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Original Article

Standards for the care of people with cystic fibrosis (CF); Planning for a longer life

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ABSTRACT

This is the final of four papers updating standards for the care of people with CF. That this paper "Planning a longer life" was considered necessary, highlights how much CF care has progressed over the past decade. Several factors underpin this progress, notably increased numbers of people with CF with access to CFTR modulator therapy.

As the landscape for CF changes, so do the hopes and aspirations of people with CF and their families. This paper reflects the need to consider people with CF not as a "problem" to be solved, but as a success, a potential and a voice to be heard. People with CF and the wider CF community have driven this approach, reflecting many of the topics in this paper. This exercise involved wide stakeholder engagement. People with CF are keen to contribute to research priorities and be involved in all stages of research. People with CF want healthcare professionals to respect them as individuals and consider the impact of our actions on the world around us.

Navigating life presents challenges to all, but for people with CF these challenges are heightened and complex. In this paper we highlight the concerns and life moments that impact people with CF, and events that the CF team should aim to support, including the challenges around having a family.

People with CF and their care teams must embrace the updated standards outlined in these four papers to enjoy the full potential for a healthier life.

1. Introduction

This is the last of a series of four papers updating the 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 experts in the field of CF in collaboration with people with CF and the CF community. "Planning for a longer life" reflects the need to reconsider goals and aspirations regarding the journey of people with CF and their families. While this change of perspective should be celebrated, people with CF continue to face challenges that are unique, significant and evolving.

1.1. Methods

Our agile, evidence-based methodology for constructing statements and gaining consensus in a timely manner are described in detail in previous papers in this series [1-3]. Briefly, the multidisciplinary core committee created the framework for the 4-paper series, and invited authors to contribute short narrative sections and more directive statements. The field of CF is changing rapidly. The evidence base to support even standard therapies is now less robust for people taking CF transmembrane conductance regulator (CFTR) modulator therapy. We undertook a stakeholder engagement exercise using Delphi methodology to address the evidence gap, establish a valid consensus and achieve agreement for statements. Statements were submitted by the section authors on themes proposed by the core committee. A threshold of $\geq$80 % agreement indicated an acceptable consensus for each statement. Comments were reviewed and some statements were subsequently adjusted for readability, without changing the sense of the statement. The final statements that achieved consensus are presented in Table 1. The Delphi consultation participants are listed in Supplementary Table 1, and detailed results of the Delphi consultation and edits to the statements are presented in Supplementary Table 2.

2. Navigating life

Charlotte Addy, Bethan Watkins, Ken De Marie

The CF team has a role to support the personal, social, and educational development of people with CF to enable them to reach their full

Table 1
Statements resulting from the Delphi consensus process (>94 % agreement achieved for all statements).

1	The CF team should support people with CF through their life journey, recognising key stress points such as changing school, gaining employment and living independently.
2	The CF team should acknowledge and respect the differing values and beliefs of people with CF.
3	The CF team should work with the family to introduce the concept of subfertility to young people with CF in a sensitive manner.
4	The CF team should provide clear, age-appropriate information about assisted reproductive technologies.
5	For women with CF who wish to conceive, the CF team should promote optimisation of pre-conceptional health including lung function, nutritional and metabolic status.
6	Pregnant women with CF should undergo regular monitoring by the CF and obstetric teams including screening for gestational diabetes and re-assessment of chronic supportive care.
7	The decision to continue or discontinue CFTR modulator therapy during and after pregnancy should be made in partnership between the CF team and the person with CF.
8	More research and high-quality evidence are needed to characterise maternal and foetal outcomes following CFTR modulator therapy use during pregnancy and breastfeeding.
9	The CF team should work in close partnership with primary care to ensure that people with CF have appropriate support and screening as they grow older.
10	CF teams should be aware of issues of incontinence (even from an early age) and provide support appropriately.
11	The CF team should evaluate for musculoskeletal problems and postural changes to facilitate early and appropriate management.
12	The CF community should work towards minimising global inequities, through collaboration, agreed standards of care and improved access to therapies.
13	The CF team should be aware of and take measures to tackle the inequalities in health outcomes experienced by people with CF from a less well-resourced backgrounds.
14	The CF community should endeavour to act on a micro and macro scale to minimise the impact of providing complex healthcare on the planet, without compromising quality of care.
15	Access to research participation should be equitable.
16	People with CF, from all backgrounds and ages, should be involved in the prioritisation and design of clinical studies, from an early stage.
17	The role of clinical trial networks is to facilitate the delivery of a wide portfolio of commercially sponsored and investigator-led studies, across multiple sites and/or countries.
18	CF registries are instrumental to guide policy and funding, improve quality of care and facilitate research for the benefit of the CF community.

potential. To do so, the CF team should work in an individualised manner that is sensitive to varying needs and fosters a partnership approach [4-6]. With longer life expectancy, new challenges and opportunities are emerging, including larger numbers of parents/grandparents with CF, and planning for a longer working life, retirement, and older age [5,6]. Key life events include diagnosis, starting and changing schools, university, living independently (leaving the family home), working, building a professional career, establishing adult relationships, and possibly starting a family [4,7] (Statement 1).

The psychosocial team plays a role in guiding, educating, and supporting the wider CF team to help people with CF achieve their life goals [3,8]. Psychologists and social workers are key members of the CF team, who should use their specialist skills and knowledge to support people with CF as they navigate through life [4,7,9]. In addition, the psychosocial team may include youth workers or support workers [4,8,9]. Social workers act as a bridge between home and family, healthcare, and social support services to facilitate access to appropriate financial, social or educational support [4]. Youth work is an emerging profession that is increasingly utilised in healthcare in some countries. Youth workers provide a unique focus on holistic advocacy for young people, supporting key transitions around education, work and becoming an adult, in a non-medically focused manner [10].

CF patient associations and charities also have a role in supporting people with CF in their journey by providing peer support, online resources, information on social care and guidance for all stages of life (Supplementary Table 3). Virtual forums and meetings provide an opportunity for people with CF to contribute to group sessions or meetings in a manner that was previously difficult due to the need for measures to avoid cross-infection [11].

