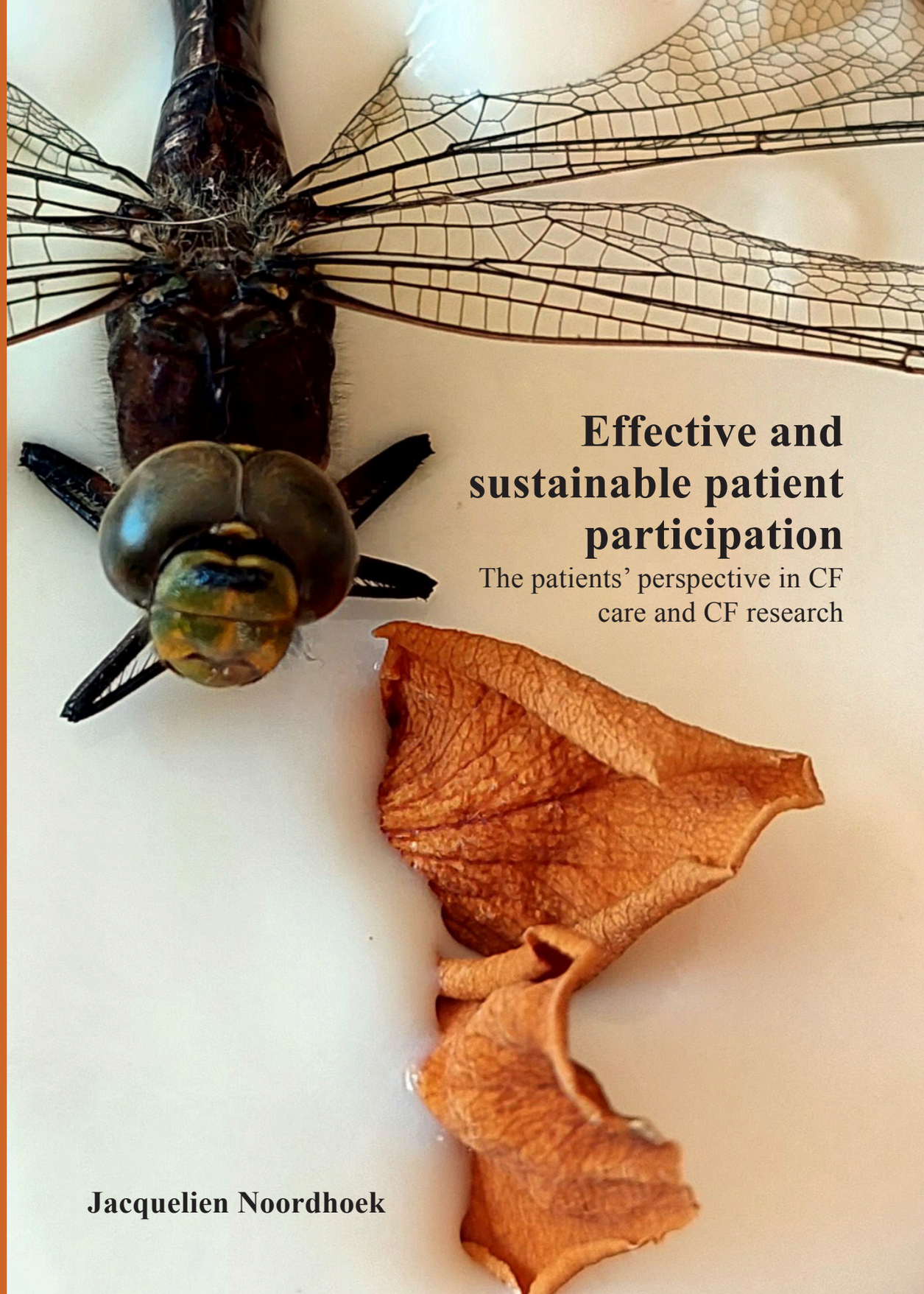
Effective and sustainable patient participation
The patients' perspective in CF care and CF research

Jacquelien Noordhoek



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Chapter One

Introduction

Introduction

Patients are the end users of research and development processes, as well as of scientific research, regulatory procedures, and guidelines for diagnostics and care of their disease. Their role and the added value of their involvement in this area becomes more acknowledged. Although the value of including patients in any of these area's has been demonstrated more frequently, the desire for evidence on their impact continues [1]. Working from the patients' perspective, i.e. taking their perspective into account, is sometimes seen as a revolution, predicating statements like 'partnership with patients should be taken seriously' [2]. In order to bridge the gap between the needs of users, patient and public involvement (PPI) is increasingly fostered in research and health care worldwide [3].

Among rare diseases, Cystic Fibrosis (CF) is often described as a model disease. Worldwide research resulted in breakthroughs in curative treatment, a process that is still going on [4]. Big patient organizations like the CF Foundation in the US (CFF), have an important share in the realization of these breakthroughs.

It is important to evaluate the patient organization's impact with regard to patient participation. The CF community (people with CF and parents of children with CF, clinicians, paramedics and researchers) is very well organized and is working together on a national, European and global level.

This thesis focuses on the impact of patient participation, specifically based on the work of the NCFS (Dutch CF Foundation).

There are 283 patient organizations in The Netherlands [5]. They represent people with a specific disease, thereby focusing on advocacy, defending interests (like access to new drugs or quality of care), organizing contact between people with rare or chronic diseases and providing patients and their families with information with regard to diagnostics and treatment of the disease. The Dutch CF Foundation is an example of such an organization. Like many other Dutch patient organizations, it has been around for over 50 years. The way these organizations operate, differs widely. Some are working with volunteers only, where others are employing staff with specific expertise in business administration, fundraising, policy development, scientific research, data processing and communication. Many of these organizations can lean on the support of volunteers, often trained in specific tasks, like reviewing scientific projects from the perspective of the patient or fundraising. The work of organizations like the Dutch CF Foundation, the impact they have, changed over time and varies per organization [6].

Besides patient organizations, in The Netherlands so called health care funds are known, traditionally focusing on fundraising for scientific disease-specific research. The Dutch CF Foundation is an example of one of the few cross-overs, because it integrates the work of a traditional patient organization and the work of a health care fund for about 20 years. Initially the Dutch CF Foundation focused on patient advocacy, the provision of disease related information and education, and provision of contact services for people with CF. Nowadays

the organization has a central role in the development of a quality of care assessment program, is setting the research agenda from the patients' perspective and is financially supporting scientific research. The Dutch CF Foundation is also chairing, coordinating and financing the Dutch CF Registry and organizes national scientific accredited symposia for professional healthcare workers in CF centers.

By describing in retrospective how the work of the Dutch CF Foundation had and still has an impact on the (inter-) national research agenda and on quality of care, basic requirements can be laid bare in order to organize patient participation in the most effective way. We try to present a transparent and theoretical foundation, that can be used as conditions needed for developing effective and sustainable patient participation.

In this thesis the role and efficacy of patient participation in the routines of the patient organization is studied. Two questions are the starting point of this thesis:

1. How can quality of care be improved when the patient perspective is taken into account?
2. How can we close the gap between the patients' unmet needs and outcomes of relevant research.

The answers to these questions are described in two different sections of this thesis. The first part of this thesis focusses on patient participation in relation to **quality of care**. These chapters describe the improvement of standards of care, taken into account that they are also based on the patients' perspective; on the implementation of patients' derived quality criteria in hospital care and an example of tailor made support for parents of a child with CF, based on their actual needs at the time they find out about the diagnosis of their child.

The second part addresses patient participation with regard to **research**. A description is given of the process that leads to a patient prioritized research agenda; the improvement of involvement of people with CF in innovative research technologies and their involvement in biobanking is an important point of attention.

Patient Participation in relation to quality of care

Chapter two is containing the European Standards of Care in CF. The standards of care provide existing and future CF centers with a framework for accessible care and criteria that have to be met in order to provide CF care according to evidence based medicine and / or best practice. Paragraph 13 of The Standards of Care focuses on national patient organizations, the way they work and how they connect to patients and other stakeholders. On an European level it is described what the European federation of CF patient organizations (CF Europe) is targeting: the European Standards of care are often used to support CF centers in countries

were CF care is not yet developed according to this standard. Patient representatives both staffed at national patient organizations and at CF Europe, took part in nearly all sessions where the outlines of the standards were discussed, thereby adding their insights to the creation of the European Standards. This paragraph was written by expert patient representatives with scientific backgrounds and reviewed by all co-authors.

In **chapter three** a quality improvement program is described, developed by the Dutch CF Foundation. A substantial amount of publications on the efficacy of quality improvement strategies is available, but only a few focus on CF [7, 8, 9, 10, 11]. These publications however, are driven by professional caregivers and focus on clinical aspects of care, like lung function or BMI. Assessment of quality of care, using criteria that are defined in close cooperation with people with CF are rare [12]. The main goal of this program is to assess and improve quality of care in all CF centers in The Netherlands from the perspective of the patient. To be able to do that, criteria from the patient perspective had to be defined – in close cooperation with people with CF and caregivers; following up on that, quality of care was assessed by patients via online surveys and site visits, followed by recommendations that were evaluated after two years.

Chapter four is describing a pilot in which parents get tailor made support at the time they need it and at a place that is convenient for them. Research shows that parents experience distress after they had their child diagnosed with CF via newborn screening (NBS). The diagnosis has a huge impact on them and interferes with the bonding between parents and child [13].
The Dutch CF Foundation wanted to reach out to parents in a proactive way and help them to overcome or even prevent stress and anxiety and to increase their resilience at an early stage. This ambition followed upon the recognition of experiences from parents who went through this process and found a listening ear at the patient organization. A coaching program was developed and offered to parents. The purpose of the program was to enable parents to cope with the diagnosis of CF in their child; to optimize the mental health status of the parents; to enable them to take care of their child, each other and their family; to optimize social and work-related functioning; to empower them in their relationship with the clinical healthcare system if needed. The aim of this pilot study was to explore the feasibility and possible effects of the program. The perception of the parents towards the coaching program was evaluated.

Patient participation in relation to research

Chapter five discusses to what level patient participation is intertwined with the work of Dutch patient organizations and Dutch health care funds. Health care funds are cooperating with patient organizations to a certain level. Some health care funds relate their work to one

or more patient organizations, depending on their primary focus. In case of the Dutch CF Foundation, the work of the patient organization and the health care fund is intertwined and based on one legal entity. It is one of the nineteen Dutch health care related research-funding organizations (HFs). All nineteen were assessed to what extent they include the patient perspective in their fundraising and research subsidizing processes. A patient participation advisory team was set up, with HF-representatives and patient advocates, who together initiated this study. An overview is given of when, why, and how patient participation activities take place in the health care funding process.

Chapter six describes a project in which a patient oriented research agenda was put together. The Dutch CF Foundation facilitates a five years routine in which all people with CF and parents of children with CF can express what their unmet needs are, or what they think is important in future research. Subsequently a patient needs oriented research agenda is put together with researchers and clinicians and carried out in five years.
Through an inventory for the entire patient population a longlist of topics is generated, which is downsized by the Dutch CF Foundation into research working areas. Patient focus groups make those items more specific, whereafter the patients' priorities are discussed with clinicians and researchers and a research program is being composed. All projects are reviewed by independent international scientists, mainly key opinion leaders in CF care and research. Only project proposals with a good or excellent review result, will be prioritized by people with CF and caretakers, who are trained in this area. A steering committee was installed for regular updates on progress of the program and regular update meetings are organized for people with CF, clinicians and researcher who participate in the program. With this way of working the Dutch CF Foundation wishes to ensure that the patient perspective is leading, at the start of the program, and during its execution.

Chapter seven gives us an insight in cooperation between basic and translational science (basic scientists and clinicians) and the Dutch CF Foundation. New therapeutics have been introduced for CF that modulate cystic fibrosis transmembrane conductance regulator (CFTR) function in a mutation-specific fashion. Despite CFTR genotype-based stratification of treatments, treatment efficacy is variable between study participants suggesting that individual factors further contribute to drug efficacy. Moreover, these treatments are licensed for a limited amount of CFTR mutations, and study participants with rare mutations that can potentially benefit from available treatments may be missed. New approaches that better support the identification of responders to CFTR modulators are, therefore, needed. This article focuses on a patient-oriented research collaboration between basic and clinical scientists and the Dutch CF Foundation as patient organization, that led to the development of a CFTR-dependent assay using primary stem cell cultures termed intestinal organoids that can measure the individual efficacy of CFTR modulators in a preclinical laboratory setting.

Chapter eight is related to the perspective of people with CF, with regard to an innovative, revolutionary research methodology, the organoid technology [14]. Patients not only have an enormous individual benefit, when their organoids are used to screen which compounds may be working for them best; it's also of importance to use patient's organoids for further research for the whole population. If we want to involve patients in research, asking them for rectal tissue, we want to be able to explain properly about the research itself, and to know what perception people with CF have towards the procedure and the use of their body materials. It helps us to find a balance between meaningful involvement of people with CF and feasible research.

Chapter nine is targeting the participant involvement of people with CF who donate their tissue for research; these tissues have to be stored in biobanks. Biobank research on patient-derived organoids has already led to successful personalized treatment of CF as mentioned before. Biobanks facilitate research with regard to drug screening, drug development, and enable large-scale data sharing and analysis. Traditionally, the interest of participants is the consent procedure. However, organoid biobanking raises specific ethical and practical challenges related to this consent procedure because of commercial access and commodification, privacy and ownership. It is of importance to elaborate the perspective of the people with CF.

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Chapter Two

European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre

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Abstract

People with cystic fibrosis (CF) have complex care needs that demand specialist, medical and allied healthcare expertise. The life expectancy has increased significantly in successive patient birth cohorts [1] as a result of more effective treatments and crucially because most patients attend CF Centres in line with the demonstration that patients who attend CF Centres for their care have better well-being and lung function than those who do not [2], [3]. Thus, the CF Centre has become the model of care for people with CF; patients should receive full care from the Centre or have local directed care supervised by the Centre [4], [5], [6]. The framework of the CF Centre is formed by a multidisciplinary team (MDT), links with other medical and surgical specialties, the buildings and facilities, and the hardware and software that combined allow the MDT to provide a level of care that meets the complex medical challenges of this disease using effective diagnostics and holistic treatment programs. The MDT members are at the core of the CF Centre and should be supported with continuing professional development (CPD), audit and research. Each discipline should establish its own rigorous framework, to ensure that patients' needs related to their discipline are met. The CF Centre should have adequate resources (e.g. staffing, IT equipment) and an infrastructure (inpatient and outpatient facilities) that allow the MDT to provide a level of care that is in accordance with the European Cystic Fibrosis Society (ECFS) standards recommended in this document, ensuring a safe, cost-effective and high-quality service. It is recognized that this may not be immediately achievable throughout Europe, particularly in countries with a low gross domestic product. It is crucial that where these standards cannot be met, procedures are put in place to enable them to do so within the short- to mid-term future, and that the hospital management commits to supporting CF clinicians. Without proper resources, a Centre is at risk of providing uncoordinated and substandard care. A lack of homogeneity in CF care will impact on patient outcomes [7]. At present, access to specialist CF services across Europe is inconsistent. Qualifications, training and roles vary considerably. Clinical practice should where possible be evidence based and reflect current research findings, clinical guidelines and consensus views. CF specialist professionals should be appropriately trained, qualified and registered by the state/national health authorities and legally recognized to practice within that country. Specialists should practice within their professional code of conduct and competency. They have a responsibility to maintain, update and enhance their knowledge, skills, efficacy and expertise through a proactive approach to continuing professional development. Participation in uni- and multi-professional audit and research, benchmarking, external quality assessment schemes, service evaluation, development and improvement, both of the specialist service and its provision as a whole is essential. As a CF Centre may be the only facility in a city or region, national and international programs to support CPD, benchmarking and service improvement are strongly encouraged. The following sections describe the ECFS recommended standards for the individual specialties within the CF Centre.

