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Original Article

Standards for the care of people with cystic fibrosis; establishing and maintaining health

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ABSTRACT

This is the second in a series of four papers updating the European Cystic Fibrosis Society (ECFS) standards for the care of people with CF. This paper focuses on establishing and maintaining health. The guidance is produced using an evidence-based framework and with wide stakeholder engagement, including people from the CF community. Authors provided a narrative description of their topic and statements, which were more directive. These statements were reviewed by a Delphi exercise, achieving good levels of agreement from a wide group for all statements.

This guidance reinforces the importance of a multi-disciplinary CF team, but also describes developing models of care including virtual consultations. The framework for health is reinforced, including the need for a physically active lifestyle and the strict avoidance of all recreational inhalations, including e-cigarettes. Progress with cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy is reviewed, including emerging adverse events and advice for dose reduction and interruption.

This paper contains guidance that is pertinent to all people with CF regardless of age and eligibility for and access to modulator therapy.

Abbreviations

ACT	Airway clearance techniques
BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CPET	Cardiopulmonary exercise testing
CRS	Chronic rhinosinusitis
ECFS	European Cystic Fibrosis Society
ETI	Elexacaftor-tezacaftor-ivacaftor
ETS	Environmental tobacco smoke
NBS	Newborn bloodspot screening
PERT	Pancreatic enzyme replacement therapy
PEx	Pulmonary exacerbation(s)
PhySIIG	Physiotherapy Special International Interest Group
RCT	Randomised controlled trial
VST	Variant-specific therapy

1. Introduction

This is the second of a series of four papers updating standards for the care of people with cystic fibrosis (CF), coordinated by the European Cystic Fibrosis Society (ECFS). These papers have been produced by academic and medical experts in the field of CF in collaboration with people with CF and the CF community. A previous editorial describes the structure, contents and new developments of this 4-paper series [1]. This paper, "Establishing and maintaining health", illustrates the changes in CF care, based on significant developments over the past two decades.

The first paper in the series "A timely and accurate diagnosis" outlines the key development of newborn bloodspot screening (NBS) [2], which has now expanded to most countries in which CF has a significant incidence. Regions with long established NBS programmes are now witnessing the benefits of early diagnosis.

NBS facilitates early treatment to address the pathophysiological consequences of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, allowing people with CF to achieve excellent nutritional status, to keep their airways free of chronic infection, and to establish a healthy and active lifestyle. These "basic" principles underpinning CF care have resulted in a steady improvement in outlook and wellbeing for people with CF.

Over the past decade a further development has emerged that directly addresses the underlying CF molecular defect. CFTR modulator therapy, to date the only variant-specific therapy (VST) available, has transformed the clinical outcomes for people with CF who are eligible and have access to these therapies [3].

The guidance in this paper reflects the changing CF landscape. Unless otherwise specified, the ethos and principles of care described relates to all people with CF, regardless of age or treatment with CFTR modulator therapy. Where appropriate, guidance may also apply to the parents or caregivers of children and young adults with CF. We support shared decision making with all people with CF and their families.

People with CF and healthcare professionals need to be aware of the changing environment in which they live and work. It is important to have an open mind to innovative approaches, but also to ensure that care continues to be based on the best available evidence and that quality of care is maintained.

The first three sections of this paper cover the essential components of establishing good health: achieving excellent nutrition, maintaining airway health and engaging with exercise. We then reflect on models of care, building on previous ECFS guidance, and consider the potential for remote care. Finally, we describe issues around managing medicines, including developments in the field of VST.

We previously described the methodology used to construct and gain consensus on this update and expansion of the ECFS Standards of Care

[2]. Briefly, a multidisciplinary core committee created the framework, invited authors and reviewed author contributions and statements. The statements underwent a Delphi consultation, with a threshold of ≥80 % indicating consensus. The core committee reviewed all comments, and adjusted statements if necessary (Table 1). Delphi consultation participants are listed in Supplementary Table 1, and Delphi results are presented in Supplementary Table 2.

Table 1
Statements.

#	Statement
1	Whenever breast feeding is possible, it should be encouraged and supported for infants with CF.
2	Infants with CF presenting with meconium ileus are at risk of both short and long-term nutritional deficits and require early support from the CF team.
3	Support from a specialist CF dietitian is essential.
4	The CF team should encourage healthy feeding behaviours early in life to promote a good relationship with food and a positive body image.
5	Pancreatic enzyme replacement therapy should be initiated if there is clinical evidence of pancreatic insufficiency.
6	Nutritional status should be monitored at each clinic visit.
7	For people on CFTR modulator therapy, special consideration should be given to the need for salt and vitamin supplementation.
8	Physiotherapy advice for airway clearance, including physical activity and exercise, should begin at diagnosis.
9	Physiotherapy for airway clearance should be individualised and provide a framework for people with CF to self-manage.
10	Adolescents should be supported to take increasing responsibility for airway clearance techniques, in preparation for independent adult life.
11	The CF team should regularly evaluate people with CF for rhino-sinus disease.
12	People with CF should avoid tobacco smoke (direct and environmental).
13	People with CF should avoid e-cigarette use (vaping).
14	Regular standardised exercise testing (as per the guidance of the ECFS Exercise Working Group and PhySIIG) should guide the advice and support given by the CF team.
15	CF teams should support people with cystic fibrosis to be physically active and exercise regularly.
16	Access to a multidisciplinary team with CF expertise and to closely associated specialties remains a key requirement for all people with CF.
17	The CF centre should adapt to reflect the improved life expectancy of people with CF.
18	People with CF should be educated by the CF multidisciplinary team and supported (including with telehealth) to help them best manage their health.
19	Remote care provides an opportunity for monitoring and interventions without hospital visits, but further research is needed to determine optimal strategies.
20	Virtual clinics and homecare offer an alternative to traditional structures but should not replace all face-to-face clinic reviews.
21	As new therapies emerge, the role of the CF pharmacist is increasingly important to optimise drug delivery and management.
22	A variety of approaches are available to monitor adherence to therapies and these should be used in an open manner to support people with CF and their families.
23	CF teams should work in partnership with people with CF and parent/caregivers to support adherence to therapies.
24	Starting and stopping therapies should be guided by the best evidence available and decided in partnership with the person with CF.
25	People with CF with eligible *CFTR* gene variants should be offered CFTR modulator therapy.
26	For young children and infants, certain CFTR modulator therapies may not yet be licensed, and options should be considered on an individual basis.
27	When initiating CFTR modulator therapy, people with CF and families should be encouraged to promptly report any significant physical or mental health changes to the CF team.
28	All adverse events experienced on CFTR modulator therapy should be reported to a post market surveillance scheme and the pharmaceutical company.

Abbreviations: CF=cystic fibrosis, CFTR=cystic fibrosis transmembrane conductance regulator, PhySIIG=Physiotherapy Special International Interest Group.

2. Eating well

2.1. Infant feeding

Chris Smith, Dimitri Declercq

Infant nutritional status has continued to improve in recent decades, largely thanks to early introduction of nutritional support made possible through NBS [4–7]. US registry data show that median weight for length of infants is above the recommended 50th percentile in the first two years of life, however median length remains below expected [8,9]. Close monitoring, as per previous guidelines, is associated with improved growth outcomes. Optimal early growth impacts long-term outcomes, including respiratory function [10–15].

Breast milk is the best nutrition for all infants, including those with CF (Statement 1) [5,16,17]. Breast feeding rates vary but are reported as being lower than in infants without CF [16]. The CF team should encourage and support breast feeding, and where available locally, seek specialist support such as a breastfeeding counsellor early in the diagnosis [13,18].

