1 Rationale for Activity & Exercise

1.1 Patient Oriented Outcomes

Exercise capacity can predict morbidity and mortality in CF, independent of lung function. Specifically, people with CF that exhibited a higher $\dot{V}O_{2peak}$ had a longer life expectancy, whereas a greater severity of disease and mortality was associated with those with a lower exercise capacity [1]. Accordingly, over the past 3 decades, exercise has been recommended in CF. In addition to the improvements in exercise capacity, people with CF can experience many other benefits of engaging in exercise/physical activity. There is substantial data to demonstrate that both children and adults with CF who are physically active report having a better quality of life compared to those patients who are inactive. Higher health related quality of life is significantly related to both reported physical activity[2] and daily accelerometer counts[3]. For example, patients have reported higher scores in quality of life when engaging in >30min of moderate-vigorous physical activity[4] or at least 90 minutes of moderate to strenuous exercise per week[5].

Due to the positive relationships between physical activity and quality of life, as little as 4 exercise counseling sessions in children with CF demonstrated a noticeable increase in the physical well-being dimension[6]. Also exercise, in children hospitalized for an acute exacerbation, was able to improve quality of well-being 1 month after discharge compared to those children who did not exercise during hospitalization[7]. When compared to no training, 12 weeks of anaerobic training, 30-45 minutes per day, 2 days a week was shown to improve the physical functioning domain of the cystic fibrosis questionnaire revised (CFQ-R) in children with CF[8]. However, aerobic training appears to be more beneficial at improving quality of life in children with CF, compared with resistance training alone[9]. Interestingly, both video game training[10] 30-60 minutes per day, 5 days

per week for 6 weeks and yoga therapy[11], twice per week for 8 weeks can improve the respiratory domain of the CFQ-R in people with CF. Additionally, supervised exercise conditioning for 3 months was able to improve subjective health perception and the improvements were still maintained at the 2 year follow-up[12]. Consistent with this, 3 years of home exercise was able to maintain quality of life in patients with CF[13]. Perhaps most important, doing what you enjoy will help engagement and motivation. Adolescent patients reported activities that enhance fun and enjoyment and integrate physical activity into everyday life would be helpful to sustain participation [14].

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1.2 Health System Oriented Outcomes

With improving health outcomes and the prospects of further advances with genetic modifiers, people with cystic fibrosis (CF) will increasingly become subject to the same health concerns as in the general population. The World Health Organisation (WHO) reminds us that exercise has significant physical and psychological health benefits but reports that 80% of the world's population is not active enough[1]. There is a growing recognition that physical inactivity has a significant global economic impact. In the United States (US) alone, it was estimated that there were more than 500,000 premature deaths and health care costs in excess of $100 billion annually were caused by physical inactivity and obesity [2]. The RAND organisation estimated that increasing activity levels across the population could boost global GDP by up to $726 billion (US) dollars by 2050 [3].

To date, there is no evidence to suggest a causal relationship between physical activity and exercise with health system-oriented outcomes such as hospitalisations or antibiotic use in people with CF. Previous research in chronic respiratory disease, such as people with chronic obstructive pulmonary disease (COPD) undergoing pulmonary rehabilitation (including aerobic and strength training) has been shown to reduce subsequent hospital admissions, bed days and decrease health-care costs [4, 5].

Respiratory exacerbations requiring hospital admission continue to be one of the hallmarks of CF, and the annual prevalence of respiratory exacerbations increases with age [6]. Hospitalisations are the primary reason for healthcare costs in CF [7]. A three-year longitudinal study found a significant association between greater aerobic fitness and lower risk of hospitalisation in 77 children with mild-moderate CF [8]. Similarly, an observational study found that greater time spent in moderate-vigorous PA was related to less hospital time at 12 months

[9] and increased antibiotic treatment over three years was linked to a lower VO2 max which thereby may impact on hospitalisations [10].

It should be noted that there is limited reporting of respiratory exacerbations as an outcome measure in physical activity and exercise interventions in this cohort. Only one study in a Cochrane review of physical training interventions in CF reported on hospitalisations [11]. This study evaluated the effect of a three-year aerobic training program and found no significant difference between the mean number of hospital days or the mean number of hospitalisations at 1, 2 and 3-year follow ups [11, 12]. In contrast, a 1-year supervised, outpatient exercise intervention resulted in a significant reduction in the use of intravenous antibiotics when compared to the previous year and reported significant cost savings as a result [13]. Weekly supervised exercise sessions led to a 23% reduction in inpatient IV antibiotics, alongside a 20% reduction in home IV antibiotics with associated cost savings in 16 children with CF [14]. Future research should further evaluate the impact of exercise interventions on health system outcomes such exacerbations, hospitalisations, and antibiotic use.

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2 Health Benefits of Activity and Exercise

2.1 Lung Health

There have been several studies examining the relationship between exercise in lung health, primarily looking at lung function as a primary study outcome specifically forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). More recent inclusions in the examination of lung health is that of lung clearance index (LCI). While it is well recognised that exercise is beneficial, the strength of the evidence to support a statement of preservation of lung health is challenging.

A study examined the longitudinal relationship between physical activity and lung health in a large cohort of 212 children. There was a significant correlation between the rates of change of activity level and change in FEV_1 decline, indicating that an increasing activity is associated with a slower rate of decline ($p \leq 0.007$) and thus the possibility of affecting survival (1).

Three systematic reviews concluded unclear effects of exercise on FEV_1, due to a wide range of study design, heterogeneous exercise training modalities and duration of intervention. (2, 3, 4). Studies that evaluated the longer time effect of exercise concluded that exercise slows the decline in lung function. (5, 6, 7). In a study with a 2-year follow up, the control group demonstrated a greater mean annual rate in decline of percentage predicted FVC compared to exercise group ($p = 0.02$) with a similar trend for FEV_1 ($p = 0.07$) (5). Another study showed a better preserved FEV_1 at 1-year with exercise intervention, small improvements in FVC in the active group but significant decline in FVC in the inactive group (6). A retrospective study including 1038 twins or siblings with a minimum of 4 FEV_1 values taken over a period of no less than 2 years, showed that those reporting exercise had a high baseline $FEV_{1\%predicted}$ than those that did not ($p = 0.001$). Also, that exercising adults with CF would experience a smaller

decline in FEV_1 compared to exercising children, suggesting adults received more benefit. Finally, that subjects with a lower FEV_1 who perform any exercise may benefit disproportionately better than those with a better lung function in terms of FEV_1 decline (7).