Framework for the paediatric and adult Centres

Paediatric and adult CF Centres have many features in common, so that the requirements outlined below usually apply to both. As the health of children and adolescents continues to improve, the emphasis in paediatric care is on the prevention of disease progression. The morbidity and almost all of the mortality associated with CF have shifted to adults. Adult services should take into account the greater demands for inpatient provision and the higher prevalence of multisystem complications. Even before the transition from paediatric to adult care, it is most important that the two Centres work closely together. Regular meetings between the teams and shared protocols can smooth the transition process for the young adult and minimize the changes to their treatment. Effective communication between teams during this period is crucial to the success of the transition process. Children with CF will have their care transferred to adult services around the time of their 17th/19th birthday. Children, and their families, should understand that they will transfer to an adult Centre at this age. The paediatrician is not trained or experienced to manage the emotional, social, or medical demands of the adult patient. In the adult population, the manifestations of this multisystem disease (e.g. CF-related diabetes, osteoporosis, renal and liver complications and atypical infection) are significantly more problematic. The adult physicians are also best placed to fully inform patients about the potential risks of pregnancy and are competent in the non-obstetric care of pregnant women with CF. The young person with CF and his/her family must be involved in planning transfer at an early stage. The topic should be introduced when the diagnosis of CF is made and reinforced at appropriate intervals thereafter. Practical discussions should start at around 11 years of age in the context of educational, social and sexual conversations about growing up with a long-term condition. There must be close liaison with an agreed protocol for transition, and coordinators from both teams should be identified. The adolescent and his/her carers should have the opportunity to formally meet the adult team on more than one occasion. This is optimally achieved by having joint clinics with the adult team during the transition process. An opportunity to visit the adult facilities should be made available to patients and parents. Written information about each patient must be given to the adult team at the time of handover.

The Centre

Many of the required features are the same for adult and paediatric Centres. The CF Centre should have appropriate staff and facilities to provide comprehensive care and be capable of treating all CF-associated complications [4]. Patients should have direct access to the Centre 24 h a day. In order to justify and maintain an appropriate level of expertise and experience, a specialist Centre should have a minimum of 100 adults or children with CF. In some circumstances, the geographical location of a specialist CF Centre, or a low disease frequency in certain populations, may mean that the number of patients seen by a Centre is less, but never below 50. Centres with fewer than 100 patients should be linked to a larger Centre until there are

sufficient patients, experience and resources to run an independent service. All patients with CF must have access to the Centre for routine and emergency care and advice. Patients should be reviewed regularly at a frequency appropriate to their individual needs. Routine appointments for people with stable disease should be every 2–3 months depending on the severity of their disease. Newly diagnosed infants should be seen more frequently (initially weekly). All patients should have an annual assessment to ensure that, as a minimum, a full medical, dietetic, physiotherapy and psychosocial review is performed once a year and that all surveillance blood tests are requested. The report should be written by a consultant who should discuss the review findings with the patient/carers, and the treatment plan should be agreed by all.

The multidisciplinary team

A core MDT of trained and experienced CF specialist healthcare professionals should be responsible for patient care. The MDT should be of appropriate size for the clinic population and should include the following CF specialists and support staff:

* respiratory paediatrician/pulmonologist
* clinical microbiologist
* medical support from trainee(s)
* clinical nurse specialist
* specialist physiotherapist
* specialist dietitian
* clinical psychologist
* social worker
* pharmacist
* clinical geneticist
* secretarial support
* database coordinator.

There should be clear medical leadership of the MDT. The roles and responsibilities of all senior doctors in the team should be clearly defined.

The ECFS concurs with the staff numbers for paediatric and adult Centres recommended by the UK CF Trust (Table 1, Table 2) [6]. These numbers may vary according to health care organization, geographical factors and local/regional variations in CF services. For example, the numbers of physiotherapists may vary according to the proportion of patients who self-administer intravenous antibiotics at home. Staffing numbers should reflect the model of shared care being used, taking into account time spent by staff from the specialist Centre in assessing and treating patients in a local hospital CF clinic. In addition, it is important that adequate cover is available for annual leave, study leave, and untoward events. All members of the MDT must be registered with their relevant national health profession's council/body, and be a member of their national or international CF special interest group.

They must have specialist knowledge and be experienced in the care of children and/or adults with CF. They must maintain CPD through attendance at local study days and national and international CF conferences.

Table 1. Whole-time equivalents per clinic size: full-time paediatric patients[a].

The MDT	50 patients	150 patients	≥250 patients[b]
Consultant 1	0.5	1	1
Consultant 2	0.3	0.5	1
Consultant 3	–	–	0.5
Medical trainees	0.8	1.5	2
Specialist nurse	2	3	4
Physiotherapist	2	3	4
Dietitian	0.5	1	1.5
Clinical psychologist	0.5	1	1.5
Social worker	0.5	1	1
Pharmacist	0.5	1	1
Secretary	0.5	1	2
Database coordinator	0.4	0.8	1

a Patients with CFTR-related disorders should not be counted.
b When clinics care for significantly more than 250 patients, additional consultants should be added to the multidisciplinary team (MDT) at a rate of approximately one additional consultant per extra 100 patients. Additional allied health professionals and support staff will also be required. There is likely to be a limit to the number of patients who can be cared for effectively in a CF Centre. This number will vary according to the facilities available in the hospital housing the Centre and the capacity of that hospital to support adequate staffing for the Centre. The MDT in individual Centres should review patient numbers annually and appreciate when resources are becoming stretched beyond the limit allowing care to be delivered to the standards recommended in guidelines. Paediatric patient numbers are likely to remain relatively stable but adult numbers are increasing every year. The need to establish a new adult Centre in any region must be considered proactively. Supply must precede, or coincide with, need.

Table 2. Whole-time equivalents per clinic size: full-time adult patientsa.

The MDT	100 patients	150 patients	≥250 patients[b]
Consultant 1	0.5	1	1
Consultant 2	0.3	0.5	1
Consultant 3	–	–	0.5
Staff grade/fellow	0.5	1	1
Specialist registrar	0.4	0.8	1
Specialist nurse	2	3	5
Physiotherapist	2	4	6
Dietitian	0.5	1	2
Clinical psychologist	0.5	1	2
Social worker	0.5	1	2
Pharmacist	0.5	1	1
Secretary	0.5	1	2
Database coordinator	0.4	0.8	1

a Patients with CFTR-related disorders should not be counted.
b See footnote in Table 1.

Access to other specialists

It is essential that there is access to other medical and surgical specialists as needed. Essential supporting disciplines and services include: gastroenterology and hepatology (with expertise to perform emergency endoscopic ligation of oesophageal varices); diabetes and endocrinology; ear, nose and throat surgery; cardiothoracic and general surgery; specialist anaesthesia and pain control; rheumatology; nephrology; obstetrics and gynaecology; psychiatry; intensive care; and interventional radiology (with expertise to perform emergency bronchial arterial embolization, and elective percutaneous ultrasound-directed gastrostomy).

Centre infrastructure

The facilities at the CF Centre must be appropriate for all age groups. There should be sufficient capacity within the Centre for outpatients to be seen urgently whether this is within a clinic session, in a day-case unit or during a ward visit. The number of inpatient beds should be sufficient to allow non-urgent patients to be admitted within 7 days and urgent patients to be admitted within 24 h. The hospital ward nursing staff who are in contact with patients should have sufficient knowledge and experience of CF care. Finally, there should be resources and staffing available for home intravenous antibiotic administration supervised by trained outreach nurses.

Segregation

All CF Centres must have a clear policy for infection prevention and control, and facilities must allow for adequate patient segregation to prevent cross-infection. Patients should not share rooms, bathrooms or toilets during a hospital stay and should not be in contact with each other in waiting areas, such as in CF clinics, wards, the pharmacy and radiology departments.

Access to specialist investigations

Within the specialists CF Centre, there should be easy access to specialist investigations. These include biochemistry and haematology laboratories for routine tests as well as analysis of sweat and measurement of fat-soluble vitamin levels, aminoglycoside levels, and measures of glucose metabolism (including continuous glucose monitoring systems). The microbiology services should have the ability to process samples from people with CF and to reliably detect *Burkholderia* spp., non-tuberculous mycobacteria, and fungal infection. Molecular pathogen typing and immunology for allergic bronchopulmonary aspergillosis monitoring should also be available.

Physiology must include lung function measures (both ward and outpatient spirometry), pulse oximetry including overnight O_2/CO_2 monitoring, exercise testing and fitness-to-fly testing. The radiology and nuclear medicine service should include computed tomography (CT) scanning, liver ultrasound, and dual energy X-ray absorptiometry (DXA scan) bone scanning. High-frequency pure tone audiometry and flexible bronchoscopy should also be available.

Miscellaneous

Facilities must exist for a parent/carer to stay with their child in hospital, and for a child to receive suitable education within the hospital if they cannot attend school due to illness. Related to these facilities should be access to appropriate play and/or recreation, with facilities for study. The CF Centre should be committed to active participation in clinical and translational research, and encourage patient participation in clinical trials. Each Centre should aim to be part of the expanding European Clinical Trials Network (www.ecfs.eu/ctn).

European policy aspects of CF Centre care

CF is a rare disease (i.e. < 1 in 2000), and as such belongs to the domain of several European Union (EU) policy initiatives relevant to research and healthcare. CF Centres, in compliance with the European Committee of Rare Disease Experts guidelines for Centres of Expertise for rare diseases, could operate within the frame of the newly established European Reference networks for rare diseases. As a rare disease, CF has a special status (Art. 54) in the Cross-Border Directive that facilitates exchange of expertise and eventually patients, and could thus address disparities in care. The development of CF Centre care in EU member states is supported by the EU Council Recommendation on action in the field of rare diseases (EC 2009/C 151/02). The introduction of orphan medical products into CF care also falls into such policy initiatives.

Framework for the specialist doctor

The CF consultant

The Consultant who works in a specialist CF Centre should have received accredited training in paediatric or adult CF care, usually within the context of respiratory specialization. The knowledge and skills that the CF Consultant should have acquired are detailed below [8].

Knowledge

The CF Consultant should have knowledge of the epidemiology and pathophysiology of CF and the aetiology of respiratory and non-respiratory manifestations and complications of CF, including massive haemoptysis, pneumothorax, respiratory failure, gastrointestinal disease, diabetes, problems of fertility and pregnancy (adult care) and psychosocial problems. The relevant investigations required, including microbiological investigations, non-invasive imaging modalities such as chest X-ray, CT imaging scans, should be familiar to the Consultant. The CF Consultant also needs to be familiar with the pharmacology of inhaled, oral and systemic drugs that are prescribed to patients and with the varied interventions employed by physiotherapists. The nutritional requirements of individual patients should be monitored and enteral tube feeding initiated when appropriate. Finally, the CF Consultant should know the indications for lung transplantation and be

experienced in discussing this option with patients and carers.

Skills

CF Consultants should be able to apply the above knowledge to the management of respiratory and non-respiratory manifestations and complications. They should also be able to interpret the results from sputum microbiology tests and evaluate the functional status of patients. CF Consultants should also have good communication skills so that they can educate their patients and carers as the disease evolves.

The CF Consultant's job plan should include adequate time allocation for CF patients, both for clinical tasks as well as managerial duties. This must include the capacity to maintain his/her own CPD in CF, which should involve attendance at national or international respiratory/CF meetings. In order to keep up to date with advances in treatment and research, the CF Consultant should spend a minimum of 50% of his/her working time dedicated to CF issues.

The clinical lead

The Director of the specialist CF Centre is usually the Clinical Lead and will be expected to lead the CF MDT. He/she should act as a link between clinical experts and the hospital management. The Clinical Lead/Centre Director will be expected to head the team and to ensure that: the needs of its members are met in terms of professional development and adequate support; that opportunities for attendance at national and international CF meetings are available; and that research is encouraged. The Director should also ensure that a team approach is maintained and that all members of the CF MDT have the opportunity to have their observations and opinions considered in patient management.

It is essential that the Director understands the financial framework underpinning the country's healthcare system in order to develop and protect the financial support needed for the CF service. The Director should lead on staff recruitment, aiming to realize the human resource numbers as recommended in these Standards of Care. He/she should ensure that CF MDT meetings are held weekly, that Centre outcome measures are audited and that the results are reported back to the team so that standards of care are improved. In order to achieve the latter, the Director needs to oversee accurate data collection and documentation and that transfer of these data to the national and European registries is carried out. In some Centres there may be co-leads/directors of the service. Clear definition of responsibility and communication is essential in this situation.

Framework for specialist nursing care

The role of the CF Clinical Nurse Specialist

The role of the CF Clinical Nurse Specialist should include [6]:

* education, advocacy and psychosocial support, particularly at important times such as:
* notification of a screening result and diagnosis
* first admission to hospital
* first course of intravenous antibiotics
* a second diagnosis (e.g. CF-related diabetes)
* transition from paediatric to adult care
* reproductive issues, pre- and postnatal care
* transplant and end-of-life issues
* provision of support and education at home, particularly for home intravenous antibiotic therapy, nebulizer therapy, enteral feeding and non-invasive ventilation
* provision of education to others about CF, including nurseries, schools, places of higher education and work places
* acting as a link between the patient and family, primary care, community services and hospital
* acting as a resource for training and education of other professionals involved in CF care.

Access, availability and facilities

There should be an adequate number of Clinical Nurse Specialists with expert knowledge of CF in the MDT [9]. The CF Clinical Nurse Specialist should deliver skilled support, advice and care directly to the patient and family wherever it is needed, both when attending hospital and at home. The service will vary according to differing patient populations, their needs and requirements. The role of the CF Clinical Nurse Specialist should continuously develop to meet the needs of the local CF population [4].

CF Clinical Nurse Specialists need sufficient time, office space, computer/printer and financial support in order to be able to provide a reliable service. They should stay in regular contact with patients and families in between clinic visits and therefore need access to technology such as email, phone and SMS texting.

Key stages for delivery of care

Diagnosis

Diagnosis through newborn screening is now common in many countries. The CF Clinical Nurse Specialist plays an active role in talking to parents at diagnosis and providing ongoing support and continuing education following the initial discussion. Where screening is not

available, the CF Clinical Nurse Specialist plays a similar role offering support, advice and education, which has to be individualized at a level and frequency to meet differing needs, whether diagnosis is within the first year of life, in older children or during adulthood. Contact between the CF Clinical Nurse Specialist and the patient/parent is therefore essential, whether this is in hospital, through home visiting, or via email or telephone.

Pre-school

For many, after coming to terms with the diagnosis and learning how to carry out treatment regimens while adjusting back to family life, the early years can seem almost normal. However, there are a few areas where the CF Clinical Nurse Specialist can provide education, practical advice and psychosocial support [10], such as: administering medication; nutrition; adjusting pancreatic enzyme replacement therapy (judging the correct amount or offering advice when the child refuses to take the enzymes) in conjunction with the CF Dietitian; recognizing chest infections and making decisions about when to ask for advice or to start treatment; managing airway clearance and exercise in conjunction with the CF Physiotherapist; starting nursery; dealing with siblings; planning further children.