Close support and regular follow-up by a CF specialist dietitian are essential following diagnosis. The requirement for pancreatic enzyme replacement therapy (PERT) should be identified promptly through clinical assessment and stool measurement of faecal elastase (FE-1) and, if available, faecal fat microscopy. Key moments regarding dietetic support and PERT dosage advice during infancy are periods when feeding methods change, such as the introduction of alternative milks and solid foods.

If growth falters, the infant may require fortification of breast milk or additional use of appropriately fortified formulas to ensure growth potential is optimised [16].

Up to 20 % of infants with CF present with meconium ileus shortly after birth and many require surgical intervention [19]. Growth failure may occur in approximately 40 % of infants with meconium ileus [20,21]. This highlights the need for proactive nutritional management, including parenteral nutrition for infants requiring surgery [21]. Early referral and involvement of the CF team is essential for these families (Statement 2).

Food intake in early life predicts longer-term eating habits [21]. The aim is to balance the importance of infant nutrition while avoiding excessive focus on weight gain that can cause unnecessary concern for the family and negatively influence eating behaviours in the child.

2.2. Supporting good eating; content and behaviours

Eddie Landau, Monika Mielus, Tacjana Pressler

Achieving optimal nutritional status for people with CF addresses malnutrition, while recognising the growing prevalence of excessive weight in all ages [22–25]. The CF specialist dietitian is essential to support people with CF in developing and maintaining healthy nutritional habits through their life (Statement 3), with consistent support and messaging from all members of the CF team. The CF team should play an active role in nutritional surveillance, as well as collecting data to understand the changing nutritional needs of people with CF [3].

Children and adolescents with CF may require increased intake of protein and calories [13-15,26]. To achieve a high calorie intake, people with CF have often consumed poor quality highly processed diets [27–29]. It is reasonable to include nutrient-dense foods in the diet, but people with CF should not rely on higher fat diets to achieve energy intake, as evidence does not link this to CF health benefits [30]. These foods should provide essential nutrients such as protein, healthy fats, vitamins, minerals, fibre and complex carbohydrates [14,15,30]. People with CF initiating CFTR modulator therapy should be encouraged to continue a high-quality balanced diet [3].

Encouraging healthy feeding behaviours early in life promotes a healthy relationship with food and a positive body image (Statement 4). Feeding principles for infants/toddlers with and without CF are similar, including responsiveness to hunger cues, and encouraging eating without coaxing and bribing [31]. It is important to support young children with CF to listen to their bodily cues, and to avoid confrontation around meals, as this can increase the likelihood of future problematic eating behaviours [13,32]. For older children with CF, behavioural

strategies can reduce conflict and lay framework for healthy eating in adult life. Strategies include viewing mealtimes as an opportunity for routine and connection [33], and involving the person with CF in meal planning [34,35].

Guidance for people with CF who have access to CFTR modulator therapy should focus on achieving excellent nutrition with acknowledgement of the long-term risks of obesity (for example, cardiovascular disease), which may be a potential issue for some.

Achieving optimal nutrition relies on coordinated support from the whole CF team, and recommendations must be based on current research, clinical guidelines and consensus views [13,36]. The CF team should provide comprehensive support for nutritional, physiotherapeutic and psychological aspects of care. This includes offering advice on nutrition, providing guidance on physical activity tailored to individual abilities, and addressing psychological factors that may impact eating habits [37].

2.3. Pancreatic enzyme replacement therapy

Chris Smith, Dimitri Declercq

Over 80 % of people with CF have exocrine pancreatic insufficiency and require PERT [38]. CF pancreatic disease obstructs exocrine enzyme delivery and causes a reduced bicarbonate secretion with prolonged acidity in the proximal duodenum [14]. Clinical features indicating pancreatic insufficiency include poor weight gain and loose frequent stools despite a good appetite (Statement 5). Low faecal elastase-1 (FE-1) levels in stool indicate pancreatic insufficiency (≤100 μg/g stool) and supports the use of PERT [39]. For people with CF with an intermediate FE-1 measurement (100–200 μg/g stool), a diagnosis of pancreatic insufficiency is likely, and a trial of PERT is appropriate if clinically indicated.

Appropriate PERT dosage and delivery is essential to correct nutrient maldigestion and malabsorption. PERT should be taken with all food containing fats, proteins, and complex carbohydrates. Guidance varies for PERT dosing and timing, especially the recommended dose with snacks [14,40,41]. Factors influencing dosage include the amount of dietary fat, the PERT formulation being used, weight gain and clinical response [14,42]. Projects, including MyCyFAPP (mycyfapp.eu) and CF Tummy Tracker (cftummytracker.org), are evaluating abdominal symptoms for people with CF to better understand and inform PERT dosage.

PERT consists of lipase, protease, and amylase. Formulations vary in strength, content, and form, including enteric-coated microspheres, tablets, non-enteric-coated tablets, lipase cartridge or powder [14,43]. People with CF and their caregivers should be advised that switching between PERT formulations may initially lead to gastrointestinal problems that can be overcome by adjustment of dosing. The enteric-coated capsules release enzymes effectively when the pH in the duodenum reaches approximately 5.5 [44].

Adherence to PERT is challenging and an individual approach is warranted. Emerging data suggest CFTR modulator therapy may impact pancreatic insufficiency in some people [45,46]. More data are required to guide PERT management in this context.

2.4. Monitoring nutritional progress

Eddie Landau, Monika Mielus, Tacjana Pressler, Anne Munck, Kevin Southern

Nutritional status should be monitored at each clinic visit (Statement 6). Monitoring weight and height (length if aged under 2 years) is a key component of CF care, to support optimal growth in childhood and as a marker of wellbeing in adult life. For older children and adults, body mass index (BMI) should be calculated [14]. BMI and BMI percentiles (or z-scores) have limitations in distinguishing whether deficits, excess stores, or changes in weight are related to fat or fat-free mass compartments. Assessment of body composition as part of nutritional assessment may provide clearer information to guide people with CF [47], particularly in the context of CFTR modulator therapy [3].

Non-judgemental weight monitoring needs to be undertaken with the family, and later with the person with CF, to support the good eating behaviours outlined. This is challenging and requires skilled partnership working by the whole CF team [36]. Comparing growth rates to standard charts is essential. Targets should be ambitious, but also reflect genetic growth potential.

For children and adults on CFTR modulator therapy, improved condition, nutrient absorption, and appetite may result in accelerated weight gain [48]. This should be anticipated and addressed sensitively, appreciating that it is difficult to alter established eating patterns.

It is important to monitor serum levels for fat soluble vitamins, A, D and E at least annually, to assess the need for supplementation [3]. CF-specific multi-vitamin preparations have become more widely available and may improve adherence. These preparations and the impact of CFTR modulator therapy means that vitamin levels (especially vitamin A) can sometimes rise above the normal reference range, requiring adjustment of supplementation [49]. Awareness of the sequelae of excessive vitamin intake should be emphasised [50–52].

There is poor evidence to guide the need for salt supplementation and its dosage [53]. However, for infants and small children, the rationale is compelling, especially when weight gain has been suboptimal [53]. In addition, some older children and adults who are very active may benefit from salt supplementation, but again the supporting evidence is limited. Salt requirements for people with CF increase in hot weather and during periods of fever. Most “western” diets have a high salt content, and this should be monitored and considered when advising families about salt supplementation. The impact of CFTR modulator therapy on reducing sweat salt loss needs to be considered when determining salt requirements and dietary advice [3] (Statement 7). Blood pressure should also be recorded at each clinic visit for people on CFTR modulator therapy [36], given the impact on salt homeostasis and reports of hypertension in clinical trial participants (see Section 7.2).

