Nicola Rowbotham ORCID iD: 0000-0003-1105-3645

Airway clearance and exercise for people with cystic fibrosis: balancing longevity with life

Nicola J Rowbotham[1]* & Tracey E Daniels[2,3]

1. Evidence Based Child Health Group, University of Nottingham, Nottingham, UK
2. York and Scarborough Teaching Hospitals NHS Foundation Trust, York, UK.
3. York St John University, York, UK

*Corresponding author: nicola.rowbotham@nottingham.ac.uk

Abstract

Airway clearance has been an integral part of cystic fibrosis (CF) care for almost as long as CF has been identified as a condition. From diagnosis as a neonate through to end-of-life care, airway clearance is an everyday aspect of life, adding a considerable treatment burden to the lives of people with CF.

There are many different techniques used for airway clearance which have evolved over time with an aim to improve effectiveness, support adherence and, more recently, to consider the impact of burden. A popular thought is whether airway clearance could be replaced by exercise. With new precision therapies in the form of CFTR modulators available, the CF landscape is rapidly changing, raising the question of whether certain treatments are needed at all.

Depending on factors such as CFTR mutation, age, and pre-existing lung damage before starting a CFTR modulator, individuals with CF may need different levels of intensity and type of maintenance treatment. Precision medicine is likely to lead to the need for increased precision and individualised management around other maintenance therapies such as airway clearance.

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Key words

Cystic Fibrosis, Physiotherapy, Airway clearance, Exercise, Treatment burden, CFTR modulators

Introduction

Cystic fibrosis (CF) is a multi-system, life-long genetic condition with a median predicted survival currently of 49 years[1]. The gene mutations responsible for CF result in dysfunctional CF transmembrane conductance regulator protein (CFTR), which, in its functional form, acts as a chloride channel. Impaired chloride secretion in CF leads to sticky and thick secretions for a range of epithelial tissues such as the airways and pancreatic duct. This results in malabsorption, suboptimal nutritional status, recurrent respiratory infections, progressive lung damage and respiratory failure[2].

Standard treatment for CF has, until recently, focused on managing the symptoms and consequences of CF. For chest involvement this treatment includes airway clearance, prophylactic antibiotics, early eradication of new growths of potential lung pathogens, maintenance antibiotics, osmotics, mucolytics and intensive management of exacerbations with oral and/or intravenous antibiotics[3].

The practice of physiotherapy, or physical therapy as it's alternatively known, for airway clearance has been an integral part of CF care almost since CF was identified (figure 1). Physiotherapy remains a continual companion throughout the life of people with CF (pwCF) who are expected to dedicate a burdensome amount of their time every day to physiotherapy from diagnosis through to end of life. Here the types of airway clearance techniques available are explored along with the perceived burden of such therapies. We discuss potential strategies to reduce such burden, including the role exercise may have to play, and how the advent of CFTR targeted therapies raises new questions about optimal airway clearance regimens.

Precision medicines, in the form of highly effective CFTR modulators, first became available around a decade ago for those with CF caused by a gating mutation, comprising around 5% of the CF population[4]. Further developments now see highly

effective modulators suitable for around 90% of pwCF[5]. This is changing the landscape for many pwCF with rapid and transformative improvements in health. This rapid change creates some uncertainty about the ongoing need for established treatment regimens.

The history of physiotherapy and airway clearance techniques for people with cystic fibrosis

Physiotherapy for pwCF covers a wide range of interventions and approaches including airway clearance, exercise, inhaled therapy, non-invasive ventilation, oxygen therapy, independent prescribing, musculoskeletal and continence management[6,7].

Historically a specific airway clearance regimen of postural drainage used in combination with percussion was referred to as chest physiotherapy[8]. Many people continue to refer to airway clearance techniques as physiotherapy or chest physiotherapy. Over time, and with a change of focus to more independent techniques, the term airway clearance techniques was adopted by physiotherapists to define the range of techniques aiming to improve sputum clearance[7 8]. For the purposes of this review, the range of interventions physiotherapists deliver will be referred to as physiotherapy and airway clearance techniques (ACT) will be used to describe those techniques designed to clear the airways.