Studies have evaluated the effect of different exercise interventions and dose response on lung function. (8, 9). A study looked at a single bout of maximal exercise displaying a significant increase in FVC ($p < 0.002$) and FEV_1 ($p < 0.002$). Pre- and post-LCI was examined, displaying a significant reduction ($p < 0.05$). This study suggested that higher intensity exercise may contribute to greater improvements in pulmonary function (8). A further study examined the potential difference between strength and aerobic training compared to controls. This RCT showed a significant increase in FEV_1 in both training groups when compared to controls ($p < 0.001$) but the effects had been lost by 18 months post exercise program (9).

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2.2 Cardiovascular Health

The increased life expectancy of people with cystic fibrosis (CF) increases the risk of age-associated pathology, such as cardiovascular diseases, which may be a primary of secondary consequence of CF (1). There is evidence of left ventricular dysfunction (2), increased arterial stiffness (3) and reduced large (4) and small (5) vessel function in people with CF. Therefore, it is important to examine whether physical activity (PA) and/or exercise can modify markers of cardiovascular health and associated risk factors.

A Cochrane review published in 2017 (6) identified 11 exercise training studies that examined body size and composition outcomes utilising either aerobic (n=5), anaerobic (n=3) or combined (n=3) exercise programmes in people with CF. The review found no consistent evidence for improvements in body mass, body mass index or body composition (fat free mass, body fat percentage). No other cardiovascular health outcomes were reported in the review. One study did measure blood pressure at baseline of a 3-year home-based aerobic exercise programme, but did not report the intervention effect (7). More recently, there are promising results showing resistance exercise may improve heart rate variability in children and adolescents with CF (8).

Data from observational studies suggests that habitual PA is positively associated with body mass percentile in children and adolescents with CF, especially in patients with mild to severe disease (9, 10). Furthermore, a recent study reported a positive association between accelerometer derived moderate to vigorous intensity PA and heart rate variability in 6-18 year olds with CF (11). Therefore, observational studies support a potential relationship between PA and a limited number of cardiovascular health outcomes in CF. However, these associations are not consistently reported (12), and are restricted to cross-sectional designs with a lack of

adjustment for key confounders (i.e. age, sex, disease severity, fitness, body size and composition).

Few studies have undertaken direct measures blood vessel outcomes in relation to either PA or exercise. Vascular endothelial function is related to markers of aerobic fitness in people with CF (4). As aerobic fitness and physical activity have been shown to be related in CF (13), this suggests a putative relationship between vascular outcomes and physical activity, but this has yet to be explored. Using an acute exercise model, adults with CF have been shown to increase blood flow during forearm exercise with no differences to healthy controls, suggesting a similar exercise hyperaemic response (14). There are also data to suggest adults with CF may experience a transient increase in central arterial stiffness in response to a bout aerobic cycling exercise (15). However, these observations have yet to be replicated and the effect of long-term physical activity and exercise interventions on heart function, arterial stiffness and large and small vessel function in CF are yet to be established.

Although there is tentative evidence that PA and exercise can improve cardiovascular health in people with CF, there is a need for well-controlled randomised controlled trials and observational studies incorporating cardiovascular health measures and associated risk factors.

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2.3 Musculoskeletal Health

Musculoskeletal alterations exist in people with CF and have various clinical consequences. People with CF have reductions in both limb muscle mass and strength, with lower limbs muscles being generally more affected (1-3), and these alterations are associated with reduced whole-body exercise performance (4-7). It is of note that recent improvements in treatment and management of CF have resulted in significant improvements in nutritional status, and caution is needed when extrapolating findings obtained over the past several decades to the current CF generation. However, recent reports still indicate a high prevalence of limb fat-free mass (FFM) depletion in young people with CF, which is associated with worse clinical outcomes(8), demonstrating the importance of developing exercise interventions that target reduced limb muscle mass and strength.

Most studies using aerobic training alone or combined with resistance training in people with CF did not find improvements in FFM (9-11). However, resistance training alone or combined with aerobic training was effective in improving limb muscle strength in several studies (9, 11, 12), highlighting that short-term changes in muscle strength are possible in the absence of muscle hypertrophy and are most likely related to neural factors. Obtaining positive changes in limb muscle mass may require longer training duration and/or individualized resistance training programs with appropriate volume and intensity tailored to an individual. For instance, an in-hospital supervised resistance training program resulted in improvements in both limb muscle mass and strength in children with CF whereas endurance training did not (13). People with CF who cannot engage in conventional exercise strategies (e.g., during severe exacerbation, pre- and post-transplant) may also benefit from adjunct approaches such a neuromuscular stimulation

(NMES). Six weeks of NMES performed prior to 8 weeks of aerobic training increased thigh circumference and quadriceps strength and decreased dyspnoea on 6MWT, compared to controls (i.e., same aerobic training without prior NMES) in adults with CF and severe lung disease (14).

Increased life expectancy for people with CF also presents new issues for chronic musculoskeletal diseases that present later in adult life, such as osteopenia and osteoporosis (15). Cross sectional studies suggest a beneficial effect of exercise and PA on CF bone health, as greater PA levels and aerobic capacity are associated with higher bone mineral density (16, 17). However, data regarding the impacts of an exercise training regimen on bone health in people with CF are very limited. A lone RCT involving one year of resistance training in children and adolescents with CF did not find significant changes on bone mineral density determined by dual energy X-ray absorptiometry (18). However, the exercise programme was unsupervised, and no measurements of muscle function were performed which casts doubt on whether a sufficient training stimulus was achieved.

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2.4 Fitness and Strength

Physical fitness has been shown to be an important predictor of health outcomes for people with cystic fibrosis (CF) [1]. Higher aerobic capacity has been associated with higher life expectance, increased quality of life and level of professional achievement [2]. The health benefits of activity and exercise on fitness in CF have been extensively researched. Numerous randomised control trials, involving interventions that varied in type of exercise, intensity of exercise, and duration of intervention have been conducted in in-patient outpatient and home settings, with varying levels of healthcare staff supervision[3–18]. Some of these studies were well powered [8,13] whilst others had significant follow up periods [7,14]. Overall, a Cochrane database systematic review concluded that there was some evidence that exercise is beneficial for aerobic fitness, and that no negative side effects of exercise exist for people with CF [19].