School age

When a child starts school it can be a traumatic experience for any parent. When the child has CF, parental anxiety about loss of control is likely. Many CF Clinical Nurse Specialists will visit the school (with parental permission) to educate and prepare teachers for managing CF in areas such as: maintaining good nutrition at school; administration of pancreatic enzymes and other medication (e.g. nebulizers/inhalers/oral); liaising with the school nurse; facilitating time off for hospital visits/admissions; dealing with the child's growing independence; advising on issues surrounding non-adherence, especially eating and airway clearance. The CF Clinical Nurse Specialist can help parents at this time, particularly with outreach contact as it gives parents time away from the clinical setting and allows them to discuss their anxieties in a safe and familiar environment. Most school-age children with CF are relatively well and take part in all academic, sporting and social activities provided by the school. Occasionally, extra treatment is necessary. Supporting treatments such as intravenous therapy or enteral feeding in the home often allows children to continue attending school. The provision of an outreach service can help, as routine checks (such as spirometry) can be performed by the CF Clinical Nurse Specialist, and problems can be identified early [11], [12].

Adolescence

Adolescents with CF go through the same physical and emotional changes and have the same expectations as their healthy peers, irrespective of the severity of lung disease [13]. The CF Clinical Nurse Specialist should be able to have open and honest discussions about issues such as: recreational drug use and the effects on CF; sexuality, safe sex and

contraception; fertility and pregnancy; further education and employment; body image and self-esteem; adherence to treatment regimens; relationships with parents; promotion of self-care, adherence and responsibility; accurate information about their disease and treatment. CF Clinical Nurse Specialists need to be sensitive and honest when giving information to young people with CF [14], [15], [16]. Much of the information they (and their families) receive is from peers, the media and the Internet. Information given by the CF Clinical Nurse Specialist must therefore be correct and up to date.

Transition from paediatric to adult care

All children with CF should move from paediatric to adult care. The importance of getting this transition process right is widely recognized [17], [18]. Transition from paediatric to adult care happens at a time when the young person with CF is moving into adulthood in other areas of their life, such as further education or employment, forming relationships and taking more responsibility for their own lifestyle. Transition can therefore be difficult for many reasons. CF Clinical Nurse Specialists involved with the transition process need to be aware of the many barriers that can prevent this process being successful [19], [20]. Both the paediatric and adult CF Clinical Nurse Specialists play an important role in ensuring a successful transition and will manage details such as: patient and parent involvement in decision making; clear communication between paediatric and adult CF MDTs; appropriate transition clinics involving the MDT; ensuring attendance at the adult clinic with appropriate follow-up. Young people may find that their first admission to the adult Centre is to an unfamiliar ward where they do not know the staff. For these individuals and their families, the first inpatient admission requires an increase in awareness and sensitivity from the ward staff and further CF Clinical Nurse Specialist support to both the patient and the family. The CF Clinical Nurse Specialist should liaise between the ward and the CF MDT.

Adult issues

CF Clinical Nurse Specialists play a vital role in helping adults maintain a balance between adhering to treatment and their lifestyle, and recognize the need to help individuals adapt treatment regimens to suit them. This will include: educating employers and work colleagues; liaison with government agencies and the work place to ensure maximum support (financial and practical) to enable patients to stay employed or to re-train; advocacy on a patient's behalf with local social services; educating and liaising with family doctors and local pharmacists; negotiating easier access to classes at school or university; increasingly, CF Clinical Nurse Specialists will work in collaboration with the family doctor, social services and the CF team to support patients caring for their ageing parents; providing education, counselling and support around reproductive issues for both men and women with CF; practical and emotional support throughout the neonatal and postnatal periods. Complications occur more commonly in older patients with CF [21], [22], [23]. An outreach service led by a CF Clinical Nurse Specialist may have to manage complex

medication regimens and organise care to help maintain a lifestyle/treatment balance.

Transplantation and end-of-life issues

When admissions become more frequent, longer in duration and the burden of treatment increases, patients or their families may wish to raise the issue of lung transplantation. Early discussion with the team raises questions and concerns for both patients and their families. The CF Clinical Nurse Specialist's role as advocate and educator for the patient is vital in this decision process.

CF continues to be life limiting. Death in childhood, although uncommon, does occur. Unlike other chronic diseases, the end stages of CF can be difficult to recognize. Patients often need opportunities to discuss their fears and anxieties but may feel uncomfortable or protective talking about these issues with their family for fear of upsetting them or 'letting them down'. Advocacy allows the CF Clinical Nurse Specialist to facilitate discussion between the patient and family. Early discussion about an individual's wishes for the terminal stage of their disease is essential to aid appropriate care planning. Issues that may be raised include transplantation, wills, funeral arrangements, writing letters or diaries to the family and where they would like to be when they die [24], [25]. The CF Clinical Nurse Specialist plays a key role in providing individual emotional support for parents/partners. Although some families are willing to return to the hospital, many find this difficult. Visiting the family at home allows bereavement support to be offered in a safe and comfortable environment. Home visiting also allows other family members, siblings or grandparents for example, to receive support.

Core competencies, qualifications and professional development

Core competencies

The CF Clinical Nurse Specialist should be competent in the following key areas.

* Clinical practice
* Diagnostic and assessment skills
* Treatment skills
* Recognizing and monitoring change
* Facilitating programs of care
* Clinical research and audit
* Education
* Knowledge of CF and associated issues
* Evidence-based practice
* Teaching and training: patients, carers, other healthcare professionals
* Communication
* Patients and carers
* MDTs
* Liaison with clinical, social, educational, employment and other lay agencies
* Support and advocacy
* Social care
* Advocacy
* Counselling skills
* Legal and ethical issues.

Qualifications and professional development

The CF Clinical Nurse Specialists must be registered as licensed practitioners in their country. They should also have specialist knowledge and be experienced in the care of children (including specific paediatric training) and/or adults with CF. The CF Clinical Nurse Specialist must contribute to research in all areas of CF, either through developing individual projects or participating in research carried out by the CF MDT, and maintain CPD through attendance at courses and conferences. CF is a demanding disease to manage for the patient, family and the CF MDT. The CF Clinical Nurse Specialist must act as a link between the patient and family, primary and community services, and the hospital. The CF Clinical Nurse Specialist has a responsibility to ensure that every patient receives appropriate care for their individual needs. Patients should receive lifelong support and good-quality treatment through the coordination of care between patient and family, community services and hospital, both practically and through support and advice.

Framework for physiotherapy care

The specialist CF Physiotherapist should take the lead in providing high-quality treatment of airway clearance, physical exercise and inhalation therapy. Physiotherapy programs in CF care are primarily preventive, and regular input is required from the time of diagnosis. The aims of therapy are to maintain ventilation in all parts of the lungs, to postpone progression of pulmonary disease, to stimulate establishment and retention of normal physical capacity and to avoid pain and musculoskeletal complications due to pulmonary or bone disease [26]. The CF Physiotherapist should also develop strategies for the management of complications or co-morbidities experienced by the ageing patient and should optimize the respiratory physiotherapy program, which includes highly technical equipment, non-invasive ventilation and physical exercise with oxygen supplementation. Physical rehabilitation is essential for patients on a transplant waiting list.

The role of the CF physiotherapist

The CF Physiotherapist should be available for regular contact and assessment of the patient for treatment, lung function testing, physical surveillance and therapy evaluation. The

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frequency of this will vary according to the patient's age and clinical status but as a minimum should happen at every routine outpatient clinic and daily during each hospitalization (including when patients are admitted under the care of other specialists and to intensive care). A more extensive assessment should take place annually.

Regular assessment and therapy

Regular lung assessments by the CF Physiotherapist should include lung function test data, respiratory signs, degree of dyspnoea, oxygenation cough characteristics and questioning about activity of everyday life. All interventions should be tailored to the individual, with consideration of their age, severity of disease, physical side-effects or complications, and social and domestic circumstances.

Inhalation therapy

As the CF Physiotherapists are responsible for inhalation therapy they should be familiar with techniques, equipment provision and appropriate maintenance of devices. There is a need for consideration of timing of inhalations in relation to airway clearance as there may be a positive interdependence between the two. Education of patients in appropriate inhalation techniques is essential for optimal deposition of inhaled drugs. The CF Physiotherapist should be familiar with the appropriate nebulizer systems proven to be safe and effective in the delivery of the medications prescribed. Cleaning and maintenance of the whole nebulizer system are essential to ensure that medications are delivered optimally and safely [26], [27].

Airway clearance therapy

Physiotherapists are responsible for airway clearance therapy. This involves knowledge and experience of the full range of techniques available and immediate evaluation of therapy, for example by expiratory sounds, sputum volume and characteristics and by ability to control cough. Alternative physiotherapy techniques should be recognized and considered for individual patients. There are a variety of effective airway clearance techniques that allow patient independence. These are based on sound physiological concepts and allow the CF Physiotherapist to individualize treatment programs [28]. There is no standard airway clearance regimen or conclusive evidence to promote one technique over another [6], [26], [29], [30], [31], [32], [33], [34], [35], [36], [37].

Postural and musculoskeletal assessment

Assessment of postural and musculoskeletal function is carried out to evaluate therapy. Physical exercises aimed at the maintenance of good posture and chest mobility should be included in the treatment from the beginning. As with all physiotherapy interventions the exercises should be individually tailored to each patient [26], [38], [39].

Exercise capacity

Exercise capacity and the opportunities for exercise prescription for the person with CF include any pre-transplantation preparation. Reduction in exercise capacity is associated with a decline in respiratory function and survival [40], [41]. Physical exercise has been reported to improve lung function and decrease habitual inactivity in children with CF [42]. The CF Physiotherapist should perform regular exercise testing with a frequency dictated by disease progression, and in cases of specific needs like transplantation assessment or evaluation of a treatment. Care should be taken when prescribing exercise activities for patients with advanced disease, particularly when they may also experience haemoptysis, exercise-induced desaturation requiring supplementary oxygenation, pulmonary hypertension, cor pulmonale, joint arthropathies and other co-morbidities [26]. The CF Physiotherapist should also assess supplementary oxygen needs, for exercise or ambulation [26], [43].

Non-invasive ventilation

It is recognized that non-invasive ventilation is a useful therapeutic adjunct to support airway clearance therapy and reduce the work of breathing and fatigue experienced by the severely ill patients during treatment. Non-invasive ventilation may also be useful during exercise management to decrease breathlessness, improve oxygenation and, consequently, to maintain or improve exercise tolerance [44], [45], [46]. Additionally, non-invasive ventilation is implemented to facilitate optimal function in patients with end-stage disease and possibly as a bridge to transplantation [45].

Other considerations and assessments

Surveillance regarding the incidence of urinary and faecal incontinence should also be the responsibility of the CF Physiotherapist. A sensitive and open approach with early recognition of symptoms should be adopted; questioning can occur as early as 10 years of age [47], [48]. The CF Physiotherapist should also be responsible for:

* management of associated complications and issues with adherence while continuing to promote independence that is age appropriate
* appropriate inhalation and airway clearance therapy and physical exercise programs during pregnancy [49]
* ensuring the appropriate maintenance and function of equipment provided for therapy and nebulization
* the education of patients, carers, teachers and local physiotherapists; the physiotherapists should work closely with the other professionals for the benefit of the patients' holistic care
* palliative care, especially in relation to relieving dyspnoea in the terminally ill, and advising on when to withdraw non-invasive ventilation.

Service provision

When patients are resident in hospital for the treatment of an exacerbation or for routine management they should be reviewed by the CF Physiotherapist within 24 h of admission, and a treatment plan focusing on airway clearance, inhalation therapy and exercise tolerance should be implemented. The CF Physiotherapist should have a comprehensive knowledge of all techniques, respiratory pathophysiology, the rationale for alternative approaches and any associated contraindications to the treatment techniques available [28]. CF physiotherapy services should be available 7 days a week, with an out-of-hours physiotherapy service available for those patients who may deteriorate overnight.

Professional development, research and availability

Education, clinical audit, research and contribution to a CF registry should be pursued. CPD is integral to the work of the CF Physiotherapist who should maintain and increase specialist knowledge by attendance at relevant postgraduate courses, lectures, and national and international conferences. They should preferably be an active member of their national CF physiotherapy group and be available to represent physiotherapy interests for their country at meetings of the International Physiotherapy Group for CF (IPG/CF) [50]. The CF Physiotherapist should contribute to research, development and evaluation by performing audits, participating in multicentre studies and contributing data to registries. They should collect annual data in order to evaluate their care [50], [51].

Framework for dietetic care

A normal nutritional status is positively associated with better lung function [52], [53]. Healthy body weight, height and BMI are positively associated with survival [53], [54], [55]. Ensuring normal growth in children and adolescents and maintaining a normal BMI in adults is essential. Specialist CF Dietitians have an integral role to play in patient management and have overall responsibility for the delivery of expert nutritional care. They should be actively involved in the nutritional training, education, development and support of other healthcare professionals involved in CF care. Dietetic intervention should be both proactive and reactive, evolving in response to the needs of each individual patient. It is essential that the specialist CF Dietitian has expertise in managing the complex nutritional challenges and rare complications of the disease.

The role of the specialist CF dietitian

The specialist CF Dietitian should take the lead in providing high-quality treatment and care to ensure optimal nutritional status, including nutritional screening and surveillance, and regular patient assessment with review of all aspects of nutrition and gastrointestinal status. The frequency and type of assessment will vary with age and clinical status.

The specialist CF Dietitian should advise and educate patients and carers about the principles

of nutritional management in CF to enable them to meet their nutritional needs and achieve optimal growth, weight and body composition. Advice may be required on the management of pancreatic insufficiency, fat-soluble vitamin deficiency, altered gastric motility, gastro-oesophageal reflux, impaired glucose tolerance/diabetes, reduced bone mineral density, renal disease and liver disease.

Age-specific individualized advice should be offered. This advice should consider psychosocial barriers (especially during adolescence) and be supported by written literature, visual, audio and/or audiovisual aids, computerized learning packages and 'apps'. This is an ongoing and evolving process and must take into account the key times that may require more intensive dietetic intervention and support, such as diagnosis, early infancy, initiation of pancreatic enzyme replacement therapy, weaning, adolescence and self-management, pregnancy, initiation of enteral tube feeding, diagnosis of CF-related diabetes, transplantation and end-of-life care. It is important to remember that patients diagnosed later in life tend to present atypically and have unique educational requirements. Improving adherence to the many prescribed nutritional therapies is a key challenge. The specialist CF Dietitian should provide a collaborative approach to increase motivation to change and support patients' efforts to change. This is based on providing information and facilitating open discussion. It is important to address emotional and perceptual barriers to adherence, e.g. a reluctance for females to gain weight during adolescence.

Clinical governance, research and quality framework

The specialist CF Dietitian should be a member of, and an active participant in, specialist interest groups locally, nationally and internationally, (e.g. European Cystic Fibrosis Nutrition Group) in order to support their practice. They should be encouraged to be an Allied Healthcare Professional Member of the European Cystic Fibrosis Society

Dietary assessment

The annual assessment

Dietetic staffing should allow for a structured annual assessment of dietary intake and nutrition. Formal assessment of dietary intake using a written diet and enzyme diary should be targeted at selected individuals only; in large CF Centres, such an exercise is unsustainable if applied to all patients and is unlikely to provide additional information for patients with stable nutritional status. The annual evaluation should address all aspects of nutritional status assessment, nutritional intake, pancreatic enzyme replacement therapy, and the management of nutritional and metabolic complications. The annual assessment will help to provide the framework for future care planning and anticipatory guidance.

The reader is referred to the document "European Cystic Fibrosis Society Standards of Care: Best Practice guidelines – Optimal Nutrition and Management of Metabolic Complications of Cystic Fibrosis" for details on the assessment of the following:

* pancreatic status and absorption

* growth and nutritional status
* bone mineral density, and
* glycaemic status.

Service provision framework
Traditionally the framework for service provision is divided into:

* inpatient care
* outpatient care
* home care
* shared care
* transitional care
* annual review.

All patients should have access to a specialist CF Dietitian at all of these times. The same dietitians should provide inpatient and outpatient advice to ensure continuity of care and to prevent the important minutiae of care being overlooked. Advances in telecommunications and technology allow opportunities to re-evaluate service delivery.