A key feature of CF is increased and tenacious sputum which contributes to infective exacerbations, inflammation, lung colonisation with bacteria and deterioration in lung function. ACTs are described in the 1950s as one of the first treatments for pwCF[9] and the use of ACTs have been globally recommended for all pwCF[6,7,10]. ACTs aim to optimise ventilation and minimise sputum plugging so interrupting the vicious cycle of sputum retention, infective exacerbation, airway obstruction, inflammation and lung damage[11]. People with CF are advised to start ACTs soon after diagnosis and perform them at least daily for the rest of their lives[6].

There are a range of ACTs (Figure 1) including postural drainage, manual techniques, active cycle of breathing techniques, autogenic drainage, positive expiratory pressure (mask or mouthpiece), high-pressure positive expiratory pressure,

oscillating positive expiratory pressure (e.g. Acapella®, Aerobika®, Cornet®, Flutter®, Pari O-PEP ®, Quake®), intrapulmonary percussive ventilation (e.g. MetaNeb ®), high frequency chest wall oscillation (e.g. AffloVest®, InCourage® system, SmartVest®, ThAIRapy Vest®, The Vest®), Simeox® and exercise.

ACTs have undergone an evolution over time moving from more passive treatments such as manual techniques and postural drainage to more active treatments (Figure 1). This evolution has largely been driven by increasing life expectancy and the associated need for independence. The focus on improving adherence and the better understanding of the potential for adverse events such as gastroesophageal reflux and desaturation with traditional techniques[12-14] have also helped direct this change.

The current role of airway clearance techniques for people with CF

Airway clearance techniques are an established and important component of care for pwCF[3,6]. Physiotherapists consider factors such as technique efficacy, age, preference, capability, comorbidities, airway pathophysiology and cost when selecting the most appropriate airway clearance technique for an individual.

Current guidance suggests that airway clearance is introduced and taught within the first weeks of diagnosis[6] although there is some variation in view about the need for routine airway clearance in asymptomatic new-born screened babies[15]. ACTs at this stage of life are carried out by the child's caregivers with baby PEP or manual techniques the most common techniques used in the UK[6]. Positioning and passive movement/activity are introduced and this gradually evolves into more active play as the child develops.

As children age, exercise and activity are encouraged with ACTs tending to become more independent. A range of techniques are used with preference varying by country. For example, PEP is favoured in the UK[1] and Canada[16], while high frequency chest wall oscillation is most commonly used in the US[17].

Despite the emphasis on the use of ACTs through the lifespan of pwCF, the evidence base remains problematic. A systematic review looking at the efficacy of ACTs

reported some evidence that ACTs increased mucus transport rate in the short-term, but could not give any detail about longer term outcomes[18]. It has been identified that the ethics of longer-term studies withdrawing such an established aspect of management could be challenging[8] although the introduction of modulators may alter this view.

More rigorous longer-term studies comparing ACTs have been possible and have shown that no ACT is superior to another[19]. However the preference and ability of people with CF to adhere to treatment are important in identifying the most effective technique for an individual[19]. The choice and views of pwCF have therefore become more central to ACT provision. Exercise and activity are established as an adjunct to existing ACTs and research is ongoing to understand the role of exercise as an independent ACT[20].

Adherence

Adherence is defined as "the extent to which a person's behaviour (i.e. taking medication, following a diet and/or executing lifestyle changes), corresponds with agreed recommendations from a healthcare provider" [21]. Individuals with CF require a complex and time-consuming regimen. This includes intravenous, oral and inhaled medication, dietary adjustments and supplements, other medications and treatments for co-morbidities such as CF related diabetes, ACTs and activity/exercise[3] as well as intensive monitoring. Suboptimal adherence to all aspects of CF treatment has been seen[22] and is associated with increased exacerbations and the need for intravenous antibiotic therapy[23].

Self-reported adherence to airway clearance in adults with CF is approximately 30%[24], which is lower than that seen for other treatments such as medication. Adherence rapidly deteriorates in adolescence as the lead role and responsibility for treatment management shifts from parents and caregivers to pwCF. A decline of up to 50% less adherence in adolescents and young adults has been seen[22,23,25,26].