2.1. Issues around school and further education

Attending school can be challenging for any child and their family as they adjust to new routines and social constructs [4,8]. On top of these challenges, families of children with CF face additional concerns including repeated delivery of medications, infection control, and missing school to attend CF clinics [4,8]. Resources to support people with CF and their families are available in some countries and centres (Supplementary Table 3), with support from CF teams (for example, members of the team visiting a school or nursery). Effective communication between children with CF, their families, the CF team, and teachers is key to a successful educational journey. This communication should continue and adapt across age ranges, reflecting evolving individual needs [4,8]. Key stress points can be around changing schools, when students try to establish new friendships without being defined by their CF. Changing school can impact adherence to treatments, especially pancreatic enzyme replacement therapy.

CF is regularly used by teachers as an example of Mendelian genetic inheritance in school lessons. Teachers should not use a student with CF as an “illustration” unless the student provides their clear consent. If the student does consent, the teacher should be sensitive, avoid content regarding life expectancy and use up-to-date information.

Transition to adult services may coincide with a move into further education. Young adults with CF should be encouraged to pursue their further education aspirations. This may include a move out of the family home, in which case, it important that support is available and arranged near the college or university they attend. This is a vulnerable time with respect to engaging with treatment regimens and the CF team should work in partnership with young people leaving home to support them pragmatically through what is potentially a challenging period.

2.2. Transitioning to adult life

Transition to adult life is a key developmental stage for all adolescents aged 10–14 years. Rapid changes in physical and sexual development, cognitive maturation, and psychosocial growth impact decision-making and worldview [12,13]. For young people with CF, additional stress is created from challenging symptoms (for example, cough or bowel upset), treatment burden, and questions around reproductive health [14]. Young people with CF should be encouraged to participate in decision-making around health and life choices [11,13].

Discussions about transition to adult CF care should start in the early teenage years. All CF centres should have a structured transition process [11,12,15]. Resources to support this process are increasingly available (Supplementary Table 3) but formal guidance on the structure of transition is limited [11,16]. Satisfaction in the transition process can be increased by effective communication between paediatric and adult teams, joint clinics, shared protocols, and active involvement of the young person [11,13,14]. It is essential that adults with CF are cared for in an appropriate adult clinic by an experienced and specialised adult CF team. The transition to adult care should include preparedness for adult life and not just emerging health needs [6,14].

Travelling for extended periods is a common pursuit; this can pose additional challenges for young adults with CF. The CF team should work to support the young adult, providing advice on aspects of care, including access to drugs and contact points across the globe. Virtual consultations may also enable continued contact with and advice from the CF team at home during travels.

2.3. Sexual and reproductive health

As people with CF transition to adult life, they may seek guidance from their CF team on sexual and reproductive health issues including contraception, fertility, sexually transmitted infections and sexual dysfunction [17]. This information should be provided routinely to all people with CF. CF teams should ensure the availability of appropriate and timely resources and should also consider whether they require additional training to support sexual and reproductive health care needs (see Section 3).

2.4. Employment

People with CF have been successfully employed in a wide variety of fields, pursuing diverse and often challenging careers. Recent data demonstrate significant numbers working either full- or part-time [18]. Global worldwide employment rates for people with CF range between 44 % and 86 % [18]. With current population trends, larger numbers of people with CF will be in paid employment in the future [19-22].

Employment guidance is needed to assist with issues faced by people with CF, including needing to stop work due to illness, altering career choices, duties or pay changes. People with CF may also encounter discrimination in their employment [23].Workplace adjustments, such as reduced hours, alternative rotas, and flexible working (including from home), can help balance health with employment, even in severe disease [23,24]. Complementary to this, social care helps optimise the balance between the professional and private lives of adults with CF.

CF teams can support people with CF to achieve career goals, assist with vocational rehabilitation and obtain reasonable adjustments. Some cases may require referral to public employment services and institutions fighting discrimination. CF patient organisations can provide help through practical information, peer support, advice on social care, and advocacy for more inclusive school/work environments and policies affecting employment for people with CF (Supplementary Table 3).

2.5. Insurance options

Even with current therapeutic advances and population trends, it is more difficult for people with CF to obtain travel, life and other insurance, especially to cover disease-related costs [25]. Social workers and CF patient organisations can guide people with CF to appropriate insurance providers or policies (Supplementary Table 3). If difficulties persist, referral to specialised providers, ombudsman or institutions

fighting discrimination may be required. CF centres, societies and patient organisations can encourage public authorities and insurers to adopt inclusive policies to promote equitable and fair access to insurance coverage for people with CF. Many CF patient organisations also provide contacts on specialised healthcare and social legal advice in case of discrimination.

2.6. Considering retirement

With increased lifespan for many people with CF [5,22,23], the number retiring will increase. Previously, people with CF may not have considered enroling in a pension scheme and this may now leave some with anxiety and stress. They may need guidance on how to achieve an adequate source of income after retirement. CF teams and patient organisations can offer guidance on this, and promote the need for financial planning for younger people with CF. An individualised approach is necessary to account for a heterogeneous population, differing disease trajectories and variation in pension access between countries. Signposting to more specialised public or private services may be necessary to ensure each individual receives appropriate advice for their employment and financial circumstances. Some links to support services for people with CF are included in Supplementary Table 3.

2.7. Respecting values and beliefs

Sarah Mayell, Lorna Allen

The concept of health reflects not just the biological absence of disease but rather a person's ability to attain their vital goals [26]. It is striking that research priorities from the CF community consistently reflect the desire to reduce treatment burden and symptoms [27].

People with CF value recognition from clinical care teams regarding their choices and decisions, and want their "lived expertise" to be acknowledged and considered. Choices and decisions that individuals make around managing treatment burden include weighing up benefits against quality of life and practicalities. Decision-making and discrete choices are more complex than the traditional medical model of adherence.