The effect of exercise on increasing and maintaining fitness has been quantified predominantly through the measurement of peak oxygen uptake ($\dot{V}O_{2peak}$) [3,5–10,13–16]. One well powered study [14], found that a six month, home based conditioning programme increased $\dot{V}O_{2peak}$ by 3.72 $mL \cdot kg^{-1} \cdot min^{-1}$ ± 1.23 $mL \cdot kg^{-1} \cdot min^{-1}$ ($p < 0.01$) in a sample of people with CF, aged between 12-40 years. These improvements were maintained more than a year after the intervention had ended, with authors suggesting the intervention encouraged participants to continue new exercise habits and therefore, maintain fitness too. Another study found 3 months of supervised anaerobic training intervals (i.e. HIIT) produced a statistically significant 5% increase in $\dot{V}O_{2peak}$ [16]. Shorter duration interventions have also been shown to be effective, with 8 weeks of supervised out-patient exercise sessions, delivered in hospital also reporting improvements in $\dot{V}O_{2peak}$ (increases of 3.9 $mL \cdot kg^{-1} \cdot min^{-1}$ $p = 0.002$) [6]. Whilst there is no published data on minimum clinically important difference in $\dot{V}O2peak$ in people with CF, it has been reported to be 1.54 $mL \cdot kg^{-1} \cdot min^{-1}$ in adults with chronic renal disease [20]. This indicates exercise

interventions in people with CF are like to result in noticeable increases in exercise capacity. Interestingly, these gains in $\dot{V}O_{2peak}$ were lost (-3.4 $mL \cdot kg^{-1} \cdot min^{-1}$, p = 0.001) following a 4-week detraining period, when participants were instructed not to exercise [6]. This illustrates the trainability of fitness in people with CF, despite ongoing disease processes. Of note, anaerobic training has been shown to produce some sustained benefits in anaerobic performance [16].

Limitations to the outcome measures used when measuring fitness in CF have been highlighted. One 3 year home-based intervention failed to report improvements in fitness, however it was suggested that this was due to high levels of participants fitness at baseline, limiting potential for improvement in $\dot{V}O_{2peak}$ [7]. Two studies identified possible limitations to measurement of the effect of an exercise intervention due to the 6MWT not being sensitive enough to detect change after treatment [9,18]. It is possible that these factors have led to the effect of exercise on fitness in people with CF to be underestimated across the evidence base.

The evidence shows that home-based exercise, designed around patient preference, not directly supervised by healthcare staff is effective in improving fitness, thereby reducing requirement to physically attend the CF centre [14,17]. However, it should be noted, that fitness and strength can also be increased with intervention during hospital admission for an infective exacerbation in patients with CF [9]. Engaging individuals in long term exercise routines regardless of setting is of key importance.

Higher intensity interventions gained better results, suggesting the presence of a dose response of exercise on fitness [3,10,11,13,16]. These included plyometric, weights-based programs, anaerobic interval training and use of a percentage of maximum effort, for example between

60-80% of $\dot{V}O_{2peak}$ or treadmill max velocity. Interventions [3,15] without intensity monitoring and progression, or insufficient frequency, did not see an improvement in aerobic fitness. Due to the heterogeneity of intensity and duration of interventions in the literature it is difficult to provide guidance on recommendations other than that increased dosage leads to increased results. Progression of intensity throughout an exercise

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2.5 Endocrine and Inflammatory Function

Several endocrine disorders are associated with cystic fibrosis (CF), including bone disease (see: Musculoskeletal health), male hypogonadism, delayed puberty and, most commonly, CF-related diabetes (CFRD)[1]. CFRD affects approximately a third of adults with CF[2,3] and is a distinct subtype that contains aspects of both type I and II diabetes mellitus, characterised by post-prandial hyperglycaemia due to insulin insufficiency[1,4,5]. Current treatment for CFRD is predominately insulin therapy[1,6], however CFTR modulators may reduce the need for insulin in individuals with CFRD[5]. In non-CF diabetes, exercise training interventions are recommended to improve glycaemic control[7,8].

While the onset of dysglycaemia is associated with a reduced exercise capacity in both paediatric and adult populations with CF[9,10], there is scarce evidence investigating the effects of exercise training interventions on glycaemic control, with one ongoing clinical trial (NCT03653949[11]). One study showed improved glycaemic control by oral glucose tolerance test, without a change in HbA1c, in 14 individuals with CF-related dysglycaemia following a 12-week combined aerobic and resistance training programme[12]. A recent multicentre trial involving 117 people with CF over the age of 12 reported no effect on glucose tolerance after a 12 week training programme involving 3 hours of intense physical activity per week[13]. The incidence of hypoglycaemia with exercise is reportedly low in CFRD[14] and precautions such as blood glucose monitoring, carbohydrate snacks or altered insulin doses with vigorous exercise are recommended[4,15]. In non-CF diabetes, a risk of hyperglycaemia has been reported following short periods of intense exercise[16,17], and while there is no evidence from CF populations, current guidelines recommend people with CFRD participate in moderate aerobic exercise[2,15].

The occurrence of hyperglycaemic events – in addition to respiratory, cardiovascular, metabolic and skeletomuscular diseases – result in chronic low-grade inflammation and systemic oxidative stress in people with CF[18,19]. While pharmacological interventions (e.g. CFTR modulators) relieve inflammation and oxidative stress by upregulating anti-inflammatory and -oxidant transcriptional factors at the cellular level[20], conflicting evidence in humans results in a requirement for adjuvant therapies[21]. One such intervention is exercise training, and the resultant improvements in physical fitness, which are associated with a reduction in inflammation and oxidative stress in healthy humans[22]; however, the evidence in people with CF is unclear.

Six-to-twelve weeks of aerobic and/or resistance training in children-to-adults with CF was not reported to modulate c-reactive protein[12,23,24]. Furthermore, c-reactive protein was either indifferent[25] or lower[26] in those who are considered physically active, compared to their sedentary counterparts. Six-to-eight weeks of exercise training was also not reported to modulate cytokine expression in the blood of children or adults with CF[12,23]. Preliminary evidence suggests that combined resistance and aerobic exercise training upregulates YKL-40 in adults with CF, which could be a signalling factor for enhanced muscle insulin sensitivity[12]. In contrast, a marker of bacterial infection-associated inflammation, procalcitonin, was downregulated by eight weeks of aerobic exercise training[23]. One observational study demonstrated that increased physical activity was associated with lower systemic inflammation (IL-6, IL-8 and TNF-α) post-CF exacerbation[27]. Neither antioxidants or oxidative stress were differentially modulated during moderate-to-heavy intensity cycling between adolescents with CF and their healthy counterparts[28]; however, no studies have investigated the effect of longer-term exercise training on redox biomarkers in people with CF. Therefore, it remains unclear

whether exercise is an effective intervention to reduce inflammation and oxidative stress in people with CF.

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2.6 Mental Health

Individuals with CF are at increased risk of depression with 10% of adolescents, 19% of adults, 37% of mothers and 31% of fathers reporting symptoms of depression [1]. In addition, 22% of adolescents, 32% of adults, 48% of mothers and 36% of fathers of patients with CF reported increased symptoms of anxiety [1]. There is growing evidence that engagement in physical activity can effectively reduce symptoms of depression and anxiety in the general population [2]. However, the role of physical activity in mental health among populations with CF is unclear.