Understanding accurate adherence levels to airway clearance is problematic. Contributing factors are a lack of objective measures and a reliance on measures

such as self-report, which have been shown to overestimate adherence in other areas of treatment for pwCF such as nebulised therapy[27]. Project Fizzyo is an ongoing longitudinal observational cohort study which is gathering objective electronic data capture adherence data for airway clearance and activity over sixteen months for children and young pwCF. An interrupted time-series design will assess ACT feedback and ACT gaming on adherence behaviours[28]. This data is likely to give a clearer picture of ACT adherence patterns in children and adolescents with CF as has been seen with nebulised medication adherence data[27].

Non-adherence to exercise has been described; however, it is suggested that the perception of exercise therapy is generally viewed more positively by individuals with CF, given its focus on health promotion rather than illness management[29]. Factors such as the impact on activities of daily living and social functioning, treatment burden, accidental or purposeful forgetting, no perceived benefit and "being unpleasant" have been identified as influencing non-adherence[26]. Barriers to ACT adherence in pwCF are multifactorial[25,30] but the burden in terms of the time ACT take is highlighted as a particular barrier[25,26].

Treatment burden

While burden of disease is well described, the burden of treatment is a less explored concept. Burden of treatment may be defined as, “the workload of healthcare and its effect on patient functioning and wellbeing” [20]. Taking medication is an aspect of treatment burden that is more visible to healthcare providers but the true burden and workload may include planning and attending health appointments, arranging and collecting prescriptions from multiple sources, setting up and taking medication[31], maintaining equipment for medication taking (e.g. nebuliser), monitoring health (e.g. measuring lung function or glucose monitoring), setting up and carrying out non medication related treatment (e.g. exercise and airway clearance) and lifestyle changes (e.g. dietary changes)[32]. The cumulative treatment workload for patients with chronic conditions, when enacting all recommendations in disease specific guidelines, can be overwhelming [33,34].

Treatment regimens for people with CF are burdensome. The median number of treatments per day for an adult with CF in 2009 was seven, with an average daily treatment duration of between 108 min to three hours[30]. By 2019 the number of daily treatments was identified as ten[35] and, given the pace of treatment development, it's likely that this now represents an underestimate of treatment regimens in 2021. The CF trust registry report 2019 signals high treatment burden detailing median days of IV antibiotics at 26 days (IQR 14-43) and 79.5% of pwCF taking at least one nebulised therapy and around 22% taking a nebulised antibiotic, Dornase Alfa and hypertonic sodium chloride or Mannitol[1]. Reports of perceived treatment complexity and burden worsen with age, as lung function declines and as treatment regimens become more complex[36]. Perceived treatment burden is also significantly higher in adults who report completing thirty minutes or more of daily ACT[37].

The challenges of balancing the aggressive management and layering of new therapies, which lead to increased survival, with increasing treatment burden in CF have been recognised for many years[30]. Treatment burden is of high importance to the CF community featuring as the number one research priority in the James Lind CF priority setting partnership and the number three area of interest in the CF Foundation's Insight CF project[38,39].

There is agreement that physiotherapy related treatments such as airway clearance and inhaled therapy are considered the most burdensome by the CF community[35,38,40] yet conversely are also perceived as one of the more important of all treatments [35]. Despite this perceived importance, ACTs are one of the most common CF treatments to miss out when busy and tired[30,35]. Around 80% of people with CF feel that their treatments impact negatively on socialising, sports and hobbies[35] so combining ACTs with a treatment in the form of exercise may help adherence and reduce perception of burden.

Measuring treatment burden

In order to continue to develop both understanding of, and effective ways of managing and minimising treatment burden, accurate and meaningful measurement

tools are needed. There continues to be debate around the best way to measure and understand the level of treatment burden among patients[41]. This lack of agreement creates difficulties for both researchers and clinicians to explore, understand and intervene in managing treatment burden[41].