Dietary advice (intake of calcium and vitamin D) should aim to establish and support bone growth and strength. An assessment of bone mineral density (DXA scan) should be undertaken before puberty to establish baseline data and then repeated at a frequency determined by the baseline results [54]. DXA scan results also provide useful information on body composition. Vitamin K is essential for bone formation; however, more research is required to determine a reliable biomarker to monitor supplementation requirements [50].

3. Towards optimal lung health; staying ahead of the curve

3.1. Physiotherapy for airway clearance

Lisa Morrison, Brenda Button, Sandra Gursli, Catherine Brown

3.1.1. Working with the family from diagnosis through transition to adult life

Following diagnosis, the specialist CF physiotherapist and the family should establish a management plan for physiotherapy and airway clearance techniques (ACT) [55,56] (Statement 8). Physiological principles and age-appropriate ACT should be used to clear airway secretions [57–60]. A range of physiotherapy interventions, ACT types and combinations exist [57], with limited evidence to guide practice [61–64].

Physiotherapists should guide and support parents to manage changing ACT needs and ongoing therapies within their family [65–67]. Parents of children with CF develop expertise and adapt to changes as their child grows and develops [68]. From an early age, physiotherapy management supports children to perform treatment with assistance, supervision, and gradual independence to attain self-mastery and self-confidence [57,59,69]. Children should be taught to understand their respiratory condition, monitor symptoms, appreciate airway

secretions and tailor ACT accordingly [59,70].

Aspirations may differ between parents and children, especially between the age of 8 to18 years. Physiotherapists must understand both perspectives and help establish mutual goals [71]. Participation in shared decision making, which is internationally recognised as a young person's right, empowers the person with CF [72] and could promote adherence to treatments.

Regular physiotherapy review and treatment adjustments allow families to develop good habits, treatment routines and motivation to maintain adherence [57,59,69,73]. Regular follow-up should continually optimise treatments to adapt to changing needs and minimise treatment complexity [59,74]. Reducing the burden of ACT promotes adherence [75,76].

Individualising treatment to the person's experience of benefit, perceived usefulness and preferences can help the person adhere to the regimen. [55,74] (Statement 9). The individual management plan should be consistent with the emerging ethos of "gentle, efficient, motivating and self-supporting" (GEMS) [74], and should include age-appropriate physical activity and exercise.

3.1.2. Adapting airway clearance in older children and adults

As older children with CF move to adulthood, they should be encouraged and supported to manage their ACT independently through shared decision making [62,77], establishing self-efficacy and a readiness for transition to adult care [78] (Statement 10). Transition should include early introduction of the adult team, collaboration between teams, and engagement with the young person [79–81]. Clear, high quality physiotherapy information, adequate support and anticipatory guidance for caregivers and young people will promote successful transition to adult care, and may improve transition experiences [82]. Motivational interviewing may support this approach [83,84].

3.1.3. Airway clearance approaches for the productive patient

Airway clearance has positive short-term effects on mucus transport and sputum rheology [64,85,86]. There is little evidence to support one technique over another with respect to short-term clinical outcomes, although more active techniques such as Positive Expiratory Pressure (PEP) reduce the frequency of pulmonary exacerbations (PEx) compared to more passive techniques such as high frequency chest wall oscillation (vests) [87]. Individualising and combining ACTs for people with CF [88] may increase effectiveness and enhance adherence [89].

A priority research question for people with CF was whether regular exercise can replace ACT [90] but more evidence is needed [91]. During an exacerbation, it is important that people with CF can competently perform airway clearance, since the person may have increased sputum load and reduced energy for exercise.

For those who are eligible and have access, CFTR modulator therapy has had a significant impact on people with established airways disease, with many becoming unproductive. The longer-term effects of VST on chronic airway infection and PEx are relatively unknown, and people with CF should remain engaged with ACT approaches [92–94].

3.1.4. The upper airways; problems and solutions

The most common upper airway disorder in people with CF is chronic rhinosinusitis (CRS), with nasal polyposis recognised as a common complication [95]. The CF team should regularly evaluate people with CF for rhino-sinus disease (Statement 11). Virtually all adults and older children with CF have radiological evidence of CRS, yet only a third report symptoms [8,95-97]. CRS can lead to increased bronchial reactivity, chronic lower airway infection and increased frequency of PEx via postnasal drip, negatively impacting quality of life [97]. CF physiotherapists play an important role in the assessment and treatment of CRS [88].

The validated SNOT-20/22 score is a generic tool to recognise CRS and upper airway disease, guide severity, prompt referral to otolaryngology, and assess treatment response [88,95].

There is evidence to support nasal irrigation (douche) and topical steroids to relieve symptoms [88,95]. Isotonic irrigation solutions are preferred, with evidence of effectiveness for 0.9 % sodium chloride solution [95]. A trial of topical steroids may be appropriate for some people with CF, but the evidence base is not strong [98,99]. Effectiveness is enhanced when gravity is harnessed during application, with the person with CF positioned with their head over the edge of the bed [95].

Evidence supports delivery of topical nebulised solutions to the sinuses using a sinus specific nebuliser compared to a standard nebuliser [96]. Tobramycin or colistin delivered topically to the sinuses may reduce *Pseudomonas aeruginosa* infection [100,101]. Nasal nebulisation of dornase alfa may reduce CRS symptoms and improve quality of life scores [102]. Further research is needed to fully establish the benefits of these therapies.

Surgical intervention such as functional endoscopic sinus surgery (FESS) can be effective for people with CF not responding to medical management of CRS. Nasal polyps recur in approximately 80 % of people following polypectomy [95]. CFTR modulator therapy appears to profoundly improve CRS symptoms and radiological findings [95,97,103].

3.2. Clean air

Ross Langley, Kevin Southern, Lisa Morrison

3.2.1. Cigarette smoking and vaping

Evidence that people with CF should not smoke is unequivocal (Statement 12), and we recommend that people with CF should also avoid electronic cigarettes (also known as e-cigarettes, vapes, or electronic nicotine delivery systems [ENDS]) (Statement 13). In the past, advice was less clear and sometimes supportive of e-cigarettes. Children are increasingly exposed to e-cigarettes, with a rapid rise in uptake and regular use in young people [104]. E-cigarettes generate a vapour by heating a liquid that may contain very high levels of nicotine, making them highly addictive. The vapour can also contain vegetable glycerine, polyethylene glycol plus multiple chemical flavourings. The user can be exposed to toxic levels of heavy metals including nickel, lead and cadmium. Many devices currently exist, some disposable, and some that can be easily modified to vaporise other harmful and addictive drugs such as cannabis.

The long-term outcomes for these relatively new products are still unclear. E-cigarettes can cause pulmonary inflammation, oxidative stress leading to epithelial damage and necrosis, airway hyper-reactivity and altered host defences [105]. In vitro studies have shown that e-cigarette liquids can impair ion channel function including the epithelial sodium channel (ENaC) and CFTR, as well as containing high levels of acrolein which is associated with chronic bronchitis [106].