Studies exploring the impact of physical activity on mental health among people with cystic fibrosis are clinically, methodologically, and statistically heterogeneous. The literature is variable in terms of study design, target population, and choice of outcome. Interventions are variable in terms of content, frequency, duration, and setting and intervention fidelity is rarely reported. Interventions may broadly be categorized as 1) prescribed exercise programs; 2) individually tailored programs; 3) dance; 4) mindfulness-based programs; and 5) active games. The is limited evidence for the effectiveness of prescribed exercise programs. One small randomised controlled trial of hospital based anaerobic exercise found no significant effect of intervention on emotional quality of life [3]. One small prospective study of low impact aerobic exercise [4] found no impact of intervention on wellbeing. However, a small (N=12) prospective study of aerobic and strength training combined with stretching and postural advice [5], a small (N=40) randomised trial of aerobic and strength training [6] and a small (N=14) controlled trial of resistance training [7] found a significant impact of intervention on emotional quality of life.

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Two small prospective studies provide some evidence for the effectiveness of a home-based individually tailored exercise programs on emotional quality of life [8, 9]. Paranjape found positive impact of individually tailored moderate to vigorous exercise on emotional quality of life [8]. Schmidt reported small improvements in emotional quality of life following participation in exercise as selected by participants [9].

One small quasi-experimental study provides some evidence for the effectiveness of dance / movement therapy during hospital stay [10]. The 24 participants in the intervention arm showed a small but significant improvement in mood as measured by the profile of mood states question in comparison to the 10 participants in the control arm.

Three small studies have explored the impact of mindfulness based activity. One small study found that 30 minutes of tai chi at home did not result in significant improvements in emotional quality of life [11]. Another small prospective study of 11 participants found no impact of 40 minuets of yoga on anxiety and depression as measured by the hospital anxiety and depression scale and the centre for Epidemiological Studies- Depression Scale for Children. There was however, a small impact of the intervention emotional wellbeing and anxiety as measured by the Speilberger State-Trait Anxiety Inventory for Children [12]. A small prospective study of 11 participants found a significant improvement in emotional quality of life following participating in 50 minutes of yoga [13].

Two cross sectional studies explored the impact of self-reported exercise on mental health [14, 15]. These studies suggest that self reported participation in physical exercise is associated with improved psychological well-being [14] and fatigue [15].

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2.7 Quality of Life

Health related quality of life (HRQoL) is a holistic concept of a person's perception of their life and is now recognised as a very important outcome measure in Cystic Fibrosis (CF) research. It has been defined as 'a multi-dimensional construct comprised of several domains as reported by the individual eg physical, social and psychological functioning, respiratory symptoms, treatment burden and body image' (1). Despite the fact that measurement of HRQoL is now increasingly being used to evaluate the effectiveness and perceived value of interventions (2), there is limited conclusive evidence as to the effects of activity and exercise on HRQoL in individuals with CF(3).

To date research investigating the impact of exercise and activity on HRQoL in individuals with CF has predominantly focussed on children (4-15) and adults (16-19) with mild to moderate disease severity. Only one study (15) included individuals with severe CF lung disease. Sample sizes in all studies are relatively small with a range of 14 (16) to 76 (12) participants. In addition a variety of outcome measures have been used with the Cystic Fibrosis questionnaire (CFQ) and the revised CFQ (CFQ-R) as the most frequently used measures with the paediatric QOL inventory (14), the SF-36 scale (18) and the quality of well-being scale also implemented (8). As a result comparison between studies is difficult. Two studies included HRQoL as a primary outcome (12, 19) with HRQoL measures in all other studies included as a secondary outcome. Few studies are therefore powered to detect significant changes in HRQoL as a result of an exercise or activity intervention. The interventions are also not focussed on interventions that may have an impact on HRQoL domains specifically. One study included exercise counselling, however this study did not report any significant change in HRQoL at the end of the study (14). Interventions were a mix of home and hospital based unsupervised and supervised exercise and activity programmes which all included tailored

aerobic and strength components. The duration of interventions also varied in length from 8 weeks to one year with the most common time period being 12 weeks.

Most studies show no improvement in HRQoL measures during the study intervention period (4, 6, 12, 16-18). Some studies have shown a non-significant impact on HRQoL but have reported a trend towards a positive change in some domains such as respiratory symptoms (10), subjective health perception (11) and physical functioning (13). Four studies (7-9, 19) have shown a statistically significant positive effect on a variety of HRQoL domains including well-being (8), treatment burden and emotional functioning (19), physical, emotional, social, body, treatment and respiratory symptoms (9) and overall HRQoL score (7). However these four studies all differ in duration and intervention type so specific reasons for improvements in HRQoL are difficult to ascertain.

In summary there is some weak evidence of impact of exercise and activity on some HRQoL domains in individuals with mild to moderate CF in the short term, however there is significant heterogeneity in the methodologies and results.

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3. Measurement of Physical Activity and Exercise

3.1 Physical Activity Measurement

Physical activity (PA) is particularly broad and complex to measure [1], with the recent holistic definition encompassing both movement *and* the context [2]. Subjective methods, such as questionnaires, diaries and log-books, are low-cost and feasible to implement and can provide an indication of the quantity *and* context of PA. However, self-report methods are susceptible to recall bias [3], low validity [4], low accuracy for measuring different intensities [5, 6], and are usually limited by factors such as age, the complexity of questions, and health status. As such, questionnaires have only been recommended as a secondary outcome measure in cystic fibrosis (CF) [7].

Device-based methods, such as pedometers and accelerometers, are capable of measuring movement or energy expended [1, 8, 9]. Pedometers, which measure vertical acceleration, are easy to use and low-cost, but are designed to measure activities such as walking and running and can only provide an indication of volume (i.e. number of steps), rather than PA intensities and patterns [10]. Alternatively, accelerometers, the most popular tool to measure PA in clinical populations, have been shown to assess PA intensities in a reliable manner [1, 8, 11-13]. Therefore, where possible, device-based assessment should be used for individuals with CF. Indeed, the most recent position statement recommended the ActiGraph accelerometer given its clinometric properties (reliability, validity, and responsiveness), but, in the absence of robust devices, the Habitual Activity Estimation Scale should be used [7, 14]. Nonetheless, the processing decisions surrounding accelerometry remain subjective, from selecting the sampling frequency [15], wear-time criteria [16] and type of data (i.e. raw vs. pre-processed) [17], to the translation of acceleration into PA patterns and intensities, such as moderate-to-vigorous physical activity [MVPA; 16, 17]. Whilst traditional methods such as cut-points and

prediction equations have been used to assess PA levels and energy expenditure in the CF population [18-20], highly accurate machine learning approaches are now being utilised in clinical populations [21-23]. The use of machine learning is facilitated by the availability of open-source algorithms that can be tailored for specific populations [24].