Within CF care, the treatment burden subscale of the CF questionnaire-revised (CFQ-R) has been most commonly used to assess perceived treatment burden[36]. The CFQ-R is a validated measure of quality of life for people with CF aged 6–24 years, and caregivers of people with CF aged 6–13 years[42,43]. Scoring for the treatment burden domain is based on three questions about the time it takes to complete treatments, whether treatments interfere with daily life and any difficulty in completing treatments. It is scored on a 0-100 point scale where higher scores indicate lower burden[42,43]. A potential limitation of the CFQ-R in assessing treatment burden is that it was developed before the introduction of modulator therapies therefore may not be fully optimised to capture the full experience of life with CF and the impact of modulators[44].

A newer measure, the CF impact questionnaire (CF-IQ), has been developed since the introduction of modulators, for pwCF[44]. It is a forty item scale which aims to assess a comprehensive set of patient focused concepts to characterise the broad experience of pwCF in the post modulator era[44]. This tool does not yet appear in the literature beyond it's development which shows content validity[44].

How can we reduce treatment burden?

Three key potential targets to reduce burden are:

1. Replace a more burdensome treatment with one perceived to be less burdensome.
2. Withdraw the use of the burdensome treatment
3. Use an intervention to reduce the perceived burden of the treatment

Here each of these targets are explored in the context of reducing the burden of airway clearance.

1.1.1 1. Replace a more burdensome treatment with one perceived to be less burdensome

A very popular question within the CF community is "Can exercise replace chest physiotherapy for people with CF?". It was included as a James Lind Alliance top 10 research priority during a global priority setting exercise in 2017, and as a topic of importance in the CF Foundation's Insight CF project at a similar time[38,39].

1.1.1.1 The current role of exercise

Exercise forms a big part of the life of most pwCF, with 96% of people surveyed doing some form of exercise[45]. These activity levels are higher than in the general population; 20% of people in the UK describe themselves as inactive[46] compared to 4% of pwCF surveyed within the James Lind work[45]. CF guidelines currently recommend regular exercise as an adjunct to ACT to help with overall health, aerobic capacity and muscle strength[6,10]. Other benefits of exercise and physical activity in CF include improvements in bone health[47], glycaemic control[48,49], quality of life[50,51] and rate of decline in lung function[52,53]. It has been noted that those pwCF with greater exercise capacity have improved survival[54-56]. Top reasons given by pwCF for exercising included for lung health, general health and enjoyment[45]. People with CF report participation in various forms of exercise but the types most popular are moderate to high intensity exercise such as walking, running, swimming and cycling[45].

Over half of the pwCF surveyed during the James Lind Alliance work reported adding exercise into their regular physiotherapy ACT routines[45]. However, nearly half of pwCF skipped their ACT when they exercised[45]. Another study in Australian adults with CF found that 43% of respondents agreed that exercise can be used as a substitute to ACT with similar numbers reporting that they had done this in the previous three months[57].

1.1.1.2 How can exercise be equal to ACT?

There is a physiological basis behind the idea that exercise could act as a valid replacement to ACT. Clearance of sputum during exercise occurs through several mechanisms including mechanical vibration, reduced epithelial sodium conductance

and nasal potential difference with improved sputum hydration and mucociliary clearance[20,58-60], increased peak expiratory flow[20,60] and reduced sputum mechanical impedance[60]. Increased clearance of mucus helps to clear infectious particles, decreasing the risk of inflammatory response and therefore the resultant damage to the lungs.

1.1.1.3 What evidence is there already?

A 2017 Cochrane review looking purely at physical exercise training in pwCF[61] concluded, from a limited number of thirteen low-moderate quality studies, that physical exercise training can improve aerobic capacity and lead to improvements in lung function and health related quality of life.

A more recent systematic review published in December 2020 by Ward *et al.* looking more specifically at exercise as a substitute for traditional ACTs in CF, concluded that exercise may be as effective as traditional ACTs[20]. They found a total of twelve studies to include. These were published between 1989 to 2019 and of short duration (a single episode to two weeks). They were heterogenous in design and mostly cross-over trials (only one RCT), with quality of the evidence (GRADE) deemed very low to moderate.