3.2.2. Hookah smoking

Hookah smoking is also known as shisha or water-pipe smoking. The user inhales through a tobacco pipe with a long flexible hose that draws smoke through water in a bowl. This form of smoking has existed for many years, traditionally in Arabic countries, and is becoming popular in the USA and Europe [107]. Variation in hookah devices and hoses (porous versus non-porous) can influence exposure to the smoke and chemicals, particularly nicotine and carbon monoxide. For these reasons the side effects may be over or underestimated. Furthermore, the humidity associated with hookah smoking facilitates deeper inhalation, potentially increasing the side effects [107]. Hookah sessions generally take 45 min in social environments, including long deep "puffs" and sharing equipment with others [107]. The levels of tar inhaled during these sessions is thought to be over 35 times greater than smoking one cigarette [108]. Sharing of mouthpieces during a hookah session can contribute to transmission of CF pathogens [109].

People with CF should avoid all forms of smoking/vapour inhalation including e-cigarettes and hookahs.

3.2.3. Passive smoking

Environmental tobacco smoke (ETS) is also known as passive or second-hand smoke. ETS is a combination of "mainstream smoke" exhaled by the smoker, or "sidestream smoke" from the burning end of a cigarette, pipe, or cigar, or tobacco burning in a hookah. Sidestream smoke has higher concentrations of nicotine and cancer-causing agents than mainstream smoke [110]. Repeated exposure to ETS increases the risk of lung cancer in adults who have never smoked by 20–30 % [106]. There are no safe levels of exposure to ETS for people with CF of all ages (Statement 12).

4. Being active

Thomas Radtke, Zoe Saynor, Anna Middleton

4.1. The rationale for physical activity and exercise

Physical activity involves activities of daily living and recreation, while exercise is purposeful and structured towards improvements in fitness and airway clearance. The type, duration and intensity of exercise depends on personal goals. Exercise facilitates mucociliary clearance, slows the progression of decline in lung function, and improves exercise capacity, which, when reduced, is a predictor for lung transplantation and death in people with CF [111–114].

The World Health Organisation recommends at least 60 min of moderate-to-vigorous physical activity per day for school-aged children and 150 min per week for adults, with the inclusion of muscle strengthening activities 2–3 times per week. Pre-schoolers should spend at least 180 min per day in a variety of different activities and reduce screen time to a maximum of one hour per day [66]. These fundamental guidelines for physical activity and sedentary behaviour are applicable and important for people with CF. CF-related comorbidities need to be considered when recommending physical activity, but people with CF should be aiming to maximise their physical activity by increasing habitual physical activity (especially moderate-to-vigorous intensity), reducing sedentary time, participating in structured exercise training and promoting positive long-term physical activity behaviours [115, 116]. Other approaches to exercise, for example resistance training which can build muscle and alter body composition, should be considered and encouraged if appropriate.

Availability of CFTR modulator therapy presents new opportunities for people with CF to lead active lifestyles, but also challenges. For example, some respond to CFTR modulator therapy with excessive weight gain [117], which seems to be fat mass rather than muscle, which is an important issue since the prevalence of obesity is steadily rising throughout the CF population [8,24,118,119].

For overweight individuals, regular physical activity and exercise are key to minimising the risk of cardiovascular and metabolic disease [120–122], comorbidities which are becoming more relevant with the ageing CF population. Some people with CF have chosen to modify their treatment regimens and use exercise as a substitute for traditional airway clearance therapy. The long-term effectiveness of exercise as an airway clearance therapy requires further research and is shorter-term effects are currently under investigation in the ExACT clinical trial (NCT05482048) [123,124] .

4.2. Approaches to measuring and monitoring exercise capability

CF-specific consensus recommendations for standardised functional and laboratory exercise testing are available [125,126]. Indications for exercise testing include establishing aerobic fitness and/or muscle strength, evaluation of potential exercise-induced risks, monitoring disease progression, guiding individualised exercise prescription, and evaluating the response to exercise programmes [125,126]. Exercise testing can also serve as a motivational tool. Dynamic endpoints, such as exercise capacity, can provide valuable insights into the integrated functioning of multiple organ systems (cardiovascular, musculoskeletal, respiratory). These modalities provide a more comprehensive understanding of an individual's health status.

The ECFS Exercise Working Group (EWG) and the Physiotherapy Special International Interest Group (PhySIIG) suggest a small selection of exercise tests performed consistently and to a high standard [126] (Statement 14). Cardiopulmonary exercise testing (CPET) provides a measure of aerobic fitness and helps assess exercise-related symptoms [125]. If CPET is not available, standardised guidance is available for other less-complex tests [125,126].

4.3. Strategies to support and maintain an active lifestyle

The CF team should promote an active lifestyle as early as possible [115]. Family engagement in physical activity influences long-term behaviours by promoting enjoyment and adherence [127]. Children with CF are encouraged to participate in club activities, integrating exercise into normal lifestyle (Statement 15).

The CF team should review exercise capacity and progress at each clinic, ideally with a psychologist to support goal setting, self-regulation and management of barriers and setbacks [127]. The most effective type, duration and intensity of exercise for people with CF remains unknown [113,115]. Programmes should be individualised with focused guidance for specific subgroups considering age, gender, disease severity, extra-pulmonary complications, access and psychological factors modulating physical activity behaviours [115,128]. Physical activity and exercise plans should be developed in consultation with the person with CF and their family [127], facilitating individual preferences for environment, modality, duration, intensity and frequency. Offering choice, diversity and flexibility can improve engagement, enjoyment and long-term physical activity behaviour, and can promote self-efficacy and adaptability in the management of unplanned setbacks [115,127].

For people with more advanced or severe CF lung disease, exercise remains important, although advice needs to be more pragmatic and alternative interventions considered, such as stationary cycling and strength training [115]. Consistent messaging from the CF team promotes favourable body composition changes and accrual of lean tissue mass (skeletal muscle) for people with CF who undertake high levels of exercise [20]. People with CF can be reassured that physical activity is safe [129,130], by identifying individual safety considerations through exercise testing and musculoskeletal assessment, followed by appropriate education. Initial supervision of prescribed programmes (in-person or via telemedicine [20]) can monitor the impact, enjoyment and avoidance of undesired physiological responses which can negatively impact long-term physical activity behaviour [115]. Regular review of progress using recommended tests is recommended to modify the programme and maximise benefits [91,115].

Adherence to exercise programmes is often poor and strategies should evolve and adapt as the person ages [131]. The CF team should work with the individual to identify factors that impact adherence, including facilitators, enabling and re-enforcing factors, and physical and psychosocial barriers. Support should focus on coping and behavioural strategies to promote motivation. These strategies can include goal setting and self-monitoring, integrating structured exercise into daily life and influencing long-term physical activity behaviour [127, 128,132-134]. Digital media and wearable technology are valuable tools for self-monitoring and motivation [132], however future research is needed to determine the best physical activity assessment tool and their effectiveness in promoting engagement [135].

5. Working with the CF team and other healthcare professionals

5.1. Expectations and models of care

Isabelle Fajac, Kris De Boeck, Audrey Chansard, Dominique Pougheon Bertrand, Scott Bell

The model of care for people with CF is based on the CF centre and the framework first described in the 2014 ECFS Standards of Care [136]. The success of centre-based care in improving survival and other key clinical metrics is clear and the principles driving this model remain relevant today [137]. However, it is appropriate to reflect on changes to the traditional care model given the continued improved life expectancy [137] (Statement 17), the health benefits following initiation of CFTR modulators [138], and the new approaches to providing care that emerged with the Covid-19 pandemic [139]. Changes that facilitate care closer to home with less frequent hospital visits may be appropriate and are popular with people with CF and their families but must not compromise quality of care. Strategies to be considered include networks with a central specialised hub, regional clinics and remote care, as described in following sections.