It is pertinent to note that prediction equations, cut-points, and machine learning models are population-specific and can lead to inaccuracies in PA intensities and energy expenditure when applied to a different population [25, 26]. This is particularly important given the higher energetic demands characteristic of those with CF [27-29], though the long-term effects of recent advances in moderators may render this largely redundant. It is therefore imperative that accelerometry data-processing techniques are developed from CF populations. Indeed, the CF-specific prediction equations [26], cut-points [30] and machine learning models [31] developed for children were considerably different to ones developed for the general population, which may explain findings which reported that those with CF spent less time in MVPA and more in light PA than their peers [19, 20]. Nonetheless, such work remains in its infancy. The development of CF-specific measurements of PA is fundamental to enhance our understanding of the relationship between PA and health, and subsequently inform interventions and recommendations in this population.

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3.2 Measurement of Exercise

Annual review exercise testing is recommended for those with Cystic Fibrosis (CF). Indeed, given the recent advances in modulator therapies and associated health and wellbeing of those with CF, exercise testing has arguably never been so important. The improvements in overall health do, however, have implications regarding exercise test selection, with more demanding tests now potentially feasible, and advocated, in a wider range of people.

Aligned with the predominant clinical focus, the assessment of aerobic fitness is considered here. However, the merits of, and need for, more holistic assessments of exercise capacity, including strength and anaerobic fitness, are increasingly recognised [1]. Indeed, there are numerous options for the measurement of exercise capacity in those with CF; the selection of which is most appropriate is dependent on i) participant-level factors, e.g. age, disease severity/progression and the presence of comorbidities; ii) centre-level factors, e.g. availability of exercise equipment, cost and space; and iii) the purpose of conducting the test, e.g. as a general assessment of exercise capacity or seeking to identify a specific cause(s) of exercise intolerance [1].

The "gold-standard" and internationally recommended method of assessment of cardiorespiratory fitness is a cardiopulmonary exercise test (CPET) to volitional exhaustion to determine peak oxygen uptake [2, 3]. CPETs offer insights into the integrated cardiovascular, respiratory and metabolic determinants of exercise (dys)function [4] and are perceived as highly beneficial by patients for their diagnostic assessment [3]. In situations where it is unclear whether a maximal effort was provided, a supra-maximal validation bout is recommended and has been reported to be safe and well-tolerated [5]. Whilst peak oxygen uptake is associated with prognosis [6], it may lack sensitivity or specificity to reflect changes in disease

progression or intervention effectiveness, especially in more well people. In recognition of this limitation, submaximal responses are increasingly being considered. For example, the oxygen uptake efficiency slope has been reported to be reliable, easily determined in comparison to parameters such as the gas exchange threshold and effort-independent [7]. Furthermore, the coordination of the dynamic responses of the cardiovascular, pulmonary and metabolic systems to the onset of constant work rate exercise has been suggested to provide a sensitive indication regarding the mechanism(s) of exercise intolerance [8] and warrants further attention.

Alternative, or complementary, exercise tests to the CPET for which appropriate evidence is available regarding their validity, reliability and clinimetric properties include the modified shuttle test, six minute walk test, three minute step test, modified step test and one minute sit-to-stand test [1]. These field-based tests are less expensive and more portable but due to their volitational and often submaximal nature (especially in more well people) and less precise outcomes, they provide less insight to the underlying cause(s) for exercise intolerance [4]. Nonetheless, given limitations regarding the availability of specialist laboratory facilities, equipment and staff to undertake CPETs, field-based tests may provide useful indications of functional ability. No single test is suitable for all clinical needs; the most appropriate test must be determined in terms of quality, utility, and psychometric properties [9].

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4. Prescription of Physical Activity and Exercise

4.1 Training Modes and Styles

The *optimal* mode of exercise training for people with CF largely depends on the goals of the patient and should be individually prescribed and varied in order to maximize long-term participation. As discussed previously, there is conflicting evidence from RCTs that regular continuous aerobic exercise training undertaken at a moderate intensity, and strength training can elicit improvements in lung function (FEV_1) in adolescents and adults with CF (1), and stronger evidence that aerobic training elicits improvements in markers of exercise capacity. Strength training alone is unlikely to be sufficient to produce improvements in exercise capacity, particularly in trained adults and children (2). The benefits of exercise have also been discussed previously, but perhaps the most noteworthy reason is to improve maximal exercise capacity, due to associations between this measure and mortality in people with CF (3).

Numerous RCTs have investigated modes of aerobic exercise of ~30 to 60 minutes of walking, running, cycling or mixed exercise at a moderate intensity or higher (i.e., 50% of VO_{2peak} or 60 to 85% of peak heart rate) (4). Habitual physical activity, including light intensity exercise, is unlikely to produce sufficient benefits in exercise capacity (5), though further investigation of the benefits of light intensity exercise in people with CF may be warranted.

Preliminary data supports the tolerability, feasibility, and initial effectiveness of interval-based training (6–9). This mode may be optimal compared to continuous moderate intensity aerobic exercise in circumstances where a person is unable to sustain continuous exercise for a sufficient length of time to elicit physiological adaptions in skeletal muscle (i.e., severe respiratory disease) (7). In addition to the benefits on symptoms (alleviation of dyspnoea and muscle fatigue during the ‘rest’ phases), high intensity interval training (HIIT) may reduce the

total exercise time, as people are able to achieve a higher total work intensity than they may possible during continuous exercise training (8). An early case study prescribed a training frequency of thrice weekly for 6 weeks in a young female with CF. Sessions consisted of 10 to 20 intervals involving 30 seconds of 'work' (50 to 90% maximal exercise capacity) interspersed with 60 seconds of active 'rest' (25%). Two small RCTs published in 2020 investigated the effects of HIIT in adults; one involved 45 minutes of biweekly interval-based training (with or without supplemental oxygen) for 8 weeks (70% of W_{peak} interspersed with 60 seconds of recovery at 35%)(9); another investigated 8 weeks of low-volume HIIT comprising 3 sessions per week and 10 minutes per session (30-seconds of 'work' [symptom limited] interspersed with 30-seconds of active 'rest'; 2-minute warm-up and cool-down) compared to no exercise (8). Others have compared the effects of HIIT to continuous exercise in people with moderate to severe disease, and found comparable effects on markers of exercise capacity (i.e. W_{peak}) (7). Supervised interval-based training may be considered in the inpatient (7), outpatient (10) and community-based setting (6).