Key considerations of service provision

Inpatients
A clear discharge plan and follow-up arrangements should be provided for patients treated in hospital, especially for those requiring ongoing nutritional support.

Home treatment
For those being treated with intravenous antibiotic therapy at home, there should be access to a specialist CF Dietitian at the start and end of this treatment, with ongoing nutritional support provided remotely (e.g. by telephone, telemedicine) or via the CF Clinical Nurse Specialist. There should be clear channels of communication between the CF Clinical Nurse Specialist and the specialist CF Dietitian.

Outpatients with CF-related diabetes
Outpatients with CF-related diabetes should have access to a specialist CF Dietitian with experience in the management of this CF complication.

Shared care
In general, due to the complexity of the dietetic needs of adults with CF, shared care is not appropriate. In paediatric Centres there should be:
protocols for the delivery of care and lines of responsibility for nutritional management
an identified dietitian within the shared care hospital who will liaise with the specialist CF

Dietitian at the Centre review of all patients by the Centre's specialist CF Dietitian at least twice a year.

Transition
The paediatric and adult specialist CF Dietitians should work together to promote autonomy, facilitate self-management and ensure a smooth transition. At the time of transfer, the paediatric specialist CF Dietitian should provide a clear and concise summary of the nutritional management and challenges for each patient. Where possible the paediatric specialist CF Dietitian should provide a written treatment plan.

Framework for microbiology

A Clinical Microbiologist with specialist knowledge of CF infection should be part of the CF MDT. This individual may be a medically trained clinical microbiologist/infectious disease specialist; alternatively, a clinical scientist with relevant knowledge and experience may be able to undertake this role. The CF Clinical Microbiologist should work closely with the microbiology laboratory providing diagnostic services for the CF MDT and also with the local infection control and prevention team.
In order to provide support to the CF MDT for the diagnosis and treatment of infection, the CF Clinical Microbiologist needs to know about the range of infections in CF. In particular, they need to be aware of the role of unusual micro-organisms, the risk of cross infection and the impact of long-term chronic infection on microbiological laboratory testing and treatment. In addition to a good basic knowledge, the CF Clinical Microbiologist should have evidence of CPD in CF microbiology and attend specialist CF meetings and conferences.

The role of the CF Clinical Microbiologist
The CF Clinical Microbiologist should ensure that appropriate laboratory microbiology provision is in place. The individual may be part of the management of the laboratory. Alternatively, these services may be provided through an external contract, in which case the CF Clinical Microbiologist should be involved with setting the terms of the contract and act as an advocate for the CF Centre.
The CF Clinical Microbiologist should advise on the diagnosis and treatment of infection including the monitoring of antibiotics. This may be achieved by attendance at the CF MDT meetings. The CF Clinical Microbiologist should also act as an advisor on infection prevention and control in the CF Centre. This may be delegated to the designated infection control doctor if such a position exists.

Overview of laboratory services
The CF Clinical Microbiologist should ensure that the full range of microbiology laboratory

tests needed for the CF Centre is available and that the laboratory service provided is based on published guidelines [56], [57], [58]. The laboratory should be fully accredited by a recognized national scheme for clinical microbiology and should participate in external quality assurance, which includes CF-associated pathogens. There should be provision to send relevant samples to a reference laboratory specializing in CF microbiology when required.

The laboratory should provide accurate and timely results to the CF Centre with an agreed system for notifying urgent and important results. The technical staff in the laboratory should have sufficient expertise and knowledge to deal with the complex microbiology of CF infections.

There should be a framework for recording and investigating errors and other incidents, with evidence of how the lessons learned are used to inform a program of service improvement. The service should be regularly audited. Examples of audits are the turn-around time (i.e. the time between the receipt of the sample in the laboratory and the time when the result is available to the CF MDT), the accuracy of identification and susceptibility testing, and the appropriate and prompt communication of urgent results to the CF MDT.

Clinical microbiology services and the CF MDT

The following items should be agreed between the CF MDT and the clinical microbiology service.

* Which respiratory samples should be taken and how should they be processed (e.g. sputum, bronchoalveolar lavage, cough swab or a pharyngeal swab).
* Which samples should be taken for the diagnosis of an infected intravascular line.
* Diagnosis of other infections including infections of the gut (e.g. enteric viruses, when and how to test for toxigenic *Clostridium difficile*)
* The level of identification of micro-organisms (e.g. genus, species, subtype) required in individual cases. This may include a discussion on the tests that can be performed in a local laboratory and what may need to be referred to a specialist laboratory with more advanced testing methodology (e.g. confirmation of first infection with *Burkholderia* spp. with accurate species identification).
* Typing methods and frequency of typing (i.e. how often the CF MDT should send samples for routine surveillance and when additional typing should be done due to suspicion of cross infection) 8 Measurement of antipseudomonal antibodies where appropriate
* Provision of diagnostic testing for fungal and mycobacterial infection together with level of identification and role of typing
* Susceptibility testing — agreement on the antibiotics to be tested and when susceptibility testing is helpful may spread between patients — both familiar (e.g. influenza virus) and emerging viral pathogens (e.g. SARS, MERS coronavirus).
* Which results need to be phoned urgently to the CF MDT (e.g. first growth of *Pseudomonas aeruginosa*, new isolation of *Burkholderia cepacia complex* and other *Burkholderia* species, MRSA, possible *Mycobacteria* seen in sputum).
* Advice on infection prevention and control.

In addition, a robust framework for communication between the microbiology services and the CF MDT should be agreed (e.g. telephone contact, ward rounds to review patients, participation in MDT meetings).

Clinical advice on treatment of infection

The CF Clinical Microbiologists should work with the CF MDT to draw up guidelines for the use of antimicrobials, including the selection of treatment for clearance of new infections, therapy for acute exacerbation and long-term suppressive antibiotics. The aim is to reduce morbidity and hospital admissions and to use antibiotics responsibly in order to limit the development of resistance.

There must be provision of therapeutic drug monitoring of antibiotics. The CF Clinical Microbiologist should ensure that guidelines and advice are available on the maintenance of optimum antibiotic levels in the patient in order to promote effective treatment while minimizing side-effects.

Infection prevention and control

The CF Clinical Microbiologist should work with the CF MDT and the local infection control team to develop a local infection control and prevention policy and procedures in line with expert national and international guidelines [59], [60], [61], [62], [63]. This policy should include:

* how patients with transmissible infections are managed, both in the community and in hospital, in order to prevent the spread of infection
* surveillance for transmissible infection (e.g. how often to screen and which samples to send to the laboratory)
* antimicrobial treatment to clear carriage of potentially transmissible micro-organisms
* guidelines for staff with infections
* the investigation of outbreaks
* the provision of facilities for the CF Centre and the outpatient department — this should include the cleaning and maintenance of equipment and

involvement in any plans for refurbishment or re-build of the department.

Role in clinical research and data collection

CF Clinical Microbiologists can have an active role in CF clinical research. They may be involved with the design of innovative research but also have a role in the provision of reliable and accurate laboratory support for clinical studies. They can also help to ensure that accurate microbiological results are available for national and international database collection.

Framework for medicines management

Optimal care of people with CF requires complex multidrug treatment plans. These drugs may be administered by oral, intravenous and inhaled routes. Adverse effects and drug interactions are common.

Many of the drugs are expensive and require specialist assessment and instruction on optimal administration. Adherence is a major challenge for patients and parents/carers. Non-adherence is associated with poor outcomes. CF Centres must have an effective medicines management programme to support patients in optimizing their therapy. The CF Clinical Pharmacist is pivotal in this process [64]. In European countries, decentralized clinical services, with a pharmacist working in the ward at least 50% of his/her time, or with pharmacists visiting wards daily, are not very common [65]. Only two countries, UK and Ireland, have developed these clinical services to a significant extent [65].

The role of the CF Clinical Pharmacist

CF Clinical Pharmacists have a central role in managing medicines effectively [66]. The overall goal of clinical pharmacy activities is to promote the correct and appropriate use of medicinal products and devices [67]. These activities aim to:

* maximize the clinical effect of medicines (i.e. using the most effective treatment for each patient)
* minimize the risk of treatment-induced adverse events (i.e. monitoring the therapy course and the patient's compliance with therapy)
* optimize the expenditures for pharmacological treatments borne by the national healthcare systems and by the patients.

The principle objective of the service provided by the CF Clinical Pharmacist is to provide patient-focused pharmaceutical care, defined as the responsible provision of medication to achieve definite outcomes that improve patients' quality of life and long-term survival. The service is the process through which the pharmacist cooperates with a patient and other

healthcare professional in designing, implementing and monitoring a therapeutic plan to produce these specific health outcomes [68].

Effective provision of a clinical pharmacy service to the CF Centre relies on the knowledge and skills of a CF Clinical Pharmacist and the quality of various support services, such as a medicine information service with experience in the problems of CF and paediatrics (if applicable), and the necessary procurement and distribution services that can provide an efficient medicine supply service for inpatients. A dispensing service should also be provided as required. Access to an on-call service for the supply of urgent medication, information and advice for inpatient care, and an aseptic dispensing service for the preparation of intravenous antibiotics including complex desensitization regimens should also be available.

The CF Clinical Pharmacist should:

* dispense medications to inpatients or outpatients as required in their institution
* attend CF wards rounds and CF MDT meetings
* support and provide information to other pharmacists in the department who may not be familiar with CF
* liaise with paediatric and adult Centres during transition of care and transfer of patients
* support and provide information to pharmacists working in primary care and other hospitals
* maintain CPD through appropriate study and attendance at relevant study days, and at national and international conferences
* network with other CF Pharmacists for advice and CPD.

Pharmaceutical care practice for CF Clinical Pharmacists

Managing formularies, clinical guidelines and treatment protocols

The CF Clinical Pharmacist should assist in the completion of formulary applications to ensure that the appropriate medicines are introduced into clinical practice. They should also assist in the development and support of homecare services, such as home intravenous antibiotics, and manage and monitor the delivery of medication in this setting. Effective communication should exist between the CF Clinical Pharmacist and other members of the CF MDT. As for all clinical professionals in the CF MDT, the Clinical Pharmacist should participate in CPD and attend CF conferences and relevant study days. They should also contribute to education and training of other healthcare professionals, including those working in primary care, as appropriate. The CF Clinical Pharmacist should act as an advisor on the legal and ethical responsibilities of using medicines, including sourcing and administration of unlicensed and off-label medicines. Any problems with medication supply should be resolved by the CF Clinical Pharmacist and communicated to the CF MDT.

The CF Clinical Pharmacist may be required to collaborate with CF research and development and assist in the completion of individual funding requests or exceptional case requests for

the supply of specific medications for individual patients where no such mechanism exists to currently fund that treatment.

Medication reconciliation/history taking

The CF Clinical Pharmacists is responsible for medicines reconciliation at admission/transfer from other institutions and on discharge, including alternative over-the-counter medications, trial medications and medications used for other conditions. They should ensure that an accurate history is recorded, including previous allergic reactions/adverse drug reactions.

Prescription monitoring and medication review service

In the monitoring and review of patient medication, the CF Clinical Pharmacists should ensure that medication and the formulation are appropriate for the patient, oversee extended prescribing for allied healthcare professionals including other pharmacists, and check for drug interactions. The CF Clinical Pharmacist is also responsible for ensuring that prescriptions are complete, unambiguous and legal, and for detecting potential medication errors.

Identifying patient and medication risk factors

It is the CF Clinical Pharmacist's responsibility to ensure that patient characteristics, including age, pregnancy or breast feeding, and organ dysfunction are taken into account when medicines are prescribed, and to check the response to previous and current medication. The use of non-drug and complementary therapies should also be taken into account when managing the patient's medication.

Preventing, detecting and reporting adverse drug reactions

The CF Clinical Pharmacist needs to document and report all reactions to newer medications and serious reactions to established medications to the appropriate national body. This includes documentation of individual toxicity/allergies/hypersensitivity reactions and contraindications, and monitoring for any adverse drug reactions. The appropriate use, storage and disposal of medicines should be ensured in order to minimize adverse events.

Individualizing drug and dosage requirements

The CF Clinical Pharmacist should aim, whenever possible, to maximize the therapeutic potential and minimize the adverse effects of medicines. Therapeutic drug monitoring of specific medicines (e.g. aminoglycosides, azoles) according to an individual's pharmacokinetic variables and monitoring and reviewing the outcome of an individual's need for medication are also required. While optimizing the use of medicines the CF Clinical Pharmacist also needs to take into account the patient's wishes and lifestyle.

The CF Clinical Pharmacist needs to keep up to date with newly available medications and therapies (e.g. new nebulized antimicrobials), and find a place for them in the treatment regimen.

Educating and counselling patients and carers

The CF Clinical Pharmacist has an important role to play in providing appropriate patient education and counselling to ensure the safe and effective use of medicines. This may include patient information leaflets about medicines and other appropriate methods of improving adherence to treatment. Pharmacists should also agree an informed plan with a patient/carer to achieve the best possible concordance with medication.

Evaluating medicine use

The CF Clinical Pharmacist's non-clinical responsibilities will include financial reporting to the CF MDT, hospital management, and other authorities, as appropriate, on CF medication usage. They should audit treatment guidelines, new therapies and homecare services.

Framework for psychosocial care

Living with CF provides many challenges for patients and their families. The CF Centre should provide adequate psychosocial care and support to help the person with CF and the families meet these challenges. In order to deliver optimal care CF Centres need a multidisciplinary framework to include access to psychosocial professionals throughout the patient's life. The core psychosocial professionals available should be a Clinical Psychologist and a Social Worker, though variations on these professions are acceptable provided core competencies are met (see below). Psychosocial professionals should be proficient in the following areas: working with children, families and adults according to the needs of the specific CF Centre; working with patients presenting with a range of clinical severity; and delivering care in all CF settings including outpatients, inpatients, community and residential care.

The variability of patient needs and availability of expertise in CF Centres prevent the formulation of a single programme. Psychosocial care should be provided within the context of the patients' development: from infancy to toddler, childhood, adolescence, young adulthood, adult life and old age. In each stage there are age-related themes as well as CF themes [69], [70] (Table 3). Key stages include the time around diagnosis [71], the transition to adult care [19], [72], [73], [74], [75], [76] and the transition to end-of-life/transplantation care [77], [78]. The disease trajectory itself also necessitates times of increased psychosocial support, for example, at diagnosis, first *P. aeruginosa* infection, first inpatient admission, diagnosis of CF-related diabetes, the need for gastrostomy tube feeding, supplementary oxygen, non-invasive ventilation, and assessment for lung transplantation. Psychosocial professionals should be included in the multidisciplinary care at all of these stages (Table 3).

The CF social worker

Role

The CF Social Worker provides expertise in helping patients and families with their emotional

and practical needs and supports patients and families in coping with CF in the different developmental and disease stages. The CF Social Worker should bridge the gap between hospital life and home life and liaise with locally available support so that local services can be accessed. The CF Social Worker is actively involved in the different transition stages, including transition to adult care and transition to transplantation care (Table 3). The CF Social Worker has an expertise that complements that of the CF Clinical Psychologist. The CF Social Worker must have skills in the assessment of practical needs and provide a range of services that are available in the patient's country. Up-to-date knowledge of the country's system of benefits and allowances is essential. The CF Social Worker has to be able to liaise with other agencies (e.g. health insurance companies, child benefit agencies, social welfare agencies, hospital administration, school, CF patient associations) and serve as an advocate for patients and families. The CF Social Worker must have expertise in educational and career issues of the country where the patient resides. They should be skilled in the implementation of child protection procedures, and ensure effective information sharing, referral and liaison to home authority teams, where appropriate. Home visits can greatly contribute to best care and should be available where needed.