An individual's beliefs are determined by societal, religious, and cultural influences. These influences are relevant throughout the life course of CF care management, from newborn bloodspot screening (NBS) and genetic diagnosis, through transition to adulthood and advanced disease (Statement 2). Examples of when a person's beliefs or values impact on their CF care include specific medicinal products that may not be acceptable to some because they contain porcine-derived products. Diet content varies between countries and cultures and through personal values. CF teams need to respect and support individual choices, such as a plant-based diet.

Supporting children and young people to understand their CF and the purpose of the treatment regimen they are prescribed can improve self-efficacy and prepare young people for transition to adult services. Young people highlight the importance of communication, collaboration and care focused on their holistic, individual needs [28].

3. Planning a family

Michal Shteinberg, Andrea Gramegna, Peter G Middleton

With improved survival and quality of life, more adults with CF are pursuing parenthood. Guidance regarding parenthood for people with CF includes the 2008 ECFS guidelines on pregnancy in CF [29], 2018 ERS/TSANZ guidelines [30], and 2021 US review and expert recommendations [31]. The multicentre, prospective study Maternal and Foetal Outcomes in the Era of Modulators (MAYFLOWERS) is planned to provide evidence to support decisions regarding pregnancy and breastfeeding in women with CF on CFTR modulator therapy [32].

3.1. Fertility of people with CF

The CF team should work with the family to introduce the concept of subfertility to young people with CF in a sensitive manner (Statement 3). Most men with CF face infertility due to congenital bilateral absence of vas deferens (CBAVD), and around 35 % of women with CF have subfertility of multifactorial aetiology [33]. Most men with CF can achieve parenthood using assisted reproductive technologies (ART). For men with CF, ART involves surgically extracting sperm from the testes, which can be undertaken under local or general anaesthesia. Women with CF considering becoming pregnant should, where possible, optimise factors associated with subfertility, including nutritional status. For women with CF requiring ART, methods vary from ovulation induction (OI) alone, to OI combined with intrauterine insemination or in vitro fertilization. In most instances, retrieval of oocytes is performed under sedation with minimal risk to the person with CF, even with advanced lung disease. The CF team should provide clear, age-appropriate information about ART to people with CF (Statement 4).

Reports of increased rates of pregnancies after commencing CFTR modulator therapy suggest that fertility in women may be improved with this intervention [34]. This increase may relate to improved health status and the direct effects of CFTR modulator therapy on uterine and cervical physiology [35]. When eligibility and access allow, a period on CFTR modulator therapy prior to starting ART may be considered for women considering pregnancy. Additionally, women with CF choosing to avoid pregnancy should be given appropriate contraceptive advice.

3.2. Preparing for pregnancy

The CF team should support women with CF and their partners in their reproductive choice. They should offer emotional support and practical comprehensive advice on planning a pregnancy. Carrier testing is recommended for partners of women with CF and genetic counselling should be available to discuss the risk of CF in their children [1,31]. In the case of a CF carrier partner, different reproductive options (including gamete donation, preimplantation diagnosis or prenatal diagnosis) should be discussed according to local guidelines and resources. Standard prenatal screening and monitoring during pregnancy should not be overlooked in pregnant women with CF.

Low lung function (percent predicted forced expiratory volume in one second, ppFEV$_1$ <50), multi-resistant respiratory pathogens, poor nutritional status and inadequate diabetic control are associated with higher risk of maternal and neonatal morbidity and mortality [31]. Identifying and addressing risk factors is beneficial for maternal and infant outcomes and should be considered a key part of pregnancy preparation [36] (Statement 5).

The effects of pregnancy on maternal health should be openly discussed, including warning of the need for increased clinical monitoring and treatment of complications. In preparation for pregnancy, current medications must be reviewed and adjusted appropriately, with support from the CF pharmacist.

3.3. Supporting pregnancy

Once a woman with CF becomes pregnant, she should be monitored by both the CF and obstetric teams every month in trimesters one and two, then every one to two weeks during the third trimester [29,30]. An oral glucose tolerance test (OGTT) should be undertaken to screen for glucose intolerance (gestational diabetes) at confirmation of the pregnancy and at 20 weeks, with earlier assessment if there are clinical concerns or risk factors. Women with CF should be warned that the risk of gestational diabetes can be up to 30 %, educated about symptoms (although gestational diabetes is often asymptomatic) and reminded to promptly report any suggestive symptoms [37] (Statement 6).

Physiotherapy routines, including exercise, should be maintained throughout pregnancy, with close support from the CF physiotherapist

and adaptation of techniques as necessary. Pelvic floor exercises to minimise the risk of pelvic dysfunction during and after pregnancy should be encouraged [38]. Nutritional advice should aim to maintain the normal pregnancy-related weight gain of 7–11 kg. The woman with CF and the obstetric team should work in partnership to optimise care for the mother and child throughout the pregnancy [31]. In addition, psychological support needs to be provided to address anxieties and concerns that may arise. As with all new mothers, the risk of post-partum depression should be considered and screened for as per national guidance. Medications should be reviewed regularly and discontinued or adjusted as needed.

3.4. Raising children and grandchildren

The usual challenges of raising children and grandchildren (sleep deprivation, financial stress etc.) are intensified for people with CF, who also need to maintain their treatment regimens and well-being. It is not surprising that some parents with CF may neglect their own well-being to focus on their children. Health decline has been reported in males and females with CF in the first year of parenthood [39]. Therefore, it is important that a balance is achieved. Support from family and the CF team is key during this period. Pragmatic solutions are required to ensure that the person with CF can enjoy their children as they grow and develop. The CF team should support parents and grandparents in providing age-appropriate information to children to inform them about CF and how this impacts on their family.

3.5. Variant-specific therapy (CFTR modulator therapy) during and after pregnancy

Jennifer Taylor-Cousar, Jane Davies, Imogen Felton, Peter Middleton

3.5.1. Impact of variant-specific therapy (VST) on fertility in people with CF

The expanding use of VST has been associated with a significant increase in rates of pregnancy in women with CF [35,40,41]. Because unplanned pregnancies are associated with worse foetal outcomes [42], clinician-patient discussions regarding contraception are important, especially on initiation of VST. Most men with CF have CBAVD from birth and VST is not expected to address this cause of infertility, but more research is needed [43].

