journal.* 2014;43(1):125.

Kettler LJ, Sawyer SM, Winefield HR, Greville HW. Determinants of adherence in adults with cystic fibrosis. *Thorax.* 2002;57(5):459.

Knowles MR, Durie PR. What Is Cystic Fibrosis? *New England Journal of Medicine.* 2002;347(6):439-442.

Konstan MW, Morgan WJ, Butler SM, et al. Risk Factors For Rate of Decline in Forced Expiratory Volume in One Second in Children and Adolescents with Cystic Fibrosis. *The Journal of Pediatrics.* 2007;151(2):134-139.e131.

Kriemler S, Kieser S, Junge S, et al. Effect of supervised training on FEV1 in cystic fibrosis: a randomised controlled trial. *J Cyst Fibros.* 2013;12(6):714-720.

Kriemler S, Radtke T, Christen G, Kerstan-Huber M, Hebestreit H. Short-Term Effect of Different Physical Exercises and Physiotherapy Combinations on Sputum Expectoration, Oxygen Saturation, and Lung Function in Young Patients with Cystic Fibrosis. *Lung.* 2016;194(4):659-664.

Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. *J Cyst Fibros.* 2010;9(4):250-256.

Lynch JP, 3rd, Sayah DM, Belperio JA, Weigt SS. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Semin Respir Crit Care Med.* 2015;36(2):299-320.

Mahase E. Cystic fibrosis: triple therapy shows promising results. *BMJ.* 2019;367:l6347.

McCarren B, Alison JA. Physiological effects of vibration in subjects with cystic fibrosis. *European Respiratory Journal.* 2006;27(6):1204.

McCloskey M, McCaughan J, Redmond AOB, Elborn JS. Clinical outcome after acquisition of Burkholderia cepacia in patients with cystic fibrosis. *Irish Journal of Medical Science.* 2001;170(1):28.

Morrison L, Innes S. Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database Syst Rev.* 2017;5(5):CD006842-CD006842.

Oermann CM, Sockrider MM, Giles D, Sontag MK, Accurso FJ, Castile RG. Comparison of high-frequency chest wall oscillation and oscillating positive expiratory pressure in the home management of cystic fibrosis: A pilot study*. *Pediatric Pulmonology.* 2001;32(5):372-377.

Orenstein DM, Franklin BA, Doershuk CF, et al. Exercise Conditioning and Cardiopulmonary Fitness in Cystic Fibrosis: The Effects of a Three-month Supervised Running Program. *Chest.* 1981;80(4):392-398.

Pryor JA, Tannenbaum E, Scott SF, et al. Beyond postural drainage and percussion: Airway clearance in people with cystic fibrosis. *Journal of Cystic Fibrosis.* 2010;9(3):187-192.

Quinton PM. Cystic fibrosis: a disease in electrolyte transport. *Faseb j.* 1990;4(10):2709-2717.

Ramsey BW, Davies J, McElvaney NG, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *New England Journal of Medicine.* 2011;365(18):1663-1672.

Ranu H, Wilde M, Madden B. Pulmonary function tests. *Ulster Med J.* 2011;80(2):84-90.

Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. *Nature Reviews Disease Primers.* 2015;1(1):15010.

Reix P, Aubert F, Werck-Gallois M-C, et al. Exercise with incorporated expiratory manoeuvres was as effective as breathing techniques for airway clearance in children with cystic fibrosis: a randomised crossover trial. *Journal of Physiotherapy.* 2012;58(4):241-247.

Ren CL, Konstan MW, Yegin A, et al. Multiple antibiotic-resistant Pseudomonas aeruginosa and lung function decline in patients with cystic fibrosis. *J Cyst Fibros.* 2012;11(4):293-299.

Rubin BK. Designing clinical trials to evaluate mucus clearance therapy. *Respir Care.* 2007;52(10):1348-1358; discussion 1358-1361.

Ruf K, Winkler B, Hebestreit A, Gruber W, Hebestreit H. Risks associated with exercise testing and sports participation in cystic fibrosis. *Journal of Cystic Fibrosis.* 2010;9(5):339-345.

Salh W, Bilton D, Dodd M, Webb AK. Effect of exercise and physiotherapy in aiding sputum expectoration in adults with cystic fibrosis. *Thorax.* 1989;44(12):1006-1008.

Sanders DB, Fink AK. Background and Epidemiology. *Pediatr Clin North Am.* 2016;63(4):567-584.

Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *J Cyst Fibros.* 2009;8(2):91-96.

Schaedel C, De Monestrol I, Hjelte L, et al. Predictors of deterioration of lung function in cystic fibrosis. *Pediatric Pulmonology.* 2002;33(6):483-491.

Schneiderman JE, Wilkes DL, Atenafu EG, et al. Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. *European Respiratory Journal.* 2014;43(3):817.

Schneiderman-Walker J, Pollock SL, Corey M, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. *The Journal of Pediatrics.* 2000;136(3):304-310.

Schrien AC, Dekker FW, Kaptein AA, Dijkman JH. Quality of Life in Elderly Patients with Chronic Nonspecific Lung Disease Seen in Family Practice. *Chest.* 1990;98(4):894-899.

Solé A, Olveira C, Pérez I, et al. Development and electronic validation of the revised Cystic Fibrosis Questionnaire (CFQ-R Teen/Adult): New tool for monitoring psychosocial health in CF. *Journal of Cystic Fibrosis.* 2018;17(5):672-679.

Stanojevic S, Ratjen F. Physiologic endpoints for clinical studies for cystic fibrosis. *Journal of Cystic Fibrosis.* 2016;15(4):416-423.

Szczesniak R, Heltshe SL, Stanojevic S, Mayer-Hamblett N. Use of FEV(1) in cystic fibrosis epidemiologic studies and clinical trials: A statistical perspective for the clinical researcher. *J Cyst Fibros.* 2017;16(3):318-326.

Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England Journal of Medicine.* 2017;377(21):2013-2023.

VanDevanter DR, Konstan MW. Outcome measures for clinical trials assessing treatment of cystic fibrosis lung disease. *Clin Investig (Lond).* 2012;2(2):163-175.

Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *New England Journal of Medicine.* 2015;373(3):220-231.

Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *European Respiratory Journal.* 2012;40(1):61.

Wen Y, Wang D, Zhou M, Zhou Y, Guo Y, Chen W. Potential Effects of Lung Function Reduction on Health-Related Quality of Life. *Int J Environ Res Public Health.* 2019;16(2):260.

Wilson LM, Morrison L, Robinson KA. Airway clearance techniques for cystic fibrosis: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev.* 2019;1(1):CD011231-CD011231.