Whichever model of care is adopted, the multidisciplinary CF team remains key, and access to this team is a requirement for people with CF (Statement 16). The CF team provides the support that people with CF and families require for their journey (Statement 18) and must include respiratory paediatricians or pulmonologists with specialist CF knowledge. Other members of the CF team should include clinical nurse specialists, respiratory physiotherapists, physical activity coaches/exercise physiologists, dietitians, clinical psychologists, social workers (and youth workers), microbiologists and pharmacists, all of whom should be experienced in CF care [136]. Although the roles of these professionals are well established, they continue to evolve with the changing CF landscape (see Section 6.1 on the increasing importance of the CF pharmacist). Youth workers are being increasingly utilised in a healthcare setting to support young people with chronic conditions on their journey into adult life [140].

With the development of CFTR modulators, it is critical that all people with CF have access to *CFTR* gene testing for diagnosis and information on their eligibility for CFTR modulators [3]. Moreover, the CF team should be knowledgeable about eligibility for CFTR modulators, modalities of prescription, possible complications, drug interactions, and follow-up [3]. The CF team should discuss the potential impact and prescribing of CFTR modulators with the person with CF as soon as eligibility is confirmed.

It is essential that the CF team establishes links with closely associated specialties, including clinical genetics, and radiology. Strong links should also exist with a wide range of other medical and surgical specialties including gastroenterology and hepatology, endocrinology with expertise in CF-related diabetes, otorhinolaryngology, cardiothoracic and general surgery, interventional radiology, specialist anaesthesia and pain control, rheumatology, psychiatry, intensive care, urology/nephrology, assisted fertility services and gynaecology/obstetric services [136]. Because of the growing number of pregnancies since the availability of the triple therapy combination, elexacaftor-tezacaftor-ivacaftor (ETI) [141], there is a need to enhance links with obstetric care teams delivering high-risk pregnancy care.

Transplant services for lung and liver should be easily accessible and approachable for case discussion focusing on CF-specific complications, education, and consideration of the appropriate use of CFTR modulators in post-transplant patients [142,143]. With the increased survival of people with CF, primary care expertise should be integrated into the CF care pathway, especially for non-CF-related diseases and disease prevention screening. Links with specialists experienced in age-associated comorbidities should also be established.

The regular visits and assessments constituting quality CF care throughout lifetime, as outlined by several guidelines documents [136, 144], have been associated with improved survival [137]. The Covid-19 pandemic prompted integration of virtual care with voice and video link consultations [139]; we discuss this further in Section 5.2. Virtual multidisciplinary consultations with the possible use of connected medical devices should be proposed and evaluated in terms of risks and benefits for the person with CF. This will inform on the optimal use of remote monitoring and care, which is still an area for further study [145, 146] (Statement 19). Care needs to be individualised to each person with CF, based on their needs and preferences [147,148]. The CF team should have regular pre- and post-clinic visit patient discussions and should have regular quality-management meetings to discuss and update general policies such as infection control, treatment and follow-up protocols [136].

The buildings, facilities, and the computer infrastructure should allow the CF team to provide effective diagnosis, holistic care, treatment and research [136]. CF centres should encourage people with CF to participate in CF registries in order to further the understanding of the disease and improve clinical care through key metrics and benchmarking [149]. Members of the CF team should keep up to date with developments in CF through continued professional development, attendance at conferences, participation in audits, and involvement in clinical research including clinical trials [136]. CF centres should network with other centres, both nationally and internationally, and link with local or national patient representative organisations to offer additional resources to support people with CF and families. Less economically advantaged regions should strive to implement best practice to deliver equality and high standards of care. Patient organisations and the ECFS help translate standards from economically advantaged regions to improve CF care in developing services by supporting skill development and resource allocation [136]. There is an increasingly recognised need to improve diagnosis and management in countries with a low incidence of CF [150] and in regions with limited resources. In these countries, even if a diagnosis is established, access to basic therapies is challenging.

It is a period of significant change for the CF community. Despite this, the basic framework of CF care remains key to good outcomes for people with CF (Fig. 1). It is imperative that CF teams work in partnership with people with CF to deliver care in the most appropriate manner without compromising quality.

5.2. Potential for remote care

Charlotte Addy, Michael Doumit and Ilan Shufer

5.2.1. Remote monitoring

Remote monitoring can supplement face to face care at CF centres to assist early detection of clinical decline [151] and to support adherence [152]. Multiple modalities are available to remotely monitor clinical progress, including lung function, vital signs, sleep quality, physical activity, height/weight and patient reported outcomes. Validity and reliability vary between modalities and devices, with interpretation and follow-up dependent on the monitoring purpose (See Table 2).

While remote monitoring is feasible, caution is needed in application. Concerns include low engagement, particularly in adolescents, and lack of improved clinical outcomes following monitoring-based interventions [152–154]. Increased monitoring can lead to health anxiety, and this may contribute to disengagement with ongoing assessment [155].

A number of accurate home spirometers are available. Disparity between home and hospital measurements exists, with caution needed if results are compared [156]. Daily variability also impacts reliability and should be considered when interpreting results [157–159]. Further data is necessary regarding individual variability using remote monitoring, both with technique and the device. Performing tests, for example spirometry, during a video link may prove beneficial. Research is needed to determine optimal monitoring strategies and subsequent interventions to improve clinical outcomes, promote engagement and balance the additional burden of remote monitoring with benefit for people with CF.

5.2.2. Virtual clinics

The use of virtual clinics for CF care was accelerated by the Covid-19 pandemic, with interest sustained by feasibility and the benefits to

Develop and/or maintain a CF centre with all necessary expertise amongst the CF team, with special attention to:

- up-to-date knowledge about CFTR modulator eligibility, prescribing, reimbursement, follow-up of adherence, tolerance
- continued support for people with CF without access to or eligibility for CFTR modulator therapy
- consultations adapted to the needs and disease severity of the person with CF
- combining face to face consultations and virtual consultations
- adapting the service to the growing needs of people with CF (for example, education, work, family, travel, and long-term plans)
- team expertise and quality evaluation management
- developing a research active environment

Develop or maintain strong links with all relevant medical specialties needed, with special attention to:

- links with primary care and enhanced screening for associated comorbidities
- obstetrics
- ageing and CF-related complications
- access to transplant services

Fig. 1. Key principles of CF care.

people with CF and healthcare teams [159,160]. Benefits include reduced financial/travel burden, reduced impact on home life and reduced risk of cross-infection. Virtual clinics promote sustainability and flexibility, and are cost effective, although funding to support equipment may be complex to access [161]. Accessibility and engagement in virtual clinics vary across racial, ethnic and socioeconomic groups [162], so care models must account for this, providing additional support as needed. Virtual clinics and homecare offer an alternative to traditional structures but should not replace all face to face clinic reviews (Statement 20). The initiation of new therapies should be monitored directly in clinic.

To address safety concerns and ensure effective monitoring, virtual clinics should mirror "traditional" face to face clinics, including provision for multidisciplinary assessments, lung function, mental health screening, blood, nutritional and microbiological monitoring. CF healthcare professionals should be trained in the principles of remote consultation, establishing a safe and meaningful consultation, and recognising cues that should trigger an intervention or face to face consultation (Fig. 2). Coming out of the Covid-19 pandemic, most centres have adopted a hybrid approach, with the balance between face to face and virtual consultations determined by the person with CF and CF team, annual screening requirements and individual clinical needs. Further large-scale evidence capturing the experiences of people with CF is needed to optimise hybrid models which minimise burden while maintaining quality.

5.2.3. *Ambulatory care*

As outcomes for people with CF improve, there is a move towards proactive ambulatory or outpatient interventions to promote health and quality of life. These include exercise programmes [163], psychological support [164], adherence interventions [152], diabetes education [165] and weight management. Virtual formats overcome the need for

Table 2
Summary of remote monitoring modalities.