3.5.2. Advice to women with CF considering pregnancy

Previous patient registry data demonstrated no difference in survival for women with CF who had pregnancies compared with those who did not [44]. However pregnancies in women with CF have more complications (e.g. gestational diabetes, need for caesarean section, preterm birth and congenital anomalies) [37,45]. The likelihood of maternal and infant complications is historically higher for women with more severe disease [46,47], though VST may improve outcomes in this group.

3.5.3. The potential implications of VST exposure in utero

With maternal VST, while components are found in foetal circulation in animals [48-51] and humans [52,53], clinical data have largely been reassuring, although cases with lens opacities have been reported [54-56]. Cessation of VST can cause acute health decline [57], therefore care providers and women with CF must balance potential risks of VST cessation with theoretical risks to the foetus. Although the licence of CFTR modulator therapies precludes use during pregnancy, shared decision-making between the CF team and the patient may result in informed consent to continue VST off label (Statement 7).

Following *in utero* VST exposure, a case report described an infant with CF with normal immunoreactive trypsinogen (IRT) at birth. When reviewing results of NBS, teams should be alert to the possibility of false negative NBS results [58-60]. Further research is required to determine whether VST exposure before or during pregnancy carries any longer-term health risks for the child [32] (Statement 8).

As VST crosses the placenta and is present in breast milk, VST-exposed infants should be referred to a paediatrician for monitoring, including interval liver function test monitoring, genetic testing and ophthalmic evaluation [48-51,61].

4. Growing older with CF

Pierre-Régis Burgel, Carsten Schwartz, Ulrika Lindberg

4.1. The changing CF demographic

In the United States, median survival for people with CF has improved from 36.3 years (95 % CI, 35.1–37.9) in 2006 to 56.6 years (95 % CI, 54.7–58.1) in 2022 [62]. Much of the increase in survival was achieved before the introduction of elexacaftor-tezacaftor-ivacaftor (ETI) and modelling suggests further significant improvement in survival will be seen following access to this therapy in the youngest age groups [22]. Increased survival is observed in conjunction with improved lung function and increase in body mass index [40,63-67]. These two key CF outcomes vary significantly between countries, partly reflecting differing access to healthcare and medical treatment [64,65,68,69]. Due to therapeutic advances, the number of adults with CF has increased and now exceeds the number of children with CF in many countries. This success creates the challenge of implementing appropriate care for adults with CF, requiring the development and expansion of adult care centres [63].

4.2. Specific health issues arising in older age for people with CF

New or more health issues may arise in older people with CF. Screening for age-related comorbidities needs to be systematically established for people with CF, even though many are clinically very stable, especially those on CFTR modulator therapy [22,70]. New and increasing challenges with an ageing CF population might include complications such as arthropathy, obesity, and hypertension [40,63,67,71-74]. Working constructively with primary care is essential to ensure high-quality care and management (Statement 9).

4.3. Maintaining health in older age with CF

To maintain health throughout life, screening for specific diseases is recommended [74-77]. An earlier paper in this series addresses CF-specific health issues such as CF-related diabetes (CFRD), CF-related liver disease, CF-related bone disease, stones and other renal issues, intestinal obstruction and cancer [3]. There is a balance to achieve between monitoring to enable disease stability and the burden of diagnostics. Point of care home monitoring and digital communications could reduce clinic visits and travelling while enabling early intervention [78-81].

4.4. Supporting older people with CF emotionally and practically

In addition to CF-specific issues, people with CF will experience the usual challenges of growing older, which may include caring responsibilities for elderly relatives and the need for multiple medications in addition to those required for CF.

Little is known about social isolation and support in the older CF population. Reduced physical and mental health are associated with reduced social functioning and social support [82-84]. A significant number of adults with CF are now working in a full- or part-time jobs. People with CF may be well integrated within society, but there is still a potential risk of social isolation for some. Innovative concepts are needed to support older people with CF, socially and mentally.

Overall, improved health in people with CF allows the community to look to a positive future. To continue to provide good care, more adult

CF centres are needed as well as an awareness of a changing spectrum of disease manifestations with appropriate screening and support for an ageing CF population. The CF team should work in partnership with primary care to ensure people with CF can access all available screening, including for hearing and vision (Statement 9). CF teams should continue to support the mental and emotional well-being of people with CF as they grow older, as described in an earlier paper in this series [3].

4.5. Pelvic health

Victoria Kendall, Catherine Brown

Pelvic health related issues are prevalent in people with CF. With improved health, fertility and life expectancy, more people with CF are having children, undergoing menopause, and reaching old age. Together with CFRD, these are common risk factors for pelvic health issues [3].

Urinary incontinence is recognised in both children and adults with CF, with prevalence ranging from 5 to 15 % for men and 30–76 % for women [85]. Under-reporting is common and assessment should include evaluation of urinary frequency and urinary urgency alongside urinary incontinence [86] (Statement 10). For adults, evaluation may include a 3-day bladder diary and assessment of caffeine and alcohol intake. Annual evaluation is recommended for adults including use of a validated screening tool. Urinary incontinence may have detrimental effect on ability to perform airway clearance, spirometry and exercise, and advice should be given on positioning and posture [85]. Management includes pelvic floor muscle training and lifestyle advice. Referral to a pelvic health specialist is appropriate if symptoms persist despite these interventions. CF teams should also be sensitive to and enquire around bowel dysfunction [3] and faecal incontinence, to support appropriate management by the CF team.

4.6. Menopause

There is limited information available regarding the age at which women with CF experience menopausal symptoms. One study suggests earlier onset of menopause compared to the general population, with half reporting concurrent worsening of CF symptoms [87,88].

Menopausal symptoms (e.g. night sweats and joint pain) may be mistakenly attributed to exacerbation of CF. Close partnership working between the CF team and primary care is important for women with CF over the age of 40 years, and recording symptoms may help clarify the role of menopause. Further investigation of the impact of menopausal reduction in bone mineral density is required in this population already at increased risk of osteoporosis. CF teams should consider the menopausal reduction in bone mineral density, in addition to the characterised risk of CF bone disease [3,89]. Women with CF should be informed of the benefits and potential risks of hormone replacement therapy.