Comprehensive routines may also include plyometric, load bearing exercises to optimize bone mineral density and flexibility exercise (11,12).

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4.2 Adherence

Habitual physical activity across the lifespan is important for everyone for optimal health and well-being. A key finding from the evidence is the generally low uptake of physical activity among children and young people, which is also reflected among those living with cystic fibrosis [1,2]. Most adults with CF have been shown to achieve recommended daily physical activity levels during clinical trials, but longer-term adherence is unknown [3].

Education about the benefits of exercise may be important in promoting adherence to regular exercise across the lifespan in CF [4,5]. Regular exercise of moderate intensity and duration has been shown to exert anti-inflammatory effects and immune cell activation associated with reduced disease incidence and viral infection susceptibility in CF [6]. Education presented in an engaging form describing different intensities of exercise and heart rate targets for age can create a collaborative way of developing a personalised exercise program for adults with CF [7, 8].

Part of the process of encouraging patients with CF to engage in regular exercise is assisting them in identifying their barriers and enablers to activity participation [9]. Activity diaries and modern exercise tracking devices such as pedometers, Smart phones and wrist devices measuring step counts, distance walked or run may be useful in terms of assessing and tracking exercise levels and may act as enablers to regular exercise programs [10,11].

To promote adherence to regular exercise a personalised approach using motivational interviewing that involves enhancing a patient's motivation to overcome barriers and engage in positive change may be useful. This includes understanding the patient with CF's own motivations, interests and preferences; listening with empathy and empowering the person. Within MI the therapist is viewed as a facilitator rather than an expert, who adopts a

nonconfrontational approach to guide the patient towards change. The overall spirit of MI has been described as collaborative, evocative and honouring of patient autonomy [12, 13].

Within the context of living with cystic fibrosis poverty of time is one of the most commonly reported barriers to habitual exercise [14, 15]. Opportunities to combine physical activity perceived to be enjoyable with other valued activities – removing the need to choose between one or the other. For example, doing something active with friends or family, or making friends in a team sport or exercise class or use of active digital technology may enable more regular exercise[16].

Building healthy habits by introducing a regular routine of physical activity, may reduce the need for relying on motivation as the behaviour becomes more habitual and automatic. Habit formation requires consistent repetition of an action in the same context. To make a new healthy activity habit may take some planning in advance. Over time this requires much less effort than actively needing to motivate oneself to do something [17].

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4.3 Staffing in Clinical Practice

Physical activity (PA) and exercise are integral to the overall management of individuals with CF, as such it is recommended that CF services should include the assessment of exercise capacity, the prescription and monitoring of exercise programmes, PA education, support and promotion in both in-patient and out-patients settings, irrespective of age and disease severity [1][2][3]. The responsibility for delivering such services is typically incorporated into CF physiotherapy services [1][4].

There are currently no guidelines for the staffing or training requirements for the provision of exercise in CF care. The gold standard exercise testing recommended annually for individuals with CF is CPET. It is recommended that two members of staff are present, with appropriate training and experience to perform the test, recognise adverse events, respond to emergencies and be aware of CF specific infection control guidelines [5].

Physiotherapy training does not currently include conducting or interpretating CPETs or the subsequent prescription of exercise. This highlights a requirement for CPD opportunities for physiotherapists in this area and/or the potential role of clinical exercise physiologists (or equivilant allied health professionals (AHP) in CF care. In those areas where CPET is not available, the delivery of alternative exercise testing should be encouraged and the prescription and monitoring of exercise programmes could be undertaken by appropriately trained and experienced healthcare professionals.

It has recently been demonstrated that the incorporation of an AHP capable of completing clinical tasks relating to exercise testing and prescription within a CF physiotherapy service

can positively impact physiotherapist's scope of practice, allowing more time for complex clinical care, management duties and research activity [6].

There is an increasing presence of exercise professionals working in healthcare and although training, roles, responsibilities and titles vary internationally there are now accreditation programmes available for clinical exercise physiologists in the United States [7], Canada [8] and Australia [9]. Clinical exercise physiologists are defined as "allied health professionals" specialising in the delivery of scientific exercise interventions for people with acute, subacute, or chronic medical conditions across a wide spectrum of health, including but not limited to cardiovascular, respiratory, endocrine, musculoskeletal, mental and neurological disease" [10]. Whilst there are examples of accredited clinical exercise physiologists working as independent practitioners with clinical populations there are few examples of this in CF care. Similar accreditation programmes are not yet available in the United Kingdom or Europe although there are examples of exercise professionals working as physiotherapy assistants or in similar roles [11]. The educational, training and experience requirements for clinical exercise physiologists working in CF are not yet standardised. Similarly, the roles, responsibilities and competency requirements remain largely undefined. Such roles will likely require a degree level qualification in sports and exercise sciences or a related field and where possible accreditation and registration with an appropriate body upholding standards of care.

Based on the current UK and Australian recommendations for physiotherapy staffing requirements in CF services (2 Physiotherapists per 50-75 pwCF) [4,12] it is feasible that a full-time (1.0 whole-time equivalent [WTE]) AHP such as an appropriately trained and experienced 'Clinical Exercise Physiologist' could provide exercise services for cohorts of ~150 patients. It should be noted that these staffing ratios may not be appropriate for all CF

clinical areas and more staff may well be required.There may be scope for individuals in lower salary grades, such as exercise professionals without an undergraduate degree (e.g. ‘exercise technician’, akin to a ‘support worker’) to assist a full-time AHP in larger centres (~250 patients), and it is likely that additional exercise support (0.5 WTE) is necessary for every increase of 75 patients thereafter in centres with more than 250 patients. In smaller centres (~75 patients) the provision of exercise could feasibly be delivered by an exercise professional on a 0.5.WTE contract or by an appropriately trained and experienced physiotherapist.

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4.4 Telehealth

Telehealth is the delivery of care via any electronic means when the patient and healthcare professional are separated by distance. This encompasses multiple modalities, including telephone and video-calls, emails, and text messaging, to support diagnoses, monitoring and therapeutic interventions [1]. To date, use of telehealth has been limited in CF, for example, it has been utilised for remote consultations [2], monitoring for detection of exacerbations [3] and preparation for transplantation [4]. The application of telehealth in CF has been systematically reviewed once [5], although heterogeneity in the interventions implemented and outcomes used currently make it difficult to identify the true efficacy of telehealth within CF management.