Remote monitoring modality	Benefits	Limitations	Current level of evidence
Home spirometry	• Ease of use • Reduced Infection Control risk • Small and Portable • Enables more frequent measurement	• Variable reliability and reproducibility • Multiple devices • Variable technique between devices • Cost of device and replacement devices • Cannot be used interchangeably with clinic spirometry • Potential for inaccurate calculation of predicted values by using historical height measures (especially for children)	Single and multi-centre studies
Home physical activity monitoring	• Ease of use • Small and portable • Multiple options dependent on age and level of information required	• Variable reliability and reproducibility • Multiple devices making standardisation difficult • Limited data linkage with healthcare systems • Devices with high accuracy are costly	Single and multi-centre studies
Quality of life /symptom measures	• Early detection of illness • Increased focus on patient reported outcomes	• Variable engagement with monitoring, especially in adolescents • Lack of standardisation of symptom scores	Single and multi-centre studies
Home sputum collection	• Results available prior to clinical review • Possibility of postage to CF centre	• Limited results linkage with healthcare systems • Reduced availability of sputum in children and those on CFTR modulator therapy • Location/country dependent policies on postage	Few single centre studies
Pulse oximetry	• Device accuracy • Small and portable	• Limited benefit outside of acute exacerbations	Few single centre studies
Height/weight measurement	• Easily accessible to most • Contemporary height measures useful for lung function values	• Variable accuracy of measurements depending on user/equipment • Cannot be used interchangeably with clinic measurements	Multiple non-CF single centre studies

segregation based on infection control issues and allow provision of group-based support previously inaccessible to people with CF. There is also potential for clinical practitioners embedded in the CF team to provide assessment, support and interventions in the home of the person with CF.

6. Managing medicines

Medicines are a large part of daily life of people with CF and their families. The rationale for each intervention should be clear and evidence reviewed regularly. In these sections we consider the expanding role of the pharmacist in the CF team, the challenge of supporting adherence and the increasing importance of stopping/starting strategies. Finally, we review developments in the field of VST, with CFTR modulator therapy now an established and important intervention for many people with CF.

6.1. Role of the pharmacist in the CF team

Amanda Bevan, Carina Hansen

The role of the CF pharmacist has become increasingly important to optimise drug delivery and management (Statement 21). Activities defined in previously published standards of care [136,166-168] have been expanded and are outlined below.

The pharmacist is a core member of the CF team, advising on all aspects of medicines. The CF pharmacist should review each person with CF and complete a full medicine history at least annually. This will include evaluation of relevant drug interactions, difficulties with adherence or medicines taking behaviour, medicines which might be discontinued, problems with medicines administration and availability, especially of new generic options. The pharmacist should review medicines against current evidence as part of the annual review. For healthcare regions without a dedicated CF pharmacist, these tasks will need to be taken on by other members of the CF team, with potential impact on quality of care.

People with CF obtain medicines from various routes including hospital pharmacies, outpatient pharmacies, community pharmacies and home delivery services. Obtaining essential medicines from several providers may be challenging [169]. The relationship with the community pharmacy is especially important for people with CF and the services they provide are complementary to those from the hospital. Communication between the two services should be clear, to best support the person with CF. The pharmacist should be available to answer queries related to medicines from people with CF or other healthcare professionals.

The CF pharmacist should attend all CF team meetings to provide input on medicines-related topics and support the team to develop and follow evidence-based guidelines within the service, and across any shared care networks. The CF pharmacist is also well placed to support clinical research.

6.2. Supporting adherence to therapies

Urzula Borawska, Kevin Southern, Ilan Shufer

The therapeutic burden for people with CF and their families is variable but always significant [170]. Supporting people with CF with adherence to therapies requires skilled partnership working, an appreciation of treatment burden and a clear rationale for each therapeutic

Environment (for the CF team and the person with CF) • Reduce background noise • Reduce disturbances/interruptions • Ensure comfortable positioning • Ensure privacy – from public and from family/pets if needed • Opportunity to assess home environment – consider safeguarding issues • Dress appropriately and avoid distractions in the background
Technical issues • Ensure effective audio-visual hardware • Appropriate internet connection with suitable speed • Clarify with the person with CF if the sound and visuals functional/acceptable • Have a backup communication option planned in case connection fails • If issues arise ensure troubleshooting carried out before terminating consultation
Communication • Consider whether consultations conducted 1:1 or with person with CF and several CF members – adjust communication style accordingly if group consultation • Consider consent issues if the person with CF is paediatric or vulnerable • Utilise different skill set to face to face assessment which may require upskilling of CF • Effective history taking critical • Reduced reliance on clinical signs • Alter body language assessment to account for limited perspective • Adapt questions as needed considering environment of the person with CF • Consider if others may be present/listening out of sight • Consider comfort of the person with CF in using this format • Maintain eye contact and visual cues – as even more important when only face/upper torso is visible • If looking away from the camera at another screen or paper results, explain what you are doing (and that you are still listening)
Effective use and integration of home monitoring • If remote monitoring in use ensure this is considered as part of consultation • If additional monitoring needed after consultation, ensure results are obtained and a clear plan of action agreed with the person with CF before consultation ended
Outcomes • Clarify wishes of the person with CF regarding future virtual consultations • Ensure outcome clear to the person with CF and the CF team • Consider whether next review is face to face vs virtual

Fig. 2. Guide to conducting effective virtual consultations with people with CF.

intervention [171]. Communication should be clear and open, with shared decision making and agreed treatment goals.

Several methods provide insight into how a person with CF manages their daily treatment burden. These include, in order of accuracy and validity: electronic data capture (EDC), medication possession ratio (MPR), regular phone diaries, self-reporting via apps or paper diaries and retrospective surveys [172,173]. Whichever surveillance method is employed to monitor treatment adherence, this should be transparent, with the CF team working openly to support the person with CF and reflect together on results (Statements 22 and 23).

Supporting optimal adherence requires an individualised approach that is flexible and considers the life of the person with CF and their family. Various strategies support improved adherence, with no clear evidence as to a preferred approach (Table 3) [174]. Clinical trial data suggest that an individualised approach can help the person with CF maintain adherence to aerosolised therapies [152]. With the increased availability of technologies to help monitor treatments and wellbeing, it is important that these advances are driven by people with CF to address their needs. Adherence monitoring should be supportive, improve quality of life and not result in an additional perceived burden for people with CF.

6.3. Starting and stopping medicines

Gwyneth Davies, Maarten Ploeger, Nicole Mayer–Hamblett, Bradley Quon

The evidence base for traditional CF medicines largely stems from clinical trials and systematic reviews undertaken before the CFTR modulator era. The implementation of CFTR modulator therapy for many people with CF has been successful but requires a reappraisal of all therapeutic approaches.

Decision making for starting and stopping chronic medicines should be shared between the person with CF/their caregivers and a clinician with expertise in CF (Statement 24), with rationale documented and reviewed at least annually. Recommendations should be guided by clinical trial evidence where available, and tailored to the individual.

Table 3
Strategies to support and improve adherence to CF therapies.