4.7. Posture and musculoskeletal health

Julia Taylor, Catherine Brown

Musculoskeletal (MSK) problems specific to CF occur in addition to those of the general age-matched population. With increasing life expectancy, MSK conditions such as chronic MSK pain, osteoporosis and fragility fracture, osteoarthritis and calcific tendonitis of shoulder (common in people with diabetes) will present more frequently and will need to be managed appropriately [90]. The CF team should evaluate for MSK problems and postural changes to facilitate early and appropriate management (Statement 11).

4.7.1. MSK pain

MSK pain is a problem for both children and adults with CF and impacts on quality of life and ability to successfully undertake treatment [91,92]. Pain is often under-reported by people with CF, under-recognised and sub-optimally managed [92,93]. The estimated incidence of MSK pain ranges from 12 to 65 % in people with CF [92,93] and back pain is reported to be a problem for up to 79 % of adults with CF [69,92].

In the CF population, there is evidence of fracture under-reporting [94], and up to 86 % of vertebral fractures may be asymptomatic [95].

4.7.2. Postural problems

Spinal pain is associated with postural changes in people with CF [96]. Altered posture results in significant morbidity, pain, poor body image, low mood, and reduced self-confidence, which all impact quality of life [97,98]. Increased thoracic kyphosis is a common postural change in people with CF [98] and is thought to occur as a result of altered respiratory mechanics (altered neuromuscular control, increased work of breathing, hyperinflation and coughing), muscle weakness [99] and thoracic fracture secondary to low bone mineral density [97,100-104].

Postural changes have been reported in children with CF [102] but thoracic kyphosis is now becoming less common in children and adolescents [105]. Standard approaches to evaluating thoracic kyphosis such as measuring the Cobb angle on an x-ray have limitations of cost and exposure of the patient to radiation, and may not fully appreciate the full contour of the thoracic spine [106]. MSK screening tools have been developed that aim to proactively identify problems, facilitate early intervention and minimise secondary MSK impairments [107, 108]. A thoracic spine movement screen and validated pain questionnaire allows clinicians to select the appropriate care pathway for optimal patient management [108].

MSK physiotherapy treatment should incorporate manual therapy, education on postural awareness, muscle strengthening and promote general exercise to help treat and prevent postural changes and non-inflammatory MSK pain, in both adults and children with CF [98,102, 109,110]. People with CF should be aware that they can seek advice and treatment from the CF team for posture, pain and MSK issues, with referral for specialist support if needed. When MSK problems or acute injuries occur, prompt assessment and treatment are essential to help maintain quality of life and enable a timely return to daily activities, sports and exercise [98].

4.7.3. CF-associated arthritis

Joint pain in CF requires a thorough diagnostic work-up. While much of this pain is mechanical in nature, it is reported that inflammatory arthritis is present in 5–10 % of people with CF, presenting with joint pain and swelling, and early morning stiffness, lasting over 30 min [111-113].

There is limited evidence to guide treatment of CF-associated arthritis (CFA) and hypertrophic pulmonary osteoarthropathy (HPOA) affecting people with CF [69]. A diagnosis of CFA requires evidence of an inflammatory arthritis with no articular infection or periosteal change (HPOA) [72] [69,114]. Synovitis with small effusion, detected by ultrasound, is also recognised [72]. Referral to a rheumatology specialist is recommended to confirm the inflammatory nature of the joint symptoms, exclude other conditions (such as rheumatoid arthritis), consider treatment options and ensure optimal patient care [69].

5. How inequalities and inequities impact people with CF

5.1. Addressing global inequities

Samia Hamouda, Dorota Sands, Milan Macek

Significant global inequality and inequity exist in CF, a condition that is more common in the white population (generally with a higher frequency of the F508del variant) compared to African and Asian populations. There is an increased prevalence (percentage of the population living with CF) in high compared to low income countries [115], although this comparison may be biased by underdiagnosis and reduced survival in low income countries.

Achieving a clear and timely diagnosis is challenging in countries

where prevalence of CF is believed to be low. Accessing high-quality care is challenging, not only through lack of resources, but also due to a lack of awareness, knowledge and cultural factors, both in healthcare professionals and the general public. In some countries, such as in Central or South America [116], Morocco, and India, some healthcare professionals incorrectly assume that CF does not affect the local population [115]. Therefore, the first challenge is to improve CF awareness amongst healthcare professionals and policymakers in countries thought to have a low prevalence of CF [117].

With advances in technology, extensive genetic analysis on dried bloodspots is now possible. This may facilitate a genetic diagnosis in low and middle-income countries (LMIC) but the potential to identify non-CF causing variants needs to be appreciated.

NBS for CF may help identify additional cases, establish better estimates of prevalence, and facilitate entry into care pathways, but is challenging in populations with a low F508del prevalence. In low-incidence/low prevalence populations, NBS may lead to the recognition of an increased proportion of unclear cases [118], requiring clear communication and follow-up in under-resourced healthcare services. It is difficult to justify to policymakers the benefits of NBS for CF in countries with a large population but low CF prevalence, for example, Egypt, India, and South Africa.

Achieving investment in multidisciplinary specialist care can be challenging and sometimes impossible. Limited resource is not the only factor; others include a lack of framework or culture of multidisciplinary team work, a disconnected health service, and insufficient specialist healthcare providers, sometimes due to emigration of well-trained staff to more developed health services abroad [119]. Global partnerships between established CF centres and emerging services can foster training, encourage leaders, introduce national registries, and facilitate the donation of equipment, e.g. for sweat testing. Where good leadership exists in emerging services it is important to support these professionals with time and resources. Even in countries where multidisciplinary team care is successfully implemented, some well-performing CF centres are not recognised by health authorities, with restricted financial resources as a consequence. This resource limitation is the case in some middle-income Eastern European countries [120,121].