Table 3. Examples of important life events where psychosocial support is crucial in people with CF

Starting kindergarten/day care/pre-school	Starting secondary school	Starting higher education
Starting school	Being a teenager with CF	Starting to work
First awareness of being different	First relationship	Starting a long-term relationship
Eating problems	First sexual experience	Parenthood
Sleeping problems	Death of a CF friend	Death of a CF friend
Behavioural problems (e.g. non-adherence)	Behavioural problems (e.g. non-adherence)	Behavioural problems (e.g. non-adherence)
Examples of key medical stages		
CF diagnosis	Diagnosis of infertility	
First *Pseudomonas* infection	Treatment of infertility	
First episode of allergic bronchopulmonary aspergillosis	Awareness of deteriorating disease	
Gastrostomy placement	Transition to the adult clinic	
Diagnosis CF-related diabetes	Transition to transplantation	
First haemoptysis and other complications	Transition to end-of-life care	
Supplementary oxygen dependence	Transplantation	

Professional development

CF Social Workers need to keep up to date with changes in healthcare systems, financial or social security matters, educational and work aspects, and patient and family welfare concerns. CF Social Workers need continuous education about CF issues. They should attend national and international conferences regularly to maintain up-to-date knowledge about CF and new scientific developments.

The CF Clinical Psychologist

During their life people with CF have to acquire specific CF-related healthcare behaviours in conjunction with acquiring normal developmental tasks. The CF Clinical Psychologist can help patients and families with these challenges and support them in coping with CF and its treatment throughout life.

Role

In relation to the patient and the family, the key responsibilities of the CF Clinical Psychologist are the assessment of, and intervention in, emotional, behavioural and psychological difficulties, using evidence-based treatments where indicated and making onward referrals where appropriate. The CF Clinical Psychologist is responsible for all the psychological work in the CF Centre. They should offer outpatient clinics as well as caring for hospitalized patients. Adherence, eating behavioural problems, anxiety and depression, demoralization, pain, phobias and sleep are day-to-day themes that need psychological care. The CF Clinical Psychologist may use mediation techniques in working with other CF MDT members. In addition, the CF Clinical Psychologist should provide a consultation and supervision service to other members of the CF MDT in their work with patients, and provide staff support in coping with 'working in CF'.

The CF Clinical Psychologist must be registered with their national governing body. They should have expertise in child/adolescent and/or adult clinical psychology and also in systemic psychology and the psychology of grief and bereavement. The CF Clinical Psychologist must be skilled in applying therapeutic techniques that have proven efficacy in patients and families with CF. These include, for example (cognitive) behavioural techniques [79], [80] and motivational interviewing [81]. Finally, the CF Clinical Psychologist has to be up to date with research on psychological issues in CF, including adherence, self-management and self-care, impact of chronic illness on human development, impact of chronic illness on family and social life, end-of-life issues and palliative care. The CF Clinical Psychologist should have or should develop, skills and experience in conducting psychological research with the aim of improving the care of patients and the understanding of psychosocial issues in CF.

Professional development

CF Clinical Psychologists have a responsibility to engage in CPD and in some countries this will be assessed as part of annual registration. Clinical Psychologists working in CF have a responsibility to update their knowledge of medical aspects of CF as well as mental health. Some countries have a national body for psychosocial professionals, such as in the UK, and membership is a requirement of practising in a CF team. CF Clinical Psychologists should attend national and international conferences regularly to maintain CF knowledge and to be aware of scientific developments.

Facilities and requirements for psychosocial care

The CF Clinical Psychologist and the CF Social Worker need sufficient time, office space, and facilities, and the support and respect of the CF MDT. The CF Social Worker and the CF Clinical Psychologist often need to stay in regular contact with patients and families in between clinic visits and therefore need access to modern media (e.g. email, phone, texting). They both need an up-to-date interactive referral system to external psychosocial professionals and institutions in order to provide problem-specific psychosocial/mental healthcare (e.g. for attention deficit hyperactivity disorder or autism) within the vicinity of a patient's home. The CF Clinical Psychologist and CF Social Worker must participate and contribute to the MDT meetings, decision making and patient consultation.

Framework for clinical genetics

Clinical Geneticists, Medical Molecular Genetic Laboratory Specialists and Genetic Counsellors have an increasingly important role in the complex diagnosis and disease management of CF, particularly in the areas of disease diagnosis, informed reproductive choices and the assessment of disease liability of *CFTR* variants detected by DNA sequencing. Furthermore, the Clinical Geneticist assesses the linkage phase through family segregation analysis, and ensures that complex alleles (which may be associated with variable CF phenotype) are not under- or misdiagnosed.

The Genetic Counsellor or the Clinical Geneticist provides counselling on reproductive options to the families of newly diagnosed children and to adult patients, and facilitates identification of at-risk family members who are genetically related to the patient. Clinical Geneticists, working within the CF Centre, also coordinate data sharing with specialized registries (e.g. the ECFS Registry) and submission of detected *CFTR* mutations to both the Cystic Fibrosis Mutation Database (CFTR1), which serves as a locus-specific database for mutations and variants identified on a world-wide scale, and the Clinical and Functional Translation of CFTR online interactive resource (CFTR2), in order to objectively substantiate the disease liability of identified *CFTR* gene variants.

If administration of CFTR modulating therapies is considered, the CF Clinical Geneticist is responsible for the laboratory verification of the *CFTR* genotype in eligible patients (optimally by independent sampling and DNA sequencing) and that the laboratory examination is performed in an ISO 15189-accredited laboratory that assures appropriate turn-around time.

Framework for data collection

CF is a multisystem clinically heterogeneous disease with variable outcomes despite its monogenic origins. Although phenotypic variation is influenced by genotype, siblings

with the same genotype differ in outcome suggesting the influence of other factors such as modifier genes, the environment, airway microbiota, social class, sex, access to healthcare and adherence to treatment [82]. Collecting data at a national and international level remains a key process to aid the understanding of the epidemiology and outcomes of the disease. It is only through accurate data collection that disease progression, outcomes, health economics and the need for change can be identified [7]. High-quality data can also be used by policy makers to focus on and prioritize future strategies and interventions. CF is a relatively rare disease with small patient numbers. Collecting data from a single institution limits the level at which clinical and translational research can be undertaken, and does not capture the significant variability in geographical outcome [83]. It is therefore essential that both small and large CF units submit data at least annually to national and/or European CF registries in order to ensure that appropriate longitudinal data are collected. The registry also acts as a monitor for an individual Centre's outcomes, providing an additional tool for ensuring standards of care and appropriate clinical governance. Healthcare professionals can find collecting and submitting data to national registries laborious and time consuming. Every effort should be made to ensure that data sets are limited to those of predictive value and that individuals can upload data through a secure intuitive interface. Funders must ensure that larger CF Centres have the resource to employ either a data clerk or alternative individual whose ring-fenced responsibilities include national data submission. To have value, such a person must have meaningful access to the management structure so that their voice counts and they can submit gold standard data

There is a need for the international CF community to adopt a standard coding structure. Creating uniform clinical terminologies and classifications of disease through a primary coding structure would allow clinical data to be mapped and shared between registries as well as other data sets. The changes would result in a common digital language allowing effective international collaboration and would remove key barriers to electronic connectivity. Addressing this issue is a matter of urgency, as a new era of medical informatics and electronic health records is upon us. Health services have started to successfully deploy electronic patient records, which automate the capture of data and have the potential to feed large continuous data sets directly into national and international registries. In Europe, a standard called XML has been adopted as a first step to harmonizing data from national registries. Almost all national organizations follow this initial standard, but this is only a first step in order to standardize the uploading; if the data collected do not adhere to common unequivocal definitions, the XML format cannot correct it. Therefore, common definitions and coding in both national registries and directly reporting individual centres are crucial. The European Commission has decided to start funding a European Platform on Rare Diseases Registration, which will provide services and tools for the existing and future rare diseases registries, in accordance with the Council Recommendation on action in the field of rare diseases (2009/C 151/02).

The interconnectivity will maximize patient benefit for minimum outlay, which is a key given

the difficult financial situation in healthcare. Adopting a detailed coded registry structure can have the added advantage of reducing costs and improving productivity [84], [85]. All such European and/or international data aggregations will have to make the best possible use of local/regional/national data acquisition and storage and intelligent ways of data sharing or retrieval will have to be developed.
Registries are here to stay and should be seen as a key part of any chronic disease management.

Challenges relating to developing health services in low income countries

The aim of the ECFS Standards of Care Guidelines is to improve the quality of care for patients with CF and to establish best practice across the whole of Europe. Immediate implementation of these guidelines may prove difficult for less economically advantaged countries where CF services are absent or inadequate. The EU EuroCareCF European Commission 6th Framework Coordination Action project identified a persisting wide difference in the standards of care across Europe, with some Eastern European countries having very basic or no recognizable CF services [7]. The likely reason for such dramatic inequalities has been the absence of appropriate funding, a lack of staff recruitment and training, and also a lack of political prioritization.
The current situation in Eastern Europe was assessed from the responses to a questionnaire distributed to most Eastern European countries by the ECFS Standards of Care Committee. The aims were to evaluate:

* a minimum number of patients who attend CF Centres in Eastern Europe
* national recognition of CF Centre networks, and
* the composition of CF MDTs and the cooperation between paediatric and adult Centres.

Each question was answered on the basis of the current situation in the country and in relation to the ECFS Standards of Care [4]. The response rate was 44% (7/16: Czech Republic, Hungary, Latvia, Poland, Serbia, Slovakia, Ukraine).
The major observations were as follows. While the number of patients per CF Centre is currently below 50 in some Eastern European countries, a requirement for a minimum number of 50 was seen to be an achievable goal. Centralized CF care has been endorsed by government authorities in only three of seven Eastern European countries. A paediatrician/pulmonologist, a physiotherapist and a CF nurse specialist were agreed to be essential team members. Many CF Centres lack a full-time CF nurse specialist, a dietitian, a microbiologist, a psychologist, a social worker or secretarial support. Collaboration between paediatric Centres and those for adults with CF had not been established in two of the countries that replied to the survey.

It is imperative that all European countries should strive to implement best practice in accordance with the ECFS recommendations. An initial stepwise approach may be needed in some low income countries where there are no established services and CF MDTs virtually do not exist. For example, initial recruitment of core medical, nursing and physiotherapy staff may be the most appropriate initial investment on the way to establishing a service that meets all ECFS standards. It is no longer acceptable to have such dramatic variation in the survival of people with CF across European nations, and every effort must be made to deliver equality and high standards of care. CF care in low income countries should be centralized in well-established CF Centres that can guarantee a reasonable standard of complex care for both paediatric and adult patients. The Centre should care for at least 100 patients, although a minimum of 50 may be temporarily considered acceptable. Because of the financial and staffing limitations in Eastern Europe, shared care with local hospitals is not a preferred model of care. Resources should be directed at establishing state-of-the-art CF care at a national level by the development of specialized CF Centres at major hospitals, and where possible at the level of University Hospitals. The minimum staff requirements for a specialist CF team include a physician and a specialist nurse (one each for children and adults in Centres that care for all age groups), and a CF specialist physiotherapist. The goal is to develop teams that include a microbiologist, dietitian, psychologist, social worker and clinical geneticist. Meanwhile the absence of these specialists should not delay the setting up of regional CF Centres. Their roles may be temporarily performed by specialist consultants of the hospital who can be accessed by the CF service, even though not primarily allocated to a CF team and therefore not able, for instance, to participate in regular CF MDT meetings.

Perspective from European CF associations

The function and role of national CF patient organizations in Europe
Most European countries have their own national CF patient organization. These vary in size and methodology but have one thing in common: they fight for the interests of people with CF, in the broadest sense of the word. They work together with volunteers, who are often experts in CF but who may be non-medical. In Europe patient organizations are developing their own in-house expertise and employing professional staff, for example in the area of healthcare quality, scientific research, communication, fund raising, information provision, and the legal and psychosocial aspects of CF. The organizations aim to support patients and their parents, both individually and collectively, and to define research agenda, to finance scientific research and to test healthcare quality. They are often closely involved in the setting up and maintenance of guidelines for the diagnosis and treatment of CF. The national CF organization can play an important role in the national CF registry. Many have helped found these registries and continue to support and finance them. In a

number of countries, the CF organization plays a role in the set-up and organization of research networks and healthcare quality improvement programs for people with CF. Fundraising is an important prerequisite to enable the organizations to successfully achieve the above aims. Over the past few years, CF organizations in countries such as the UK, Germany, Belgium, France, Italy and The Netherlands have invested millions of Euros in scientific research and healthcare quality. As a result, they have made important contributions to the progress that has been made in many healthcare areas of CF. Patient participation is an important part of the work achieved by patient organizations, as it is exactly the patients' perspective that can and should be expressed by the national CF organizations.

National organizations

The national CF organizations have responsibilities to provide information. This material, which is made available to people with CF and their parents/carers, is often developed in collaboration with the CF Centres and covers all aspects of life with CF: diagnosis, treatment, growing up with CF, raising a child with CF, going to school with CF and building a life with CF. National CF groups should work closely with CF Centres in the organization of healthcare, a cooperation that may vary in its infrastructure in different countries. However, in all cases, representatives of those Centres should be present on medical advisory boards and scientific councils. CF organizations should organize meetings for parents and, with the use of information technology to safeguard against cross-infection risks, for the patients themselves. E-health has many advantages and is a subject that is being researched and developed. CF organizations are the obvious parties to represent and protect the interests of patients and their parents/carers, for example by supporting ready availability of new medications, securing reimbursements for medication and access to high-quality healthcare. CF organizations should lobby and exert pressure on the authorities, government and insurance companies in this regard. They should also organise congresses, symposia and other meetings (in collaboration with or under the supervision of the healthcare organizations), in which the specific (scientific) aspects of CF are discussed.

CF patient organizations are non-medical yet through close cooperation with CF Centres have developed a lot of CF expertise. It is important that the Centres and the organization exchange information on a regular basis in order to facilitate a proactive approach to developments in the healthcare industry and scientific research. This collaboration will help to improve communication with patients, facilitating their inclusion in scientific studies and solving problems on a national level more swiftly.

European organizations

The European CF patient organizations are united in a single European society — CF Europe (CFE). The importance of collaboration in Europe is growing, especially with regard to healthcare access, which is not uniform, or even available, in all European countries. As a result, collaboration in the fields of research, research financing and fund raising is continually increasing.

The European collaboration should lead to the CF organizations in countries where CF healthcare is already at a high level accepting their responsibility and offering their expertise to countries in which adequate healthcare, access to healthcare and the ready availability of medication are not universal. This should take place in close collaboration with the CF Centres. Collaboration through CF Europe has made it easier to lobby effectively on a European level with regard to subjects such as organ donation, accessibility, quality and affordability in healthcare.

Another level of European collaboration is partnering with the European overarching patient support organization (Eurordis), which is representing the majority of rare disease national and regional organizations (including CF) in e.g. terms of awareness building, access to care, reimbursement policies, development of European guidelines for centre care, fundraising, introduction of orphan medicinal products into therapy, including training courses on various aspects of patient advocacy.

CF patient organizations are working increasingly with the ECFS, for example by participating in the executive boards of the EFCS Patient Registry and the EFCS Clinical Trials Network. The latter is financially supported by a number of patient organizations. Through the CF patient organizations, patients and parents have become more involved recently in the assessment of the ECFS Clinical Trials Network research protocols.

Conflict of interest

S. Conway, K. De Rijcke, P. Drevinek, J. Foweraker, T. Havermans, H. Heijerman, L. Lannefors, A. Lindblad, M. Macek, S. Madge, M. Moran, L. Morrison, A. Morton, J. Noordhoek, D. Sands, A. Vertommen, and D. Peckham have no conflicts of interest to report. I. M. Balfour-Lynn declares personal fees from Vertex, outside the submitted work.