Five crossover studies compared exercise to rest but not all outcomes were measured in each. There was no difference in FEV^1 or FVC but moderate evidence that peak expiratory flow rates are increased after treadmill exercise when compared with rest and that exercise also results in significantly greater clearance of mucus from the whole lung. Greater sputum weight was expectorated after mixed exercise, trampolining and cycling when compared to rested control. Nine studies compared exercise versus ACTs (two of these also compared to rest, eight cross-over, one RCT). The data were unable to be combined into a meta-analysis but overall, no significant differences were noted in any of the trials between respiratory function tests or sputum clearance so concluded that exercise may have a similar effect as traditional ACTs. Huffing/forced expiration, when included with ACTs but not exercise, led to significantly less sputum expectoration during the exercise intervention but similar amounts after[62,63]. This suggests that including

huffing/forced expiration in exercise regimens will maximise airway clearance. The authors rightly note that the important outcomes of health-related quality of life, burden and adherence need to be investigated further. A Cochrane review on this subject is pending[64].

1.1.1.4 Trials in the pipeline

When the James Lind research priorities were decided in 2017, there were only two interventional trials that were looking into the possibility of exercise as a replacement for ACTs[65].

- Exercise alone versus exercise and positive expiratory pressure as a form of airway secretion clearance in adults with mild cystic fibrosis-related respiratory disease - a feasibility study[66].
- Effects of treadmill exercise versus Flutter® on respiratory flow and sputum properties in adults with cystic fibrosis: a randomised, controlled, cross-over trial[67].

The first trial was a feasibility study which has since been published[68] hopefully paving the way for a larger multicentre trial investigating if exercise alone can be substituted for ACTs. The second trial was included in the systematic review commented on above.

On updating this search using the same inclusion and exclusion criteria as in the Kalatis *et al.* paper referenced above, but modifying the search terms to include exercise, from 2018 to end of April 2021 (see Appendix B for search terms), nine exercise related interventional trials were found with three of these ongoing (Table 1, see Appendix C for Prisma flow chart.).

1.1.2 2. Withdraw the use of the burdensome treatment – withdrawal trials

Removing treatments can be an attractive target to reduce burden of treatment[69]. Following the introduction of modulator therapy, there is an emerging confidence in planning the trials needed to endorse any largescale stopping of treatment. Trials

have already been designed to bring more certainty around the place of osmotics and mucolytics in the presence of modulator therapy.

SIMPLIFY is a US based study aiming to evaluate the stopping of nebulised hypertonic sodium chloride or Dornase alfa over a six-week period in pwCF who are taking the triple combination modulator, elexacaftor/tezacaftor/ivacaftor[69]. CF Storm is a UK based study which will allocate participants over the age of twelve, and established on the triple combination modulator, elexacaftor/tezacaftor/ivacaftor, to either stop or to continue their daily nebulised mucoactive therapies (Dornase alfa, hypertonic saline or both). The aim will be to demonstrate that stopping mucoactive therapies does not result in a significant decline in lung function over 12 months[70].

A systematic review looking at interventions to reduce perceived burden of treatment in adults with long-term conditions identified eleven studies which reported positive outcomes[71]. These interventions included reducing dosing frequency, improving background therapy, offering home care or providing simpler medical devices. Two of the studies were in pwCF[72,73]; one reported decreased treatment burden with an altered regimen which included decreased frequency of dosing, a more efficient delivery device and a different medication[72]. The other study reported decreased treatment burden when a CFTR modulator was added to the treatment regimen[73]. Given that the removal of treatments is a popular target to investigate in terms of reducing treatment burden, this finding that adding a highly effective treatment can reduce burden is interesting and significant.

The Cochrane review by Warnock *et al.* looked at ACT versus no ACT with some leaning towards short term benefits with ACT[18]. This review was completed before the approval of triple therapy modulators so didn't evaluate evidence for stopping ACTs in the presence of modulators. Despite the consistency of ACTs being perceived as the most burdensome treatment for pwCF, there are no trials registered to assess the place of withdrawal of ACTs in the modulator era (see search strategy in Appendix D and Prisma diagram in Appendix E). The heterogeneity of ACTs and

uncertainty around selecting helpful outcome measures have been highlighted as limiting factors for trials focusing on withdrawal of ACTs[69].