In relation to exercise testing, videoconferencing has been utilised to remotely monitor 3-minute step tests, finding no difference in outcomes when compared to tests completed in person [6]. In relation to exercise training, video-calling has been utilised to engage children [7] and adults [8,9] in instructor-led training, either through their own clinical team [8] or third-party providers [9]. Moreover, telehealth has been utilised to engage adults with CF in physical activity via a novel website [10]. These studies have, for the most part, been single-group feasibility studies with relatively small numbers of participants ($n \leq 10$) and therefore differences in physical function, fitness, physical activity, and quality of life are either not reported using conventional statistics [7,8], or show no statistically significant differences [10]. The one trial to compare a home-based video-based programme versus an outpatient, hospital-based, pulmonary rehabilitation programme showed no differences in post-trial outcomes between groups, although a small sample size, high withdrawal and heterogeneity in function due to severe disease status makes true effects difficult to establish [9]. Finally, use of video-

calling to deliver exercise sessions has also been reported, but not peer-reviewed [11–14], and therefore findings cannot be confidently utilised.

Whilst these studies have yet to establish a significant benefit to telehealth, encouragingly these studies reveal high acceptance of, and desirability for, telehealth [7,8,10] as well as increased adherence relative to hospital-based regimens (albeit only reported in a singular study [9]). Only a small number of adverse events have been reported, albeit in a group of people with severe lung disease who were listed for transplant [9]. This therefore indicates remote delivery of exercise is indeed feasible and worthy of further consideration. Moreover, initial evidence suggest there may be economic benefits to using virtual exercise classes over face-to-face exercise support in the community, although such data has not been peer-reviewed as yet [13]. Currently, randomised control trials are ongoing to investigate the impact of remote physical activity promotion [15], physiotherapy consultations [16] and activity monitoring [17] upon parameters of fitness and activity, although results have yet to be reported.

Finally, it should be noted that the role of telehealth has been predominantly investigated prior to the global COVID-19 pandemic, and this public health crisis has brought about rapid change in overall acceptability and use of telehealth platforms, in particular the use of video-calling platforms. Initial surveying of clinical teams in the UK suggests that use of telehealth to deliver exercise training will continue as part of standard practice following the pandemic [18]. Therefore, how this modality of healthcare delivery will be adapted and implemented in the future is worthy of consideration by clinical teams. However, long-term viability and acceptability of telehealth is unclear, particularly with the notion of ‘virtual meeting fatigue’ [19], likely induced by rapid and high-volume implementation, induced by the COVID-19 pandemic, and therefore studies should assess how to ensure this promising tool remains viable

for the future. Therefore, this modality is likely to be a complement, rather than a replacement, to continued face-to-face contact with clinical teams.

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5. Clinical Considerations for Activity and Exercise

5.1 Exercise for airway clearance

Daily performance of airway clearance techniques (ACTs), such as the active cycle of breathing techniques, autogenic drainage and the use of positive expiratory pressure devices, are one of the cornerstones in the management of CF lung disease [1]. There is widespread agreement among people with CF and healthcare professionals that exercise may also improve airway clearance [2] and many people with CF already substitute traditional ACTs with exercise [3]. Whether or not exercise is a satisfactory substitute for traditional ACTs in people with CF has been identified as a top 10 research priority, as deemed by people with CF and healthcare professionals [4]. Adults with CF spend on average nearly one hour per day on ACTs and exercise regimens [5]. If exercise could adequately replace traditional ACTs for people with CF, it may also reduce treatment burden, another of the top 10 research priorities [4].

A recent systematic review, which included 12 studies of 187 children and adults with CF, investigated the effects of moderate intensity exercise for airway clearance compared to no intervention and compared to traditional ACTs [6]. Most studies were conducted when participants were clinically stable, however results were pooled with studies during hospital admissions for exacerbations of lung disease. All except one study were randomised cross-over trials with small sample sizes ($n \leq 32$) and short duration (ranging from a single-session up to two weeks), so there were no data for longer term outcomes, such as exacerbation frequency and quality of life. Due to significant heterogeneity of the exercise and ACTs, however, meta-analyses were limited. Exercise compared to no intervention resulted in positive trends or statistically significant improvements in mucus clearance and expectorated sputum weight [7-9]. When exercise was compared to traditional ACTs, there were distinct differences in efficacy

if the exercise did or did not include a forced expiratory manoeuvre, such as huff or cough. All studies that did not include huff or cough reported significantly less mucus clearance or expectorated sputum weight compared to the traditional ACTs [8, 10-12]. Whereas all studies that did include huff or cough reported no significant difference in mucus clearance or expectorated sputum weight compared to the traditional ACTs [13-17]. This difference may exist because exercise without huff or cough does not create the 10% expiratory airflow bias (i.e. PEF:PIF>1.10)[6] thought to promote cephalad mucus movement[18]. It is likely, however, that some of the studies were underpowered, so the review cannot exclude small differences between exercise and traditional ACTs that may not have been detected. Comparisons were not made according to exercise intensity, type of exercise, clinical stability or severity of lung disease.

The clinical implications are to recommend including huff or cough with exercise if intending to improve airway clearance and that it is possible a single session of exercise (with huff or cough) may have similar effects as traditional ACTs. There is no evidence, however, to answer the question whether or not exercise can act as a substitute for traditional ACTs in the medium or long term, as none of the included studies had a duration of more than two weeks. That highly relevant clinical question will only be answered with a long-term randomised controlled non-inferiority trial comparing exercise to traditional ACTs with meaningful outcomes, such as exacerbation frequency and quality of life. There is interest and good will to investigate this topic, as a recent survey reported 48% of people with CF skip their ACTs if they have exercised and 73% of healthcare professionals would support a trial of this design [2].

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5.2 Modulators

Cystic fibrosis transmembrane regulator (CFTR) modulator therapies target the basic biochemical defect (defective CFTR protein) in CF. Treatments work by correcting CFTR (e.g., Lumacaftor, Tezacaftor, Elexacaftor, VX-121 - Vertex Pharmaceuticals) or potentiating CFTR effects (e.g. Ivacaftor) by allowing CFTR-dependent chloride channels to remain open for longer and enhance chloride transport.

Ivacaftor (Kalydeco®) is a CFTR potentiator which increases 'open probability' for the CFTR-dependent chloride channel at the cell surface [1]. Kalydeco® has been shown to increase FEV_1 by > 10% in people with CF (pwCF) with at least one copy of the G551D mutation [2, 3], with similar lung function benefits for other gating mutations [4]. Case reports suggest Kalydeco® positively impact exercise capacity [5, 6], whilst a randomised, double-blind, placebo-controlled, cross-over study (n=20) demonstrated improved exercise duration.[7] In contrast, a phase IV placebo-controlled trial (n=70) of Lumacaftor in combination with Ivacaftor (Orkambi®) reported no exercise outcome differences [8].