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2

Chapter Three

Development and outcomes of a patient driven Cystic Fibrosis Quality of Care Improvement project

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Abstract

The Dutch CF Foundation (NCFS) developed a quality improvement program, to assess and improve quality of care in all CF centers in The Netherlands. Criteria to assess quality of care from the patients' perspective were defined and quality of care was assessed by patients via online surveys and site visits. Recommendations were addressed to all centers to improve quality of care. Most recommendations were related to communicational issues. All centers were given the quality mark of the patient organization, although two of them needed extra time to meet the lower limit of the core set of criteria. After two years, over 75 % of the recommendations given to the centers were fully or partly implemented, showing a high efficacy of the program.

Keywords
Patient perspective; patient participation; patient involvement; quality mark; quality of care

Introduction

Seven CF centers in The Netherlands are specialised in the treatment of people with CF, all with adult and pediatric departments. Multidisciplinary care is provided according to the treatment guidelines of the ECFS [1]. Centered care enables to measure quality of care and to achieve improvements per center or team.
A substantial amount of publications on the efficacy of quality improvement strategies in general is available, but only a few focus on CF care [2,3,4]. Most publications are driven by professional caregivers and focus on clinical aspects of care, such as lung function (FEV1) or Body Mass Index (BMI). The development of quality criteria and measurements in close collaboration with patients is very rare. Only two studies [4, 5] address patient-driven quality of care improvement strategies. The findings show positive attributes and opportunities for improvement of quality of care, being the rationale for patient-developed quality of care. An overview of experience of care not only draws the attention to unmet needs of the end user of care, but incorporates people with CF and their caretakers into improvement efforts. To measure and improve care for people with CF, the Dutch CF Foundation (NCFS) developed quality criteria in collaboration with patients, parents and clinicians focusing on the needs and expectations of patients. The Dutch CF Foundation accredits CF centers after following this quality assessment program.
This article describes the development of a quality improvement project with criteria that focus on the patient perspective and the immediate and long term effects on quality of care for people with CF.

Methods

Development of criteria from the patients' perspective
A panel of four people with CF and four parents of children with CF, under supervision of the NCFS research coordinator, reviewed reports and programs from the Cystic Fibrosis Foundation (US), Mukoviszidose E.V (Germany) and a national program [2,3,5] and selected quality criteria from the perspective of the patient. First, a general set of criteria, relevant for all aspects of care was drafted [1 to 17, Table 1]. Subsequently additional criteria were drafted related to diagnosis, individual care planning / treatment / guidance, reintegration / participation of the patient, and end-of-life / palliative care (Table1). In a first round members of the panel were asked to select criteria they considered to be important out of the first draft based on the mentioned existing reports. They could also add other criteria. These were considered in the second round. Criteria were selected, if at least 6 out of 8 panel members (75%) agreed to a criterion.
After evaluation of a pilot accreditation visit at one hospital, the set of criteria was finalized [Table1]. Online questionnaires were composed for patients / parents and for centers in order

to address all criteria.

Assessment of quality of care

Seven CF centers are providing CF care in The Netherlands for 1600 CF patients [7]. All these centers have an adult and a pediatric department. All respective patients or their caretakers were invited by a standardised email to complete the online questionnaire. NCFS compiled an anonymized overview of the results per center, showing the responses of the patients and caretakers. The results were shared with each center. An audit committee was installed, consisting of a person with CF, a parent, a CF nurse and two representatives of the patient organization (NCFS) and they were trained and prepared for a formal visitation of the centers. The committee reviewed and discussed the questionnaire results and visited all centers.

The visitation committee spent about half a day per CF center, in order to meet the complete multidisciplinary team and discuss the results of the online questionnaires. The visitation was prepared extensively, with a taylor made agenda for each center. The visits started with an invitation to the CF team to explain or illustrate the results from the questionnaire. A guided tour through the hospital was organised, visiting all facilities, like the wards, physiotherapy, consulting rooms, lung function facilities, and waiting rooms. The guided tour was respecting confidentiality with regard to inpatients by asking them permission before the tour. In clinic patients' privacy was guaranteed by not visiting waiting rooms and other wards when patients were around. In case an inpatient with CF agreed to receive the visitation committee in his room, the person of the audit committee with CF did not enter that room, to prevent cross infection. Finally the visitation committee discussed their findings with the hospitals board of directors. This program would take approximately three hours and was organised by the CF team on the instructions of the visitation committee of the patient organization.

Within six weeks every center received a report, reflecting on the site visit, the amount of criteria met by the center and a set of recommendations. Recommendations were given for every criterion that was not met by the center, in the following categories:

1. Workload distribution within the team, the need for extension of full time equivalents, administration, a CF nurse, etc.,
2. Facilities like parking, catering, access to internet / tv, technical condition of the building,
3. Aspects of care, like access to all relevant disciplines, coordination of care for home IV-courses, audiometry, transition to adult care,
4. Communication about test results, hospital admissions, online communication,
5. Segregation policy and hygiene.

Accreditation was awarded when centers met at least 80% of the core criteria [criteria 1 to 17, Table 1] and at least 70% of the remaining criteria [criteria 18 to 61, Table 1]. Centers were enabled to check the facts of the report, before they received the final version. In case a center did not meet an adequate percentage of criteria for accreditation, they were given half a year to demonstrate improved care in order to meet a sufficient percentage of criteria to obtain accreditation.

Assessment of Quality Improvement

After two years conclusions and recommendations given to the centers were evaluated. Either directors of the team, or clinicians representing the team, were contacted by a research staff member of NCFS and asked which recommendations were implemented and, if this was not the case, why. The responses were scored on a 'yes / no / partly' scale.

Assessment of the Quality Improvement Program

All centers were questioned about their perception of the procedure as developed by NCFS with regard to their invested time, the procedure, results and added value to the quality of care. We used a five point scale, ranging from very good to not good at all or very high to very low.

Table 1. Overview of the results per criterion (with categories A-E) in adult centers and pediatric centers.

Criteria (category)		Adult centers	Pediatric centers	All centers
1 (A)	Patients should receive multidisciplinary care, since the disease can manifest in multiple organs. All clinicians involved in treating CF patients are part of a CF- team. This team will assemble once a week to discuss their patients.	100,0	100,0	100,0
2 (A)	The CF-team comprises a (pediatric) pulmonologist, pediatric gastroenterologist, physiotherapist, dietician, social worker, psychologist, medical microbiologist, hospital pharmacist and nurses trained in treating CF patients.	100,0	100,0	100,0
3 (C)	If necessary, a consult with clinicians of other disciplines, such as gastroenterology for adults, internal medicine, surgery, clinical genetics, ENT, radiology, obstetrics, sexology, fertility, cardiology, transplant medicine, stoma care and hospital hygiene should be possible.	100,0	100,0	100,0
4 (A)	Treating CF should be a part of the daily work of CF team members. Therefore, at least 50 patients should be treated at the CF center.	83,3	85,7	84,5
5* (D)	Protocols on the treatment and counselling of CF patients should be present and accessible to patients.	50,0	85,7	67,9
6 (D)	Members of the CF team should inform patients and/or parents of the various aspects of care, such as treatment, attending clinicians, accessibility, appointments, test results, mutual expectations, collaborations and agreements with local clinicians.	83,3	100,0	91,7
7 (B)	The CF center should inform patients or parents of possible personal contributions for certain treatments in advance. More over, the CF center should act as a mediator between patients and insurance companies to enable reimbursements.	100,0	100,0	100,0
8 (D)	The (pediatric) pulmonologist should be available 24 hours a day for consults with patients or colleagues. More over, the CF center should inform patients of the contact details of the center, such as the phone number and email address.	83,3	100,0	91,7

Table 1. Continued.

Criteria (category)		Adult centers	Pediatric centers	All centers
9* (D)	The CF center should provide clear information about the deadline to answer questions, that have been raised by patients	66,7	71,4	69,0
10 (D)	The CF center should provide information about the center on their website. Additionally, a link to the NCFS should be present on the website.	100,0	100,0	100,0
11 (C)	Research should be an essential aspect of care at the CF center. Therefore, a center should evaluate the data of their own patients once a year. More over, the center should participate in scientific research.	100,0	100,0	100,0
12* (A)	A framework to facilitate participation in research should be available at the CF center. In addition, a CF center should employ a research assistant. Finally, each center should maintain a database of patient medical information.	66,7	64,3	65,5
13 (A)	Each year data from the local CF database should be shared with the NCFS for the purpose of the Dutch CF registry. All CF centers should participate in the annual meeting for CF centers and the Dutch CF Research Network.	100,0	100,0	100,0
14 (D)	The CF center should arrange education and in-service training for nurses, pediatricians, pulmonologists, paramedics, aid workers and students. Additionally, the CF center should provide education for patients, parents and the CF team.	100,0	100,0	100,0
15* (A)	The CF center should have access to sufficient secretary support in order to ensure that administrative work can be performed adequately.	83,3	64,3	73,8
16* (A)	The CF center should have access to sufficient financial aids in order to provide care according to the CF guidelines and quality criteria.	50,0	71,4	60,7
17 (C)	The CF center agrees to participate in site visits from relevant professional groups and the four-yearly site accreditation visits performed by the NCFS.	100,0	100,0	100,0
18 (C)	The CF center should provide diagnostics, care and counselling to children and parents that conform the national guidelines and protocols.	100,0	100,0	100,0
19 (D)	The CF center should provide information about CF to parents.	100,0	100,0	100,0
20 (D)	The CF center should provide information about the NCFS to parents.	100,0	100,0	100,0
21 (D)	The appointments/ examinations of the annual check-up should be planned with the agreement of both CF centers and patients.	100,0	85,7	92,9
22* (D)	Lung function test result, laboratory results, prescriptions and treatment plans should be accessible to patients, through a secure and patient-friendly, online program.	0	0	0
23* (D)	The CF center should provide clear information on the deadline for clinicians to discuss test results and the outcomes of the annual check-up with patients.	33,3	42,9	38,1
24 (C)	Each patient should visit the CF center once every three months for the purpose of check-ups, to evaluate the patient's condition, discuss treatment and if necessary for consultation with other specialisms. An exception can be made for patients with a mild form of CF.	100,0	100,0	100,0
25 (C)	Once a year, patients should undergo extensive examination at the CF center.	83,3	100,0	91,7
26 (C)	Sputum or throat culture samples should be taken at every outpatient visit in order to enable early treatment.	100,0	100,0	100,0
27 (C)	The Oral Glucose Tolerance Test (OGTT) should be performed in all patients over 10 years with exocrine pancreatic insufficiency to detect CF-related Diabetes Mellitus.	100,0	100,0	100,0

Table 1. Continued.

Criteria (category)		Adult centers	Pediatric centers	All centers
28 (C)	Out patient check-ups can take place at local hospitals under a "shared care" agreement on condition that the local hospitals treats a minimum of 10 CF patients a year.	100,0	100,0	100,0
29 (C)	The CF center should have access to a microbiological laboratory, clinical chemical laboratory, lung function laboratory and X-ray department. More over, two clinical tests can be outsourced to other centers. Firstly DNA analyses can be outsourced to the university hospitals in Groningen, Rotterdam and Amsterdam (VUMC). Secondly, measurement of differences in action potentials in the mucous membrane of the nose or rectum can be outsourced to the university hospitals in Rotterdam and Utrecht.	100,0	100,0	100,0
30 (B)	During out patient visits, a personal consultation room will be assigned to CF patients	100,0	100,0	100,0
31 (B)	Travelling time of patients should be taken into consideration whilst planning out patient visits.	100,0	100,0	100,0
32 (B)	The waiting time between examinations by different specialists during out patient visits should be limited to 30 minutes.	100,0	100,0	100,0
33 (E)	The CF center should have separate, multidisciplinary, outpatient office hours for CF patients. More over, arrangements need to be made to maintain segregation.	83,3	92,9	88,1
34* (E)	In order to maintain segregation of CF patients during hospital visits, several measures need to be taken. First, the use of waiting rooms should be avoided. More over, consultation rooms, furniture and other equipment should be cleaned with 70% alcohol after each visit.	66,7	71,4	69,0
35* (E)	A checklist of cleaning activities should be present in in all waiting rooms and consultation rooms.	16,7	14,3	15,5
36* (D)	Before admission, a representative of the CF center should discuss expectations and treatment plans with patients. More over, patients should receive written or digital information.	66,7	78,6	72,6
37 (D)	The CF center should have an open approach towards second opinions if requested by patients. The center should cooperate in adequately transferring information.	100,0	100,0	100,0
38	Once a year, the clinician in charge should evaluate the entire medical treatment with the patient.	100,0	100,0	100,0
39* (C)	The CF center should be responsible for effectively organizing the various forms of home therapy, such as atomizers, physiotherapy, supplemental oxygen therapy, administration of intravenous antibiotics and basis lung function test.	66,7	78,6	72,6
40 (C)	The decision to start home treatment with intravenous antibiotics should be carried out within 48 hours.	100,0	100,0	100,0
41* (C)	Monitoring of blood antibiotic levels should be possible at home.	50,0	42,9	46,4
42 (C)	If needed, administration of a PICC line should be possible within 24 hours.	100,0	100,0	100,0
43* (C)	The CF center is responsible for providing proper instructions on the use of nebulisers.	50,0	57,1	53,6
44* (A)	Nurses specialized in treating CF or diabetes patients should be available on weekdays.	50,0	64,3	57,1
45 (C)	In the case of a sudden admission, continuation of care should be guaranteed. More over, clear communication should be maintained with patients on which treatments and test are necessary and whether these can be performed in weekend.	100,0	100,0	100,0

Table 1. Continued.

Criteria (category)		Adult centers	Pediatric centers	All centers
46 (C)	Collaboration between pediatric and adult clinicians should be present at the CF center so as to make transition from pediatric care to adult care easier.	83,3	85,7	84,5
47 (D)	The CF center should provide digital or written information about the beneficial effects and side effects of medication, possible treatment options and its complications.	83,3	85,7	84,5
48 (B)	The CF center should provide patients with a private room with a toilet and bathroom.	83,3	100,0	91,7
49* (B)	The CF center should provide various facilitations for patients upon admission (such as a television, Internet, a laptop with webcam and fitness equipment) without any additional costs.	50,0	85,7	67,9
50 (B)	In the case of hospital admission, patients should be allowed to receive visitors at least six hours a day.	100,0	100,0	100,0
51 (B)	Family and friends of patients should have the option to spend the night at the CF center or a nearby location	83,3	100,0	91,7
52 (B)	In the case of a hemorrhage, embolization should be performed within 30 minutes, 7 days a week/ 24 hours a day.	100,0	100,0	100,0
53 (E)	The CF center should have enough means at its disposal to maintain segregation of patients upon admission.	100,0	100,0	100,0
54* (C)	The CF center should have protocols on the administration of medication. Moreover, nurses should be educated on and experienced in administrating intravenous medication to CF patients.	66,7	85,7	76,2
55* (C)	All patients receiving treatment with aminoglycosides should undergo audiometry prior to and after starting treatment.	33,3	42,9	38,1
56* (C)	Following discharge from hospital, agreements should be made with patient on the (dis) continuation of medication.	66,7	85,7	76,2
57 (D)	The CF center should proactively provide information about specific opportunities and arrangements for individual patients.	83,3	100,0	91,7
58 (C)	If necessary, patients should have the option to receive psychosocial counselling at the CF center.	83,3	100,0	91,7
59 (C)	Family functioning, the well-being of parents and siblings and daily functioning should be particular points of attention during consults with patients or family members.	100,0	100,0	100,0
60 (C)	End of life treatment of patients will be determined by mutual agreement between clinicians and patients and/or family members.	100,0	100,0	100,0
61 (B)	Family and friends of patients should have the option to spend the night at the CF center or a nearby location. Additionally, rooming-in facilities should be available at the center.	83,3	100,0	91,7
Over-all score		83	87	85

* indicates the criteria which are met by less than 80% of the centers.
A: Workload distribution within the team
B: Facilities of the hospital
C: Aspect of care
D: Communication
E: Segregation policy and hygiene

Results

Assessment of quality of care

All seven centers, except for the adult department of one center (G) agreed to participate in the program. The response rate of patients / parents on the online questionnaire varied between centers from 33% to 76% (mean 49.2%, SD 13.0).