The biggest challenge in resolving global inequities remains the availability of funds allocated to CF, especially to pay for therapies such as inhaled antibiotic therapy and CFTR modulator therapy. LMICs may struggle to access high-cost drugs. A global drive for access to high-cost drugs is important for all medical conditions; CF clearly illustrates the impact of this global inequity [122]. This issue may be further exacerbated if gene-based therapies are introduced for people with CF, as these will have high production costs.

Generic formulations of various correctors and potentiators used in CFTR modulator therapy combinations were approved by the Argentine Food and Drug Regulatory Agency [123]. This approval was possible because the original formulations were not patent protected in Argentina. The cost of these formulations in Argentina is still significant, but approximately a third of that of the original patented formulation [123]. Producing alternative CFTR modulator therapies in countries outside exclusivity patent agreements may facilitate access, but such production may still be at a significant cost. It is important that as exclusivity patents expire, generic products are produced to improve access worldwide. Barriers to accessing generic products must not be created.

CF services in LMICs need to ensure full genetic characterisation of people with CF to evaluate eligibility for CFTR modulator therapy. International initiatives and collaboration between countries can help to overcome these barriers, but more support is needed to ensure both availability and applicability of international databases (e.g. CFTR2) to non-European populations [123,124].

Addressing CF inequities is a global responsibility and, if no action is taken, these inequities will likely worsen as new high cost therapies become available, such as gene therapy. The established CF community needs to support CF teams and inspire leaders to establish high-quality care across the globe, including access to high-cost drugs (Statement 12).

5.2. CF health inequalities from poverty

Michael Schechter, Lidia Salvatori, David Taylor-Robinson

In addition to global inequalities, there are stark differences in outcomes for people with CF resulting from the complex interplay of multiple dimensions of social disadvantage, including socioeconomic status, race, ethnicity, and gender. These have been reported from within individual countries and across country of residence. These inequalities become evident early in life, whereby disadvantaged groups have lower birth weight, worse nutritional status, more pulmonary exacerbations, worse health related quality of life, lower lung function and worse survival throughout life [125-128].

CF health inequalities are caused by differential exposure to determinants such as lack of material resources to maintain health, harmful environmental exposures, and reduced access to healthcare and protective conditions that help promote and maintain good health. Specific drivers include limited resources and policies (social, economic and health), unfavourable housing and living conditions, indoor and outdoor pollution, limitations in food access, unhealthy behaviours (for example, smoking and a poor diet) and increased stress affecting parental caregiving and mental health [129].

Addressing health inequalities in CF requires public health action at a higher societal level of policy. In parallel, more individually focused actions to support the health of people with CF living in disadvantaged circumstances are needed (Statement 13). Health risks and problems tend to cluster amongst individuals who are already vulnerable because of economic conditions and other structural factors. Routine screening for adverse circumstances, especially food insecurity, can be effective, particularly when the screening is backed up by referrals to available resources to meet patient needs [130]. Some interventions to address clustered risk factors lie within the conventional boundaries of clinical care and are familiar to healthcare providers. Such interventions, which should be consistently applied, include augmented health education to improve adherence and disease self-management, mental health screening, and drug, alcohol and tobacco cessation counselling [131].

Some health system structural characteristics need to be addressed. CF NBS protocols can be designed to be more inclusive and not discriminative to non-European populations [132]. Many lung transplantation policies, including the use of race-based spirometry equations [133], disadvantage minority, marginalised and socioeconomically vulnerable patients. Clinical trials that recruit convenience samples of participants tend to under-represent minority and socially disadvantaged patients [134]. Measures are required to make CF life-saving treatments more affordable and accessible to all patients, regardless of their socioeconomic background or geographical location.

Finally, efforts to reduce health inequalities in CF require advocacy to reduce the consequences of economic instability, support educational and employment opportunities, address unequal access to quality education and healthcare, and mitigate adverse neighbourhood environmental exposures [135].

6. CF and the changing planet

Sarah Mayell, Lidia Salvatori, Oren Pearlsman, Thomas Daniels

Chronic health conditions such as CF heighten vulnerability to the effects of climate change. In addition, the healthcare industry itself has a significant climate footprint, accounting for 4.4 % of all global net emissions [136,137]. The responsibility for reducing emissions does not fall on people with CF and their families any more than the general population but must be integrated into healthcare settings with support and responsibility from the pharmaceutical industry.

6.1. How planetary health impacts people with CF

6.1.1. Air quality

There is no safe level of air pollution. Adverse effects of poor air quality on health have been demonstrated across all populations, and people with respiratory diseases are more vulnerable [138]. Complex relationships between air pollution, climate change and allergens impact respiratory allergic disease. Poor air quality adversely affects lung function and increases pulmonary exacerbations in CF [139].

Long term exposure to poor air quality leads to higher rates of cardiovascular disease and malignancy [138] which are increasingly relevant as the CF population becomes older [137].

6.1.2. Climate

Climate change brings changes in humidity and extreme weather events. Warmer climate and increased humidity are related to lower FEV_1 in people with CF, changes in the CF microbiome and changes in the respiratory infection profile [140].

Limited evidence is available on the disproportionate effect of extreme weather events on people with CF, but adverse effects are documented in other respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) [138]. In people with CF, extreme heat may cause specific difficulties due to dehydration and salt loss, and potentially increase the risk of distal intestinal obstructive syndrome (DIOS) [3,141].

The exacerbation of inequalities caused by climate change is likely to impact people with CF, whose health is already demonstrably affected by socioeconomic factors [122,127].

6.2. How healthcare impacts the planet

All human activities, including healthcare, impact planetary ecosystems. 71 % of healthcare emissions arise from supply chains and 29 % from direct sources at the organisational level. The pharmaceutical industry contributes 12 % of healthcare emissions [137].

The environmental impact of healthcare cannot be attributed to individuals with chronic conditions, and neither can they hold, or perceive, responsibility. Healthcare can and must reduce its impact on the planet, while continuing to deliver high-quality care. This balance is the responsibility of policymakers, politicians, and the pharmaceutical industry. Healthcare workers must also be sensitive to their individual responsibility to promote sustainability (Statement 14).

Awareness of healthcare environmental impact may be low amongst the wider CF community and may not be considered a high priority [142]. Research on the views of patients or healthcare professionals and education is required to help promote change.