1.1.3 3. Use an intervention to reduce the perceived burden of the treatment

It is a commonly held view that the best way to reduce treatment burden is to reduce the time or volume of treatments, especially in the post modulator era[4]. Although simplifying treatment has been shown to improve adherence in other disease areas such as hypertension[74], there isn't an established link in reducing perception of burden. It was not possible to find any completed trials that demonstrate a link between reducing the treatment regimen and reducing perception of treatment burden in pwCF (see Appendix F for search strategy and Appendix G for associated Prisma diagram). One study; qualitative understanding of experiences with the SIMPLIFY trial (QUEST)[75], is currently recruiting and is designed to complement the SIMPLIFY trial[69] by exploring the perspectives of SIMPLIFY participants about treatment withdrawal research and treatment burden. This study is due to complete in January 2023.

The way treatment burden is perceived varies between individuals, and there is not always correlation with volume of treatments, it can just be the act of having to do anything treatment related; twenty tablets or two tablets can be just as burdensome[76]. This is highlighted using asthma as an example where treatment regimens using inhalers are significantly less time burdensome than the nebulised regimens for pwCF, however adherence levels remain suboptimal and the perception of burden high[77]. This individuality and variation in perception of treatment burden may be explained by the objective and subjective aspects that have been suggested as important. Objective aspects may include number of treatments, time to administer and monitor treatment, while subjective may include feelings of guilt, hopelessness and fear about treatment[78]. Reducing treatments may give a short "honeymoon" of perceived improvement in burden but the less that has to be done, the more burdensome that less may become.

The suboptimal effect of taking practical approaches on decreasing perceived treatment burden suggests that other approaches such as behavioural interventions may be helpful to explore[77]. Habit formation has been suggested as a mechanism to reduce perceived effort and burden with treatment[79]. This has been supported within the literature for inhaled therapies in pwCF with a reduced perceived treatment burden in those with established and stronger treatment habits[80,81]. A UK multicentre randomised controlled trial; ACtiF (development and evaluation of an intervention to support adherence to treatment in adults with Cystic Fibrosis), assessed the effectiveness of a self-management intervention with a focus on habit formation. It showed higher adherence, higher habit strength and lower perceived burden among the intervention[82,83].

Effect of modulators and future therapy – will ACT be needed at all?

Although success is yet to be seen with gene therapy in CF, there has been success with modulator therapy. CFTR modulators improve defective CFTR protein function in pwCF by binding to CFTR protein to potentiate action. They address the basic defect of CFTR dysfunction, modify the disease process and are highly efficacious. The first approved CFTR modulator was Ivacaftor, which works for people with Class III and some of the Class IV mutations and are found in around 8-10% of the UK CF population[4]. More recently combined therapies such as Kaftrio/Trikafta (Elexacaftor-Tezacaftor-Ivacaftor) working together to fix the defective protein in more common mutations such as Phe508del, have opened up the hope of a less restricted life to the majority of the CF population[5].

The phase III trials of CFTR modulators were carried out with modulators as add on therapy in addition to usual care, including ACTs[4,5]. However, the significant changes in physiology in pwCF on modulator therapy create uncertainty about the effects of and need for maintenance therapy such as ACTs[40]. This uncertainty is particularly present for children and young people who are less likely to have significant, pre-existing lung damage at the point of commencing modulator therapy. As the use of highly effective modulator therapies is extended earlier into the life of children with CF, it is anticipated that an effect will be the slowing or even prevention of

pulmonary complications[84]. This may give a different trajectory of lung involvement and therefore less need for lung focused treatments than those with established lung involvement and bacterial colonisation. Precision medication may in this case lead to the need for precision condition management.

We should not forget the approximately 10% of pwCF who do not yet have any modulator therapies available[85]. The many years of CF centres experiences and honing of treatments to get to the improvements in life expectancy achieved prior to modulator therapies must not be forgotten either. Even for those with modulators available, adherence can wane with time[86] and not all can tolerate the side-effects so there will still be the need for holistic, multisystem CF care. It will be important to acknowledge and consider this divergence of the CF population as trials and withdrawal trials of traditional therapies are designed.