Adult and pediatric departments ranged from 77 to 93% in the percentage of criteria that were met [Fig1].

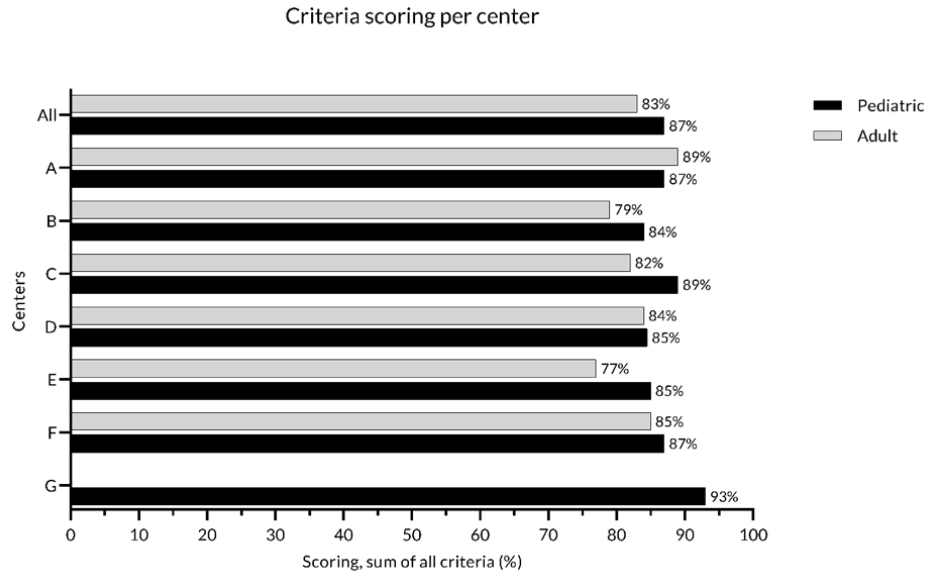

Figure 1. Criteria scoring per center

The results at pediatric centers were more positive compared to adult centers: 87 versus 83%. Pediatric departments at five centers had higher scores than the adult departments. Center A was an exception.

For each criterion not met by a center, a recommendation was given. The amount of recommendations given by NCFS to the centers varied from 9 to 16 recommendations per center [Fig 2]. All together 82 recommendations were given; 16 of them were related to the workload of the team; 16 related to hospital facilities for the patient; 14 related to different aspects of care; 27 of them are related to communication and 9 recommendations related to segregation policy and hygiene. The high number of recommendations with regard to communication referred to better communication about the patient within the team; a better insight in the test results within short notice; better communication either by phone or

online; better coordination between home care facilities and the local or hospital pharmacy. Two sites did not reach the pre-set accreditation criteria, but did after re-assessment after 6 months.

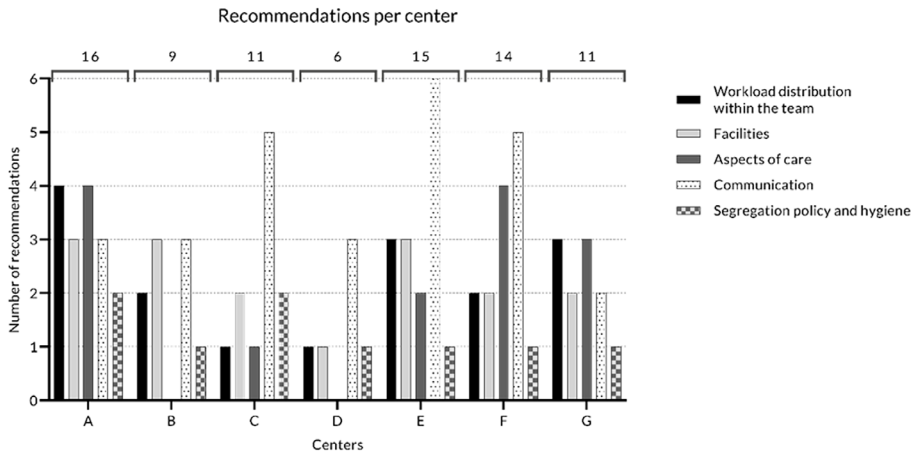

Figure 2. Recommendations per center

Assessment of the level of Quality Improvement after two years

After two years 51.2% of the recommendations was successfully implemented. 25.6 % of the recommendations was partly implemented and 23.2 % of the recommendations was not addressed. Figure 3 reflects the applied recommendations per category, showing that especially hospital facilities are more difficult to improve. Figure 4 displays the implementation of the recommendations per center, with variation in the degree of implementation between centers.

Assessment of the Quality Improvement Program

All the centers judged the invested time per center as low and the added value to the quality of care was perceived as high. All centers expressed their willingness to participate in a second round, and the adult center not participating this time, wishes to participate in the next round. Most centers have put the quality mark on their websites or at the reception desk in their outpatient clinic.

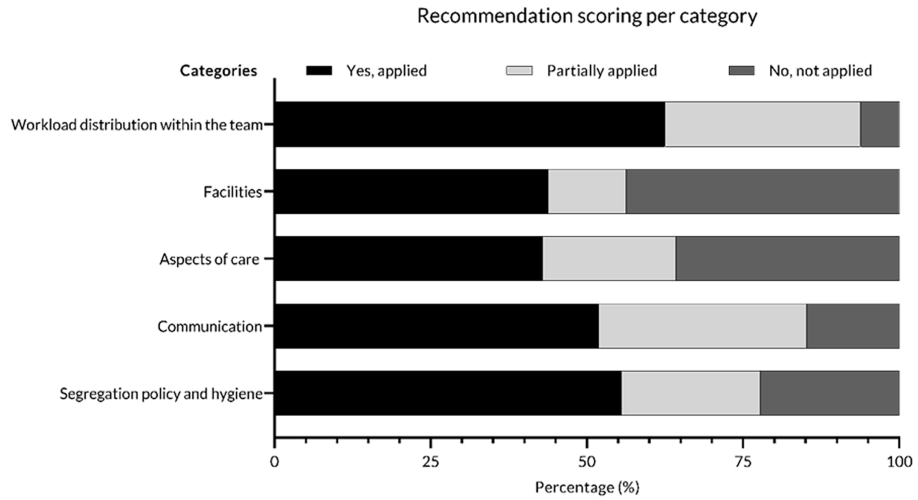

Figure 3. Recommendations per category

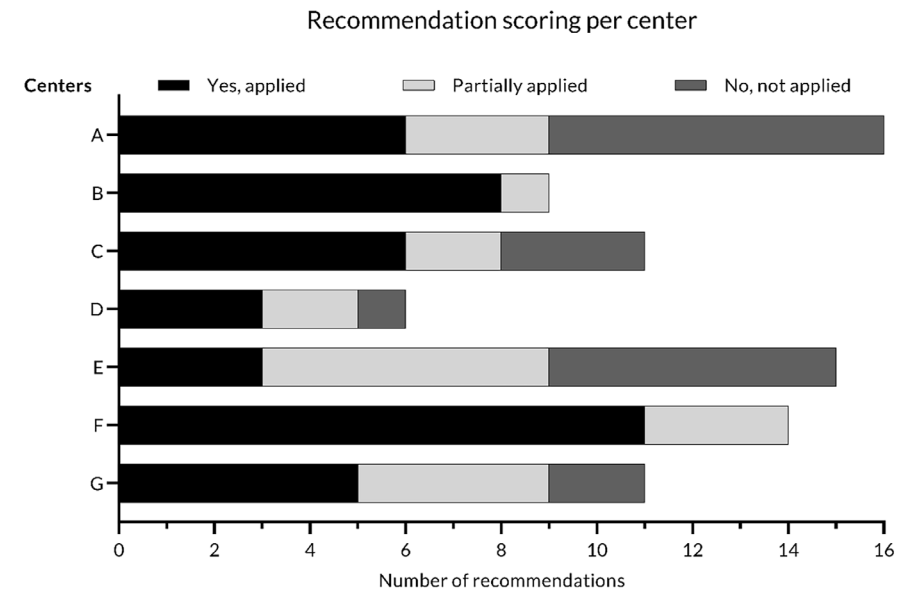

Figure 4. Recommendation scoring per center

Discussion

This project is an example of a quality improvement strategy, that is not hard to develop and implement in the more general quality improvement strategies, and that takes the perspective of the patient into account. The way this project was conducted, was appreciated by the centers: some expressed hesitations to participate initially at the time the project was announced, yet during the program they experienced limited investment of time, and very concrete, easy to adapt recommendations. All centers were approved and accredited with the patient organization's quality mark. They used the accreditation in their communication, the quality mark was put on their websites and some put the accreditation in a frame on the reception desk of the clinic. After two years more than half of the recommendations were implemented in daily practice, varying from more full time equivalents for CF nurses or administration, to more guidelines about communication and segregation policy. Over 25 % of the recommendations was partly successfully implemented; this sums up to a high score on improvement of the quality of care with regard to criteria that matter to patients. Improvement of care does not only relate to communication with patients, but also to factors like the workload of the team. Contrary to our expectations, recommendations with regard to the workload distribution of the team had the highest rate of implementation. This can be explained by the fact that the audit committee met with the board of directors of the hospital, conveying their concerns with regard to their observations. Subsequently, some centers were enabled to hire extra CF nurses to address their high workload. Improvement of facilities, like parking or catering are more difficult to implement, since these are hospital wide facilities. The board of directors of all hospitals was open and willing to discuss the observations of the audit committee. At the same time they seemed to feel somewhat unaccustomed to the fact that the audit committee was chairing the meeting and setting the agenda for urgent topics from their point of view. Furthermore, CF centers have to pay more attention to guaranteeing segregation in the view of the patients. CF centers can play a more prominent role in home treatment of patients. Better logistics to ensure high standard participation in research was a topic in some centres. Finally, CF centers tend not to present accessible protocols on treatment and counselling of CF patients. Although we expected a higher overall response rate in some centers on the surveys from patients and caregivers, the ratings and comments of the respondents offered enormous input for the discussions during the site visits. CF-teams were not always aware of certain gaps or areas for improvement in their care and started improvement activities to meet those criteria immediately. The limitation of this program is, that we do not have a clear insight how CF centers implemented the recommendations. In the second round this has to be measured. The results of the assessment did not seem to make patients change their CF center. However, this topic was not part of the follow up of the assessment. The follow up concentrated on the improvement of care by measuring how many of the recommendations were implemented. In the next round, the possible change of CF center from the patients side has to be included in the online questionnaire.

From the second round on, we have to bear in mind that consistency in the level of quality for each CF center is important. At this point the quality mark as such, has not yet enough authority to stop a center from providing care in case the lower threshold is not met. However, if a quality mark would be withdrawn from a center, there are other options, like alarming health care authorities and payers.
The program is reasonable cost effective and easy to develop. It makes it doable for patient organizations to carry out, although they have to own experienced staff in order to guide the program in an effective and professional way.
All developed criteria were aligned with the European guidelines on diagnostics and care for CF [1]. NCFS decided not to start a second round yet, because of the expected update of the national guidelines and due to the SARS-CoV-2 pandemic. All centers agreed to participate in the second round.

Conclusion

The organization and implementation of a quality assessment and improvement strategy with trained patients and caregivers is feasible for a patient organization and perceived as not very much time consuming for the CF clinic or the hospital in general. However, the patient organization needs staff with skills and expertise in the area of quality assessment. The overall performance of CF centers in the Netherlands is satisfactory from the patient perspective, with paediatric centers performing slightly higher. Substantial improvement was reached within two years, by implementation of the recommendations given by the patient organization.

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Chapter Four

A Coaching Program for Parents with a Child, Diagnosed with CF after NBS, Feasibility and Possible Effects

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Abstract

Newborn screening for Cystic Fibrosis was introduced in The Netherlands in 2011. Parents, who have a child diagnosed with Cystic Fibrosis, are faced with a sudden and impactful life event that evokes anxiety and stress. A parental coaching program was set up by the Dutch Cystic Fibrosis Foundation in order to support the parents. Feasibility and possible effects of the program were studied in a pilot. The program seems to have positive effects on the psychological wellbeing of the parents. After the intervention, levels of anxiety and distress of the parents significantly decreased, compared to the start of the program. Overall, the program was rated very positively by the participants and 90 % stated they reached their personal predefined goals. Both the structure and the content of the program are feasible for them. They would highly advise the program to future parents with a child diagnosed with CF.

Introduction

Newborn Screening (NBS) for Cystic Fibrosis (CF) has positive effects on nutritional, respiratory and survival outcomes [1] and is expanding across Europe. In countries where CF is implemented in NBS programs, this is done according to the standards of the European Cystic Fibrosis Society (ECFS), although techniques and procedures are variable [2]. In the Netherlands NBS for CF was implemented in May 2011. Parents are predominantly in favour of NBS, being aware of the advances when treatment starts as early as possible. At the same time the diagnosis has a huge impact on them and interferes with the bonding between parents and child [3]. Coaching of individuals and groups has been developed during recent years as an addition to psychological interventions to promote coping with life events and resilience [4].

The Dutch Cystic Fibrosis Foundation (NCFS) wanted to reach out to parents and help them to overcome or even prevent stress and anxiety and to increase their resilience. A coaching program was developed and offered to parents. The purpose of the program was to enable parents to cope with the diagnosis of CF in their child; to optimize the mental health status of the parents; to enable them to take care of their child, each other and their family; to optimize social and work-related functioning; to empower them in their relationship with the clinical healthcare system if needed. The aim of this pilot study was to explore the feasibility and possible effects of the program. The perception of the parents towards the coaching program was evaluated.

Methods

Participants

Parents of children diagnosed with CF after NBS were offered the coaching program via the CF centres and via the information for parents of newly diagnosed children at the NCFS website. They could apply for participation within two years after the diagnosis. NCFS supported the project financially and parents were not charged when participating.

Intervention

Qualified and registered mental health coaches, with knowledge and experience in guiding parents with regard to chronically ill children and parenting, formed a team. The coaches worked along the lines of family therapy with a systemic approach. The coaching team was educated about the many different aspects of CF, like its clinical symptoms and the care system that the parents became acquainted with. The program was announced by NCFS and supported by all Dutch CF centers, that perceived the program as additional to their own mental health care routine. The coaching program consisted of four sessions at home (individually or with both parents) with the coach. In the first session parents defined their

personal goals and subsequently worked on these goals with the coach in an individualized, tailor made program. Parents were in control of the period of time in which the four sessions took place. Finally, after their individual program, they were offered one group session with other parents, under the guidance of a coach.

Measurements

A pre post study design was used. At start of the program (T= 0) and after finishing the program, usually around 12 months after the start (T=1), participating parents filled in standardized questionnaires, developed by the NCFS, concerning:

i. Goals: the personal goals of the parents and the level of achievement of these goals using a 5-point scale.
ii. Distress: to assess the level of tension, concern and anxiety, three questions from the HADS [5] were used on a five-point scale.
iii. Satisfaction: about the information, content and organization of the program, using a 5-point scale. All 5-point scales had the same structure: 5=very good, 4=good, 3=sufficient, 2=not sufficient, 1=bad. For a complete list of the questions see addendum.