6.2.1. Mitigation

An effective way to minimise the environmental impact of healthcare is to provide universal high-quality care, keeping individuals well and reducing the need for hospital admission. Achieving these goals helps people with CF to make choices to minimise their environmental footprint.

Interventions to reduce the environmental impact of healthcare frequently benefit health at both the individual and population levels. Improving medicine usage reduces waste and promotes adherence, reducing carbon emissions and air pollutants [143]. Virtual consultations can reduce travel, but quality of care needs to be sustained as outlined in the second paper of this series [2].

6.2.2. Reducing admissions and waste

Waste reduction begins at source and continues throughout the supply chain. Sustainable medication production and supply requires renewable energy manufacturing, ecological packaging, optimal stock management by distributors, and appropriate prescribing and dispensing. Shared decision-making and patient-tailored interventions are likely to be most successful in reducing medication wastage [144]. Pressurised metered dose inhalers (pMDIs) currently contain various greenhouse gases. The type of inhaler device used varies greatly across Europe, suggesting scope for altering practice and reducing emissions [145]. People with CF, including children, should be involved in decisions on devices, focusing on the ability to regularly use devices correctly.

Knowledge of local recycling initiatives by healthcare teams is crucial. Large frequency packaging (e.g. blister packs) and high impact waste (e.g. pMDIs) represent potential targets for recycling and correct disposal.

The climate emergency coincides with major changes in CF care due to widespread uptake of CFTR modulator therapy, and changes in models of care necessitated by the Covid-19 pandemic. Virtual consultations, remote monitoring and reduced frequency of clinical review could potentially reduce travel-associated emissions. While environmental considerations are important, these should not drive changes that compromise the quality of care. For example, attendance at meetings is important for healthcare professionals to maintain professional development, but CF teams should reflect on and minimise air travel if possible.

6.2.3. Healthcare teams as advocates

CF teams are well-placed to raise awareness of environmental issues and advocate for change. The pharmaceutical and healthcare industries, encouraged by healthcare professionals, should strive to reduce and mitigate against environmental impact. Research strategies should explore patient views around the environmental impact of health. Consideration of healthcare emissions and waste should be part of daily practice and reflected in guidelines to support people with CF and reduce the environmental impact of care.

7. Engaging with CF research

7.1. Stakeholder engagement to direct research priorities

Alan Smyth, Sylvia Hafkemeyer

Research priorities have traditionally been driven by the academic interests of investigators, drug development pathways and the financial considerations of the pharmaceutical industry. In recent years, clinicians and people with CF have increasingly worked together with other stakeholders to agree on research priorities and attract funding to address these priorities. Cystic Fibrosis Europe (CFE), the federation of European patient organisations in Europe, is committed to highlighting the patient perspective for any developments to improve care. The CFE has established a CF community advisory board (CAB) and the patient organisation research group (PORG) to stimulate CF research in line with the needs and priorities of the CF community. This commitment is extended to basic science as well as more patient facing research, as illustrated by an annual patient-led symposium at the ECFS Basic Science Meeting.

A survey on research priorities, performed by CFE in 2021 within the member organisations, suggested discrepant perspectives about CF research between Eastern and Western European countries. In the UK, the James Lind Alliance (JLA) is a conduit for bringing the CF community together to agree research priorities. The JLA initiative for CF produced a top 10 list of research priorities [146] and the group has subsequently refreshed this list, following increased access to CFTR modulator therapy [27]. At the time of the first JLA exercise, only one third of clinical trials conducted mapped onto a JLA priority [147]. In the refreshed JLA CF priorities 45 % of 1400 participants were from the UK and almost 40 % from other parts of Europe, with contributions from North American and Australasia – indicating global reach [27]. This was facilitated through the support of CFE and patient organisations who translated and promoted the surveys. The UK patient organisation has responded to these priorities by providing over £10 million of research

funding over 5 years, and importantly this has directly resulted in a further allocation of £13 million from government funds [148]. This example illustrates how patient organisations can use patient priorities to leverage extra funding from governments.

In other parts of the world, different approaches to patient engagement have been used. The US CF Foundation is committed to increasing patient engagement in research and has surveyed patients and families to identify under-represented research topics that are of importance to them [149].

In the Netherlands, a collaboration between people with CF, parents, researchers and clinicians was established, in which lay participants received online interactive training in research [150]. The process led to a top five list of research themes. These were ultimately refined into one translational programme called HIT-CF, which inspired the development of the EU-funded project HIT-CF Europe, which aims to identify new therapies for the basic defect of CF using intestinal organoid technology (www.hitcf.org).

Training lay participants in research issues seems sensible and may lead to more meaningful engagement, but may make them less representative of lay views. A prioritisation exercise in Italy showed that different topics were prioritised by lay participants who had research training compared to those who received no training [151]. Indeed, there may be different perspectives driven by the heterogeneous therapy access in European countries. Therefore there are probably complementary roles for both wider engagement via online surveys and more detailed discussions with smaller numbers of lay people who have received research training.

In a rapidly changing research environment, engagement with the CF community is imperative and there is good evidence of significant strides forward in this regard over the past decade, to place people with CF and their families at the centre of research initiatives.

7.2. Facilitating involvement in research

Gwyneth Davies, Damian Downey, Barry Plant

The contribution of people with CF to research goes beyond participation, encompassing patient and public involvement (PPI) through the lifecycle of research. There is a scarcity of studies examining the lived experience of the CF community to research. Often studies focus on the patient/caregiver research priorities [146,151]. Where patient/-caregiver perspectives are assessed, the majority of people with CF and caregivers express satisfaction with the way research teams handled initial stages of their participation, however, reporting of results to participants was suboptimal [152,153] and insufficient communication around the consent process and the need for plainer language/brevity were highlighted as issues [153].

Research about CF should aim to be representative of the diversity of people with CF (Statement 15). Suspicion or mistrust of research is more prevalent in minority ethnic populations with chronic disease [154]. It is also important for children with CF to be included in all stages of research to improve disease understanding and to benefit all children with CF [155]. Improving equitable access to clinical trials and ensuring informed consent with clear communication is vital across all groups.