Conclusions

Airway clearance techniques are a long-established treatment for pwCF, almost since CF was identified. They are consistently reported to be the most burdensome treatment for pwCF, yet evidence outlining the dose needed is lacking.
CFTR modulators are changing the landscape of CF care and are driving an environment focused on reducing the burden of treatment for pwCF. Three potential targets to address burden of treatment are replacing a more burdensome treatment with one perceived to be less burdensome, withdrawing the use of the burdensome treatment or using an intervention to reduce the perceived burden of the treatment. The literature suggests that exercise already plays a role in the lives of pwCF and that ACTs are often omitted in favour of exercise. Studies indicate that exercise may be as effective as ACTs in some circumstances and for some outcomes but there are still gaps in this knowledge base and further trials are planned or underway.
Withdrawing the use of burdensome treatments has been identified as successful in some conditions but not yet in pwCF. Conversely it has been demonstrated that for pwCF, adding a highly effective treatment can reduce treatment burden. Trials assessing the place for ACTs when modulators are commenced are needed but not

yet planned. Withdrawal trials are planned for other aspects of CF care but not yet for ACTs.

Using a behavioural intervention to reduce the perception of burden for pwCF has been successful for nebulised therapy; a treatment with similarly high perceptions of burden as ACTs. Work is ongoing to understand if other interventions such as gaming may reduce the burden of ACTs.

As the CF community remains at an early stage of highly effective modulators being available for most pwCF, uncertainty, caution and curiousness remain about the best way to design the research questions and studies which will shape future care. It will be important to work collaboratively across all areas of the CF community including pwCF, clinicians, families and researchers to best achieve research plans and designs that will be acceptable to the community while moving knowledge forward.

There is much to discuss on the design of such future studies;

- How do we decide what is “safe” to try?
- Which population? (age, disease severity/on modulators or not)
- How long do we try for? (short term/ long term (will there be a “honeymoon” period and then exercise becomes as burdensome as the original ACT?))
- What do we want to achieve? (equivalence/ non-inferiority/ superiority)
- How do we measure this? What outcomes do we use? (lung function/ burden/ adherence/ acceptability). Do we have the validated tools necessary to measure the outcome?
- What are the acceptable trade-offs for pwCF? Should we aim for best long-term physiological outcome at the cost of a continuing burden of treatment? Or decreased burden but at the potential cost of sub optimal long-term outcomes?

For the current population of pwCF at least, ACTs are likely to remain an important part of their daily CF care. Investigating ways to reduce perceived burden and tailoring management plans to the individual will be important to ensure that longevity does not come at the expense of living.

Declarations

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Table 1. Trials of exercise in CF since publication of the JLA top ten priorities

Title of trial	Status
ActivOnline: Physical Activity in Cystic Fibrosis Trial UK	Active, not recruiting
Effects of Innovative Aerobic Exercise Training in Cystic Fibrosis	Recruiting
Effects of Aerobic Interval Training on Glucose Tolerance in Children and Adolescents With Cystic Fibrosis	Recruiting
Exercise With or Without Electrical Stimulation in Cystic Fibrosis (Part I): Effects on Physical Fitness	Completed
Effects of an Individualized Exercise Program on Health-related and Skill/Performance-related fitness in CF.	Completed
The evaluation of a 12-week partially supervised, self-regulated exercise intervention in patients with cystic fibrosis	Completed
Acute effects of combined exercise and oscillatory positive expiratory pressure therapy on sputum properties and lung diffusing capacity in cystic fibrosis: a randomized, controlled, crossover trial[1]	Completed
Effects of exercise and airway clearance (positive expiratory pressure) on mucus clearance in cystic fibrosis: a randomised crossover trial[2]	Completed

Effects of a partially supervised conditioning programme in cystic fibrosis: an international multi-centre randomised controlled trial (ACTIVATE-CF): study protocol[3]	Completed

1. Radtke T, Boni L, Bohnacker P, et al. Acute effects of combined exercise and oscillatory positive expiratory pressure therapy on sputum properties and lung diffusing capacity in cystic fibrosis: a randomized, controlled, crossover trial. *BMC Pulm Med.* 2018;18(1):99.

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Figure 1. Timeline of airway clearance techniques