Focused on relationship with CF team
• Establish a relationship with the person with CF and their family based on cooperation, honesty, and trust
• Normalise challenges with adherence and acknowledge the person's efforts
• Ensure that all members of the CF team deliver a consistent message to the person with CF and their family
• Emphasise the potential benefits of therapy and the realistic trajectory of the disease without inducing anxiety (avoid using fear-based approaches)
• Collaboratively develop an individual behaviour change plan with the person with CF, and consider using motivational interviewing
Focused on the person with CF
• Assess patient/family resources, coping skills, and experience of resilience
• Support emotional wellness and provide interventions to prevent decline in mental health
• Monitor mental health – annual screening of depression and anxiety symptoms is recommended
• Offer suitable interventions utilising various treatment modalities if/when symptoms increase, and/or refer to mental health specialists when needed
• Assess the beliefs and attitudes of the person with CF and their family regarding the treatment
Focused on treatment
• Monitor the educational needs of the person with CF and their family, and deliver comprehensive knowledge through diverse methods
• Help to establish treatment routines and habits
• Collaboratively establish an individually tailored treatment plan with the person with CF and their family
• Help to develop accurate time-management strategies e.g., using electronic devices, reminders

Factors such as CFTR modulator prescription, pre-existing lung disease, age, comorbidities and treatment burden should be considered. Treatments should balance therapeutic burden and side effects with health optimisation, minimising decline in pulmonary function and occurrence of PEx.

Studies are evaluating if it is safe to stop chronic medicines in people established on triple combination CFTR modulator therapy (ETI). The randomised controlled trials (RCTs) SIMPLIFY (NCT04378153) and CF STORM (EudraCT 2020–005,864–77) explore stopping nebulised mucoactive therapies, according to the research priorities set by the CF community. Observational studies such as HERO-2 (NCT04798014) and NEEMO (NCT05519020) are evaluating the role of long-term treatments more broadly. In SIMPLIFY, people with CF on ETI who discontinued inhaled mucoactive therapies did not have a drop in lung function. However, the study participants had predominantly mild to normal lung function and the 6-week study period was short [175].

There is no evidence to support or refute stopping medicines in young children (<12 years) on CFTR modulators, and at present there is inconclusive evidence to guide decision making in individuals with moderate to severe CF lung disease (ppFEV$_1$<60 %). Similarly, there is no evidence available to inform when chronic therapies should be newly initiated in those already established on CFTR modulators. These remain important questions for the CF community.

When applying clinical trial findings to clinical practice, it is important to consider these results in the context of study design, participant demographics, intervention and timing of outcome measurement. Where high quality evidence is available, it may be appropriate to monitor treatment reduction (dose-tapering or stopping). Short- and long-term treatment-specific considerations should be discussed, acknowledging any unknowns and communicating clear criteria for re-starting.

Data collection in CF registries regarding treatments and clinical outcomes should be optimised, to maximise the value of these data for the benefit of the community.

7. Variant-specific therapy (CFTR modulator therapy) to correct the underlying defect

7.1. Progress since interim guidance (January 2023)

Kevin Southern, Mark Chilvers, Elise Lammertyn

CFTR modulator therapy has been a significant intervention for people with CF who are eligible (genotype and age) and who have access [3]. These oral therapies, generally taken twice daily, have proven efficacy and a good safety profile [3]. People with CF with eligible *CFTR* gene variants should be offered CFTR modulator therapy (Statement 25).

The first CFTR modulator, ivacaftor, is licensed for a limited range of responsive *CFTR* gene variants, which are carried by <5 % of people with CF. Ivacaftor has been available for eligible people with CF since 2012 and is currently licensed for people with CF from 1 month of age in the US (4 months in Europe) [176].

The dual modulator therapies, lumacaftor-ivacaftor and tezacaftor-ivacaftor expanded the population eligible for CFTR modulator medicines, but with reduced efficacy compared to ivacaftor. These dual therapies were initially licensed for people with two copies of the c.1521_1523delCTT (F508del) *CFTR* variant, followed by label extensions to some compound heterozygote combinations for tezacaftor-ivacaftor [3,177].

The triple combination therapy ETI has better efficacy than dual modulator therapies and has been licensed for people with just one F508del variant, increasing the pool of eligible people with CF. In 2023, ETI was approved for children from 2 years of age in the US [178]. The approval process is ongoing in Europe.

There is strong evidence to support the use of ivacaftor or ETI for people with CF who have eligible *CFTR* variants. The evidence for dual

therapy is less robust [179] and this treatment should be considered on an individual basis.

Some people established on ivacaftor therapy may be eligible for ETI if their second *CFTR* variant is F508del and clinical trial data suggest some additional benefit. The decision to switch to ETI should be made on an individual basis, balancing the potential additional benefit with the risk of adverse reactions caused by the additional agents in the ETI triple combination therapy.

CFTR modulator therapy is expensive, with inequitable access worldwide [150]. In countries and regions that have funded access to CFTR modulator therapy, CF teams should promptly offer these medicines to eligible people with CF, with systems in place to monitor response and adverse reactions [3]. Independent lists of eligible variants are available and should be checked regularly for updates [3,180]. For people with rare uncharacterised *CFTR* variants, n-of-1 trials are appropriate to assess efficacy, although funding may be a challenge for off-licence indications, reflecting a licence that is genotype dependent. For young children and infants, certain CFTR modulator therapies may not yet be licensed, and options should be considered on an individual basis (Statement 26).

The impact of CFTR modulator therapy on the lives of people with CF is considerable and these updated guidelines reflect that changing landscape. A small but significant number of people with CF do not have *CFTR* gene variants that are responsive to current CFTR modulator therapy. For these people, emerging technologies such as gene replacement or editing to correct the underlying CF defect are required [3]. The principles of care outlined in this paper remain essential to achieve good outcomes in all people with CF, especially for people who are ineligible for CFTR modulator therapy or who live in a country or region without access.

7.2. Monitoring for adverse events on CFTR modulator therapy

Kevin Southern, Martin Hug and Anna Georgiopoulos

The safety profile of CFTR modulator therapy for people with CF is good. Preclinical studies were reassuring and concerns over lens opacities from animal studies have not manifested significantly in humans. This has been confirmed by regular eye examination of people with CF exposed to CFTR modulator therapy [3].

However, despite the overall safety profile, impactful side effects from CFTR modulator therapy are seen. Side effects related to the physiological changes associated with the therapy include increased airway secretions, abdominal pain, rhinorrhoea (especially in younger children), sinusitis, and testicular pain [3]. Adverse reactions relating to the mechanism of action are generally transient and resolve in days or weeks. Idiosyncratic side effects include skin rash, headache, drug-induced acne [181], mastitis, transaminitis (raised liver enzymes), muscle pain, creatinine kinase elevation and raised blood pressure. Raised blood pressure was most clearly associated with the dual combination of lumacaftor-ivacaftor but has also been reported with other modulator combinations [182,183]. Elevated liver transaminases have been reported in up 25 % of people with CF taking ETI and the summary of product characteristics recommends routine monitoring, with more frequent evaluation if there is evidence of liver disease [184]. Transient dyspnoea was often observed on initiation of lumacaftor-ivacaftor [185]. This side effect was not regularly reported with other CFTR modular combination therapies [179].

Neuropsychiatric side effects have been reported for all available CFTR modulator therapies [186]. An increasing number of reports have accompanied the widespread availability of ETI, including alterations in mood, anxiety, sleep and neurocognition, as well as suicidal ideation/-attempts. Most remain limited to case reports/series and single-centre studies [187–190], although national survey data are emerging [191, 192]. Some changes in mental health may be positive or unrelated to starting a CFTR modulator, while negative experiences may reflect psychological adjustment to living in the modulator era, direct physiologic impact of the modulator, or drug-drug interactions, highlighting the importance of careful assessment [190,192]. The Pharmacovigilance Risk Assessment Committee (PRAC) for the European Commission recently determined that there is at least a reasonable possibility of a causal relationship between ETI and depression [193].