There may be barriers to research participation. Clinical research protocols often include eligibility restrictions relating to age and comorbidities. These restrictions may impact generalizability of findings to the overall population. Reasons for under-representation of certain groups may relate to geography or patient characteristics. Research teams should consider and overcome biases that reduce participation, for example, ethnicity and financial inaccessibility especially for those living more remotely [153,156].

Participating in clinical trials can be burdensome, which may limit equitable opportunity for participation. The ECFS Clinical Trials Network (ECFS-CTN) attempts to minimise burden by including the views of patient and family reviewers in protocol review of clinical trials to be conducted in Europe. Ineligibility criteria should be appropriate, informed by outcomes measured and the phase of study. Efforts should be made to broaden participation where appropriate, with a roadmap for timely evaluation in, for example, younger age groups. Commercial studies are compelled by regulators to incorporate plans for paediatric studies in their programme.

National and international clinical trial networks can work closely together to facilitate a broad portfolio of clinical trials and engage with key stakeholders, including the CF community, early and often as programmes develop [157] (Statements 16 and 17).

To ensure inclusivity and equity of access, advocacy is necessary to expand clinical trials to individuals in LMICs, many of whom are affected by a lack of access to or eligibility for CFTR modulators or have yet to be diagnosed [115,157].

Increased racial and ethnic diversity in trial leadership and research teams will also be essential to enable trial designs that will be inclusive of individuals who have been disproportionately excluded from previous research [157].

7.3. Registries to drive quality improvement

Gwyneth Davies, Egil Bakkeheim

CF registries are a key resource for the CF community, providing a powerful tool for quality improvement and research. Registries collect data into a safe repository from consenting people with CF. The European CF Patient Registry (ECFSPR) collates data from over 54,000 people with CF from 40 countries in Europe (approximately 75 % of available European countries, as defined by the WHO). Patient data are recorded via transfer from established national CF registries or from individual submissions from CF centres in countries where no national registry exists [67]. Annual reports from registries can summarise population-level demographics and health data such as airway microbiology, lung function, nutritional status, treatment data and survival predictions. These reports should be available and accessible to people with CF as well as the clinical and research community.

Registry data have several strengths, including large numbers of individuals, high rates of population coverage, the ability to rapidly respond to emergencies such as the global Covid-19 pandemic [158,159], and the opportunity for longitudinal follow-up [160]. Examples of research involving registry data include projecting changes in population demographics [161,162], predicting clinical outcomes, health technology appraisals and post-authorisation safety studies. Research questions may be addressed within registries that are not feasible within randomised clinical trials (RCTs) or have not yet been conducted [163]. CF registries may also be harnessed to support clinical trial feasibility (e.g. number of potentially eligible participants according to a specific genotype) and host innovative pragmatic registry-based RCTs (for example, the CF START and CF STORM trials hosted on the UK CF Registry).

Data quality and governance are key, with focus on adequate design, good maintenance, internal quality control mechanisms and long-term sustainability on a robust platform [164,165]. International comparisons and linkage of registry data may help understand healthcare system-level impacts on outcomes [164,166]. Variation in data definitions (as well as access to medicines and underlying health care systems/standards of care) may exist between CF registries, which should be considered if comparisons are intended. Global collaboration between registries to report acute outcomes during the Covid-19 pandemic has advanced efforts in data harmonisation [167]. Historically, there has been a lack of recording of patient reported outcomes, but a number of registries are now addressing this.

CF registries across the globe have been essential in driving forward the quality of CF care. High quality registry data remain key to understanding present and future CF epidemiology for the benefit of all people living with CF and their clinical teams (Statement 18).

8. Conclusion

This paper is the final of a series updating standards for the care of people with CF. That this paper "Planning a longer life" was considered necessary highlights how much CF care has progressed over the past decade. Several factors underpin this progress, most notably increased accessibility to CFTR modulator therapy for many people with CF.

As the landscape for CF changes, so do the hopes and aspirations of people with CF and their families. This paper reflects the need to consider people with CF not as a "problem" to be solved, but as a success, a potential and a voice to be heard. People with CF and the wider CF community have driven this approach, reflecting many of the topics covered in this final paper. This exercise has involved wide stakeholder engagement and listening to the community. People with CF are keen to drive research priorities and be involved in all stages of research. People with CF want healthcare professionals to respect them as individuals and consider the impact of our actions on the world around us.

Navigating life presents challenges to all, but for people with CF these challenges are heightened and complex. In this paper we follow the CF journey through many stages. We highlight the concerns and life moments that impact people with CF, events that the CF team should consider and aim to support, including the challenges around having a family.

The four papers that constitute this exercise concern the care of all people with CF. We appreciate that the CF population is heterogeneous and whilst "planning for a longer life" is a worthy aspiration for many, it is a less realistic possibility for some. We are sensitive to this but feel that the messages contained within this paper are relevant and helpful to all people with CF and the teams around them.

The ECFS will continue to update standards for the care of people with CF, and an urgent priority will be the translation of these standards into practice. Future work will explore models of care and extensive engagement with people with CF and their families will be at the core of that process. It is important that the CF community contributes significantly to the new framework for care.

The world of CF and the life of a person with CF has come a long way, but there is still much to do. A significant cohort of people with CF are unable to access CFTR modulator therapy or are not eligible. These people need access to modulators or, if ineligible, alternative therapeutic interventions to correct the underlying molecular defect. Much work, outside the scope of this exercise, is underway to identify feasible and efficacious approaches. These interventions will not only benefit people who are not eligible for modulator therapy but will likely provide further improvement in outcomes for those established on modulator therapy. Implementation of modulator therapy has not been the end of the CF journey but represents a new journey for many.

People with CF and their care teams must embrace the updated standards outlined in these four papers to enjoy the full potential for a healthier life.

Author credit

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 skills to produce a consistent document.

Declaration of competing interest

The authors had no declarations of interest in relation to the current work. Declarations of interest for each author outside the current work are summarised in Supplementary Table 4.

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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.2024.05.007.

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