Elexacaftor, Tezacaftor and Ivacaftor in combination (Trikafta® [North America], Kaftrio® [Rest of World]) is associated with 10-14% FEV_1 increases, with concomitant improvements in weight and quality of life [9,10]; however to date there is no published evidence showing the effects on exercise capacity or physical activity levels. It is anticipated that the greater stability offered by Kaftrio® will improve life expectancy and reduce treatment burden such that withdrawal trials of some existing treatments (e.g. nebulised mucolytics [CF-STORM]) are about to begin. Given that CFTR is expressed in many tissues including muscle and bone, benefits during exercise may be expected and pwCF taking Kaftrio® may be more 'trainable'. A further exercise consideration is that weight gain is reported with all CFTR modulator

therapies, and whilst a beneficial effect for many pwCF, if excessive, may be problematic. The promotion of exercise for a healthy lifestyle in pwCF is, thus as important as ever.

There is, therefore, a unique opportunity to understand the 'before' and 'after' of exercise physiology (and also exercise behaviours – does being 'more trainable' equate to 'more training') for pwCF with regard to modulator therapies. Careful consideration needs to be given to the best measurements for such studies (CPET, physical activity monitoring, tests of muscle function), as well as avoiding pitfalls encountered by others e.g. ensuring standardisation of equipment, correcting measures for lean body mass to eliminate weight gain as a confounder, and taking into account the effects of baseline fitness [8]. An attempt should be made to ensure that similar, individualised exercise counselling is given to participants in such studies – standardising their 'trainability'.

As increasing numbers of pwCF are treated with modulator therapies, we suggest that a standardised, combined approach to collecting clinical data including that from exercise testing within CF registries may represent an important next step in advancing our understanding of how the pathophysiology of CF and new treatments *truly* impact physical function. Furthermore, the study of exercise behaviours will also be invaluable in understanding how health improvements in CF impact time and intensity of physical activity undertaken.

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5.3 Risks of Physical Activity and Exercise

Evidence-based guidelines for physical activity and exercise prescription for people with CF have been published [1] and risks for participating in physical activity and exercise have been described [2] [3]. Reports of serious adverse reactions (SARs) related to exercise in patients with CF have ranged from none [4], [5], [6], [7], to an incidence of less than 1% [8], [9]. SARs of pneumothorax and haemoptysis are associated with risk factors of older age, poor pulmonary function and infections and may occur with exercise [10]. Of note, breath hold during weight training should be avoided. More commonly, mild adverse reactions have been documented during exercise and include muscle fatigue, productive cough, wheezing, shortness of breath and headache [10]–[12] and muscle stiffness [13], as might be expected with exercise.

The risk of developing exercise induced hypoxemia (EIH), where SpO_2 falls below 90%, is higher in patients with CF than in than healthy individuals [8], [14] and is correlated with increased disease severity in CF [15], [16], [17]. As disease progresses, people with CF may require supplementary oxygen to ensure saturation levels are maintained > 90% during exercise [10], [14]. The risk of hypoglycaemia exists for patients with CF-related diabetes mellitus (CFRD) [10]. For these patients, care should be taken to regularly monitor blood sugar levels and develop a pre, during and post-exercise nutrition plan to ensure their levels remain within the acceptable range.

It is well recognized that people with CF are at an increased risk of sodium deficiency due to increased sweat production and altered sweat composition [18], which may increase the risk of dehydration and hyponatraemia, particularly during prolonged exercise and/or in warm or hot conditions. Sports drinks may be an appropriate recommendation for people with CF for before, during and after exercise, especially in hot conditions or for longer durations.

There are certain activities that present specific risks for patients with CF, such as exercise at high altitude which may increase the risk of desaturation and right heart failure [19], [20] and scuba diving which may increase the risk of pneumothorax [19]. Furthermore, contact sports should be avoided in patients with advanced lung disease, liver disease, low bone density or a portacath [21]. Finally, cross contamination among patients with CF must be considered in any exercise plan.

While the advantages of physical activity and exercise for most patients with CF far outweigh the risks, there are contraindications which need to be highlighted for patients and their families, especially once disease severity is increased. Since adverse reactions to exercise may occur, individual counselling based on medical history, physical examination and further assessments, including exercise testing, are of high importance [10]. Measures can be then taken to mitigate risks for patients with CF that can ensure that exercise and physical activity remain accessible.

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5.4 Nutrition and Hydration

Maintaining an active lifestyle in Cystic Fibrosis is crucial for all patients (1) in order to optimise quality of life and best prognosis (2). Since CF patients are susceptible to electrolyte dysregulation and dehydration which are potentially exacerbated during intense physical activity, a series of concerns should be addressed to accomplish the best exercise results.

Nutrition in Cystic Fibrosis also plays a vital role in the health of patients. High energy, high fat intake diet along with pancreatic replacement therapy (PERT) -if pancreatic inefficiency is present- remains the cornerstone of adequate CF care (3). As CF individuals have been found to present less energy cost of daily activities (ECA) (4) and also tend to show decreased exercise capacity if undernourished (5), a nutritional program oriented in providing the energy required is essential. In this direction, all CF patients should be educated about their nutritional status and caloric needs to achieve maximal adherence (6). A high-calorie, high-fat, well-balanced meal two to three hours before rigorous activity should be encouraged, along with a small carbohydrate snack about sixty minutes before exercise. At least two hours after physical activity, a full meal rich in carbohydrates should be acquired to replenish energy balance, while at all times, proper adherence to PERT should always be kept in mind (7). Every exercise/diet plan should be discussed with the physician and dietician to meet the CF individual's BMI targets, caloric goals, and diet preferences.

Individuals with CF-related diabetes (CFRD) should also be encouraged to adopt a daily physical activity program to improve their exercise capacity and lung function(8, 9). It is advised that all CFRD individuals should obtain blood glucose measurements before and after exercise to avoid post-exercise hypoglycaemia (10, 11). Possible nutritional strategies to avoid exercise-induced hypoglycaemia are considered a pre -exercise snack, proper insulin

adjustment for the meals pre/post exercise along with the addition of a snack before bedtime. However, every nutritional strategy in the CFRD patients should be individualized to meet the patient's glycaemic goals (12).

Avoidance of electrolyte dysregulation during exercise and maintaining proper hydration poses a challenge for CF individuals. All patients should commence exercise fully hydrated. If physical activity is of low intensity and lasts less than 30 minutes, adequate water intake would be enough for replacing the fluid loss. However, for higher intensity, longer-lasting physical activities (requiring heart rates>120-140bpm for more than 30 minutes), or when performing under excess heat conditions, additional salt supplementation should be encouraged (13). Isotonic drinks are well absorbed and can be used to replace water (14, 15). CF individuals should always be cautious for early signs of dehydration during physical activity (sore mouth, dizziness, headaches).

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