When discussing the risks and benefits of CFTR modulator therapy, potential physical and mental health impacts should be considered. People with CF and their families should be encouraged to report both positive and adverse experiences to the CF team, regardless of presumed causality (Statement 27). As people with CF are established on modulator therapy, surveillance is required based on the above events, including eye examination, measurement of liver transaminases [194] and blood pressure. Mental health should be monitored in accordance with CFF/ECFS guidelines, including screening for depression and anxiety before and no later than 3 months after initiating VST [3].

The importance of post market surveillance was illustrated by reports of five cases of raised intracranial pressure in younger children on ETI [195,196]. In three children, this was identified from papilloedema seen on routine eye examination, and in two children because of sixth nerve palsy.

As with any new drug, all adverse events, regardless of causality should be reported on a national database or registry and to the company as part of a post market surveillance schedule (Statement 28).

7.3. Adjusting the dose of CFTR modulator therapy after adverse reactions

Mark Chilvers, Martin Hug, Peter Middleton, Jane Davies

No evidence-based approach to dose interruption, reduction and re-introduction of CFTR modulators has been reported. Side effect management is based on clinical context, local experience and emerging evidence from case studies (Table 4).

Mild skin rashes or acne can be unpleasant but can often be managed with symptom-based treatment without CFTR modulator dose interruption [181,197]. More severe rashes may require dose interruption and initiation of desensitisation protocols ranging from weeks [198] to several months [199,200].

Real world data show that variations in transaminases with CFTR modulators rarely lead to liver injury [201] but may be managed with dose interruption or adjustment.

Neuropsychiatric issues have been effectively relieved by dose interruption or reduction [187,188,202] (Table 4). Some people with CF have chosen to not re-introduce CFTR modulator therapy because of the adverse reaction [188,190,203].

There have been reports of benign intracranial hypertension in people on CFTR modulator therapy which, in some cases, may have been associated with hypervitaminosis A. Dose interruption was needed for some people, whereas in others symptoms resolved with reduction of vitamin supplementation [195,196,204].

Ultimately the decision to continue CFTR modulator therapy is determined by patient preference and clinical guidance. Sweat chloride as a marker of CFTR modulation can be used to support dosing regimens [188,203]. Recently developed drug assays [205,206] can measure drug levels and titrate drug dose against clinical markers of benefit. This has helped resolve CFTR modulator therapy side effects in some cases [207]. Further work to standardise these assays and make them more widely available is a clinical priority.

7.4. Adjusting the dose of CFTR modulator therapy during pregnancy

Mark Chilvers, Martin Hug, Peter Middleton, Jane Davies

The number of pregnancies has tripled for women with CF established on ETI therapy [8]. Interrupting CFTR modulator therapy during or before pregnancy is an option but has been associated with clinical deterioration in pregnant and non-pregnant women [3]. Real world safety data are emerging [208] and clearly many women with CF are

Table 4
Suggested dose adjustment of CFTR modulator therapy
Note: some countries may apply stricter criteria for discontinuation, especially with transaminitis.

Event	Severity	Dose adjustment	*Re*-introduction	Other actions
Rash	Mild	Continue standard dose[1] [197]	N/A	Treat with antihistamines, topical steroids
	Severe	Stop	Once symptoms resolve, restart at full dose, or start desensitisation process [198–200]	Treat with antihistamines, topical steroids
Transaminitis	>3 X ULN	Continue standard dose	N/A	Repeat LFTs monthly
	>5 X ULN	Dose reduction[2] [211]	*Re*-introduce at reduced dose. Titrate dose with clinical response ± sweat chloride	Repeat LFTs after 2 weeks
	>8 X ULN	Stop [211]	*Re*-introduce at reduced dose. Titrate dose with clinical response ± sweat chloride[2]	Repeat LFTs 1–2 weekly [188]
Pre-existing liver disease	Moderate hepatic impairment: VST treatment if clear medical need & benefits outweigh risks [184].	Dose reduction[2] [184]	*Re*-introduce at reduced dose. Titrate dose with clinical response ± sweat chloride[2]	Repeat LFTs 1–2 weekly [188]
Insomnia / daytime fatigue		Standard dose	Consider switching am/pm dosing times	
Neuropsychiatric, mood or anxiety symptoms	Moderate	Dose reduction[3]	12 weeks after[4] symptoms resolve, increase dose [203] Titrate dose with clinical response ± sweat chloride[2] [188,190,203]	Consider initiation or dose adjustment of psychopharmacologic therapy [190]
	Severe	Stop	Once symptoms resolve, consider re-introduction with a reduced dose[3] or alternate drug[5] Titrate dose with clinical response ± sweat chloride[2] [190,203]	Consider initiation or dose adjustment of psychopharmacologic therapy [190]
Pregnancy		Standard dose [3] or stop VST to 2nd trimester		Review with obstetrician CF clinic[6]

Abbreviations: LFTs=Liver Function Tests, ULN=upper limit of normal, VST=variant-specific therapy.
Footnotes:
[1] Currently three different age and weight based dosage formulations are available for modulator treatment [184]. All are based on the following Standard Dose Regimen: 2 tablets each of elexacaftor, tezacaftor and ivacaftor in the morning and one tablet of ivacaftor in the evening.
[2] Dose reduction to: 1 tablet each of elexacaftor, tezacaftor and ivacaftor in the morning and one tablet of ivacaftor in the evening, OR 1 tablet each of elexacaftor, tezacaftor and ivacaftor in the morning 3 times a week.
[3] Dose reduction to: 1 tablet each of elexacaftor, tezacaftor and ivacaftor in the morning and one tablet of ivacaftor in the evening.
[4] Consider earlier reestablishment of standard dose if clinically indicated.
[5] Consider alternative agent, either a dual or mono modulator combination dependent on patient genotype.
[6] *In utero* VST exposure may reduce neonatal serum immunoreactive trypsinogen and result in a false negative newborn screening result.

choosing to continue ETI throughout pregnancy [209], however some may choose to interrupt medication throughout pregnancy. In certain jurisdictions access to CFTR modulator therapy is denied for pregnant women with CF. The decision to continue or stop CFTR modulator therapy during pregnancy and breastfeeding should be made considering the risks for the mother and the baby [195,210].

8. Conclusion

This comprehensive paper provides guidance for people with CF and healthcare professionals, based on the best available evidence. The paper provides background and context, while the accompanying statements (Table 1) are more directive. The tone of the guidance reflects the changing landscape for the CF community and promotes activities and interventions to both establish and maintain a healthy life. The pro-active ethos that runs through this paper is illustrated by sections and statements on physical activity and exercise, clean air and models of care. The next paper in this series will explore interventions for complications of CF and when life gets more challenging.

The guidance was developed in partnership with people with CF and the wider CF community. Whilst a good level of evidence was identified for some recommendations (13 Cochrane systematic reviews cited), overall, the evidence base to support guidance was not strong. This reflects the rapidly evolving CF field. The Delphi methodology enabled us to develop relevant statements in a timely manner. Responses to the Delphi exercise were informative and resulted in statements being modified (improved) or rejected by the Core Committee. The process helps to identify research questions that require new or further clinical trials to provide an answer and improve the evidence base. The guidance is translatable to both established and emerging CF care services and provides a framework for living a healthy life.

CRediT authorship contribution statement

The core committee established the framework for the exercise and identified experts to produce each section (highlighted in the paper). All members of the faculty contributed to the Delphi process and had oversight of the final paper. Fiona Dunlevy provided overall administrative support and medical writing to produce a consistent document.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.12.002.

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