Statistical analysis

Descriptive analysis consisted of frequency analysis of the HADS scores and 5-point scales. Differences between T0 and T1 on the level of distress were analysed using a Wilcoxon Signed Rank Test.

Results

Participants

One third of the parents (n=76), confronted with the diagnosis CF after NBS, participated in the program, according to data from the Dutch CF Registry 2011-2016. 67 of them (31 males and 36 females) filled in the questionnaires at T0 and T1.

Outcomes

i. Goals: personal predefined goals were reached by 93.6% of the parents, ranging from sufficient to very good (Figure 1).
ii. Distress: the percentage of parents that felt ‘very concerned’ or ‘concerned’ decreased from 52,2% at the beginning of the program to 35,7% at the end of the program ($p< 0.001$). The percentage of parents feeling ‘mostly distressed’ and ‘often distressed’ decreased from 48,2% at the start of the program to 31,2% at the end ($p< 0.04$). The percentage of parents who experienced feelings of anxiety ‘very often’ and ‘often’ decreased from 51,8% to 39,6%, compared to the end of the program ($p< 0.018$) (Figure 2).

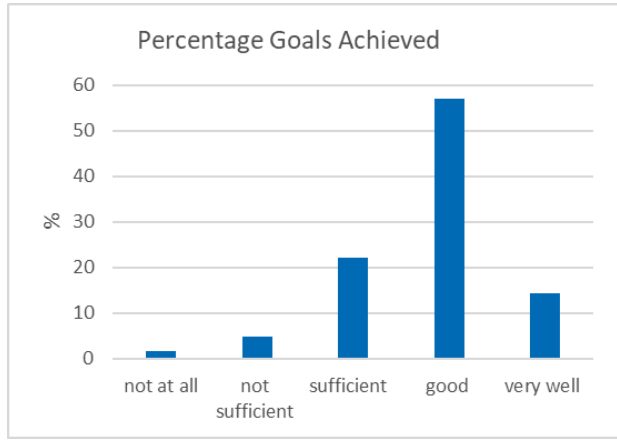
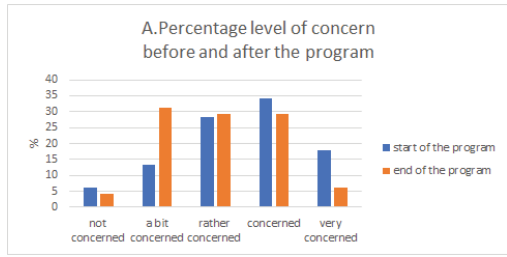
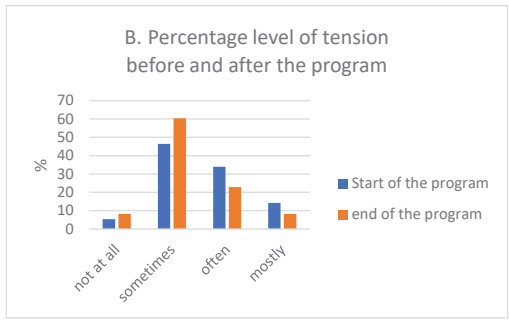


Figure 1. Perceived achievement of predefined goals





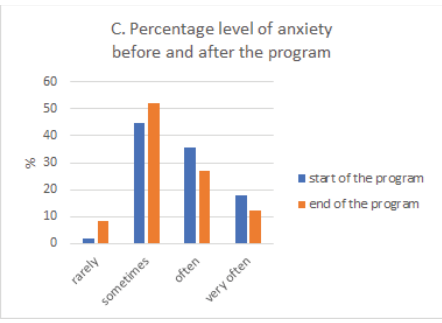


Figure 2. Perceived distress (concern (A), tension (B) and anciety (C)) at start and end of the program.

iii. Satisfaction: at the start of the program over 80% of the participants rated the information about the program 'good' or 'very good', in relation to their expectations, the methods being used (approach), the definition of the goals, and the organization of the program. According to 96.9% of the parents, the coaching program contributed to their personal development. The implementation of the content of the coaching program into their daily lives on a practical basis was doable for 88.9% of the parents. The program gave 88.9% of the parents greater insight into their functioning. The program fitted into the family circumstances for 95.3% of the respondents and 88.9% described the program as fitting to their personal situation. The content of the program was considered as relevant by 87.3% of the respondents. The number of sessions offered in the program was rated as 'good' or 'very good' by 71.5% of the participants. The other 28.5% stated to be in favor of more sessions. The distribution of time in between the total amount of sessions was rated as 'good' or 'very good' by 88.8% of the responders. Of all respondents, 92.4% stated they would recommend the coaching program to other parents with a child, diagnosed with CF (Figure 3).

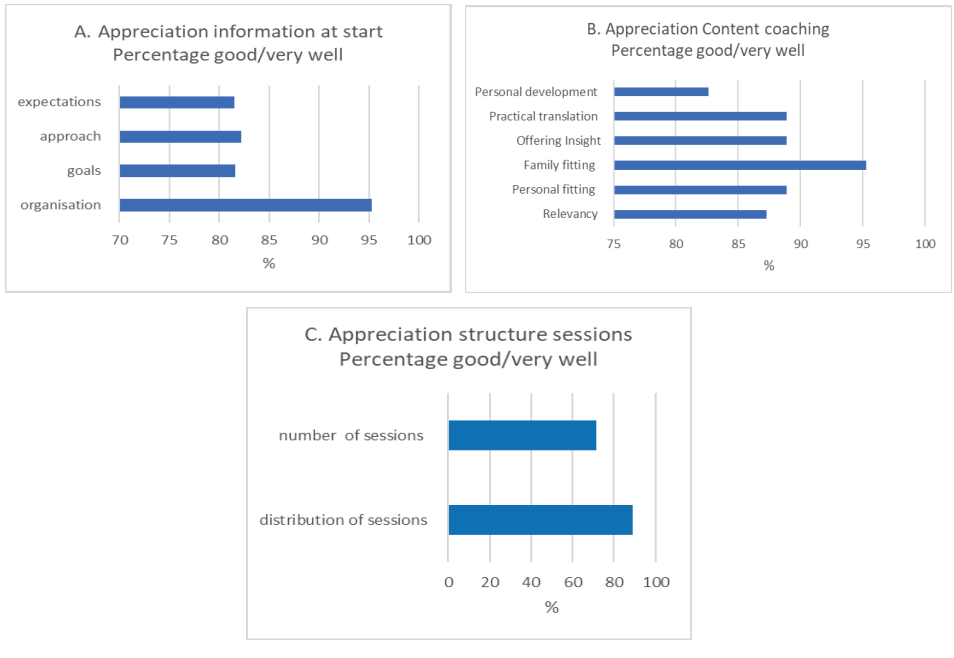


Figure 3. Satisfaction on the information (A), content (B) and structure (C) of the program

Discussion

As far as we know this is the first description and evaluation of a coaching program for parents after NBS. The coaching program, as developed by the Dutch Cystic Fibrosis Foundation, seems to be feasible and helpful for parents with a recently diagnosed child with CF. It helps parents to achieve the goals they predefined for themselves and they are very enthusiastic about the program. However, this pilot study has its limitations. The lack of a control group makes it difficult to define what caused the changes in the parents' level of distress, at the start and after the program. Yet, a systematic evaluation of this new intervention took place, to have an overall impression of the feasibility of the program and to explore its effects. The results strongly support continuation of the program and further research, including the use of a control group. The study is also limited by the fact that the HADS questionnaire was not used completely. The researchers wanted to gain experience in this sensitive area, when reaching out to the parents. Thus, the number of topics on the questionnaire was limited, to prevent the parents from withdrawing from this pilot. In further research it is recommended to use the entire HADS questionnaire.

The pilot focuses on Patients Reported Experience Measures (PREMS), which are becoming more important to include in scientific research [6-8]. We have a clear insight in what parents go through when confronted with the diagnosis of their new born; it would be possible to implement certain measures to prevent negative impact as a result of the diagnosis. Eventually, we would like to know in what way the diagnosed child is influenced by this program, psychosocially and clinically.

The results of the pilot indicate that this program is manageable and feasible for a patient organization to organize and monitor. Further research is required.

Conclusion

The coaching program, developed by the Dutch Cystic Fibrosis Foundation, seems an effective way of guiding parents through some common and well-known psychosocial phenomena that occur after a child is diagnosed with CF via NBS. Anxiety and distress of the parents decreased significantly and over all the program was rated very positively by the participants. They highly recommended this program to future parents with a child diagnosed with CF through NBS.

Acknowledgements

The authors wish to thank the parents participating in this project, who were willing to evaluate the program. The coaches are acknowledged for their cooperation and willingness to learn about Cystic Fibrosis and its psychological effects on parents. They are the backbone of the program.

Conflict of Interest

The authors have no conflict of interest.

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Chapter Five

Patient participation in research funding: an overview of when, why and how amongst Dutch health funds

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Abstract

Background

Patient participation in decision making on health related research has gained ground. Nineteen Dutch health related research funding organizations (HFs) have taken up the challenge to include patients in their funding process. A 'Patient participation (PP) advisory team' was set up, with HF-representatives and patient advocates, who together initiated this study. We provide an overview of when, why, and how PP activities take place in HFs' funding processes, share main challenges and identify possible solutions.

Methods

A qualitative research design was used. Data was gathered by questionnaires (n = 14) and semi structured interviews (n = 18) with HF employees responsible for patient participation, followed by a workshop (n = 27) with involved employees of HFs and key players in PP from national patient organizations and research organizations. A descriptive analysis was used for the questionnaire. A semi-directed content analysis was used for the interviews and the workshop.

Results

Three stages can be identified in the funding process in which HFs carry out PP activities: (1) strategic decision-making about focus of research (e.g. shared research agendas); (2) call for and receipt of research proposals (e.g. mandatory inclusion of letter of recommendation from patient organization); (3) decision-making about the funding of research proposals (e.g. patients reside in a patient panel to co-review research proposals). Main challenges identified to carry out PP activities include: how to accommodate diversity of the patient body (mainly encountered in stage 1 and 3); to what extent should patients receive training to successfully participate (mainly encountered in stage 1 and 3); and who is responsible for patient-researcher dialogues (mainly encountered in stage 1 and 2). All nineteen HFs agree that patients should be included in at least one stage of the funding process for health-related research.

Conclusion

Further broadening and optimising patient involvement is still needed. The proposed solutions to the identified challenges could serve as inspiration for national and international research funding foundations that aim to structurally include patients in their funding process.

Summary

Health research is important for patients: it helps to discover new ways to diagnose disease, to develop effective therapies and to improve quality of life. Dutch research funding organizations increasingly want to involve patients in deciding which research to fund, each finding their own way in how to work with patients in a meaningful way. This is not an easy process. Therefore they, together with patient advocates, asked for an overview of when, why, and how patients are currently involved in these decisions and how this process could be optimised. We gathered information with questionnaires, organised a group discussion with patient advocates, patient organizations, health foundations and interviewed employees of the different health foundations. We discovered that all foundations include patients in their decisions, but they do it in different ways, at different stages, and not at the same depth. Nevertheless, they all face the same challenges: they find it difficult to find patients from different sociocultural backgrounds; they find it difficult to decide if and what training they should provide for patients in order to become participants/partners; and they feel that not all researchers are open to, and take up the responsibility to actually involve patients in their research. We conclude that more cooperation and (inter) national exchange of knowledge is needed, to address the challenges and we provide some first ideas to start with.

Background

Patient participation (PP) initiatives in the research process have been appearing since the 1970s, for example the founding of a National Association for Patient Participation in the UK and a testimony written by an American patient regarding her disease which led to her reviewing research proposals for a funding organization for cancer research [1, 2]. It is however only recently that PP has gained ground and become more widely accepted [3–5]. Previously, decision-making on health related research was mainly dominated by experts such as medical doctors, researchers and policymakers [6–8]. Patients were invited to provide information on living with a disease and issues related to quality of life. Since then, PP has evolved, and patients are increasingly engaged in decision making on research, initially in setting research agendas [9, 10] and more recently in appraising research proposals [5]. In this study we use 'patient participation', (in literature) this is also known as patient involvement or engagement.

The new role of patients is characterised as a transition from a supply-driven towards a demand-driven health research system [11, 12]. Such a transition is considered necessary, not only from a normative perspective (patients have the right to be involved in decisions affecting their lives), but also to increase the social impact of research [13, 14].

Research funding organizations are often mentioned as actors in the health research system which could take up a role as change agent, facilitating the transition process [3, 4, 8]; they

have the power to pressurise researchers to involve patients in their projects, while they can engage patients in their own funding procedures. By taking up this role, more effective patient participation can take place. This is unlikely to be an easy or straightforward process, given the prominent position of researchers and medical doctors on the advisory committees of research funding organizations. Nevertheless, several research funding organizations have taken up the challenge to include patients in their working procedures, including the UK and the Netherlands.

Previous research sets the stage for patient participation in research in the UK and the Netherlands and shows that patients' experiential knowledge can contribute to the relevance and quality of health-related research [6]. The majority of the Dutch private and public, non profit, research funding organizations are disease specific health funds (HFs) that together support a significant proportion of health-related research in the Netherlands. Several of these HFs are also a patient organization, others have an official partnership with a patient organization or work together project based without an official partnership. Nineteen HFs (at time of research) had joined forces in the umbrella organization Collaborative Health Funds (Samenwerkende Gezondheidsfondsen, SGF). Their overall goal is to positively impact the lives of (future) patients. Their core business is the financing of scientific research; in 2016 they contributed for about 200 million euro in scientific research in the Netherlands. Financial support comes from approximately 3 million donors and about half a million volunteers support the HFs in their fundraising activities. Under the SGF the HFs work together on mutually relevant themes, such as PP in research, policy and care [15]. PP in research is defined by the SGF as giving experiential knowledge an optimal place in order to influence research. HFs carry out several PP activities in different stages of their research funding decision-making process. There are differences in how long HFs have been working on PP and also in the time, money and manpower allocated to it; PP may be structurally incorporated, project-based or in a pilot phase. The Dutch HFs who are member of the SGF want to collaborate on strengthening patient participation in their re- search funding decisions, leading to the formation of a PP advisory team. The advisory team consists of 10 HF representatives who are responsible for PP in the activities of their HF or are interested in doing so, furthermore a patient advocate is part of the team as an advisory member. The PP advisory team initiated this study on PP amongst the HFs, based on, amongst other things, advice given by patient organizations on giving patients a serious voice in health-related research decisions [16].

Unfortunately, there are few scientific studies on patient involvement in research funding decisions. As a consequence, organizations cannot learn substantially / systematically from the experiences of others. At the same time, the literature shows that concerns have been expressed regarding tokenism (mere symbolic participation to appear inclusive). For example, in a UK-based study, funding bodies found that sometimes PP was merely a 'tick-the-box' exercise [8]. Some studies address these issues, most often in a specific setting, such as PP in funding decisions for specific diseases [3–5]; papers written from a patient organization's point of view [16]; and based on national views ([17]; van [8]).

We use the flowchart presented in O'Donnell and Entwistle's study to provide an overview of when, why and how PP activities take place by the Dutch HFs; we share the main challenges experienced by the HFs and identify possible solutions and directions for the future. The flowchart shows how research-funding foundations involve consumers in funding decisions of health-related research in the UK [18]. Consumers included "patients, carers, long-term and potential users of health services, and organizations representing consumers' interests" (p.282). Involvement meant "some form of active partner- ship between consumers and researchers in the research process, rather than the use of consumers as 'subjects' of research" (p.282). They developed a flowchart which identified three basic stages within the research funding decision- making process (henceforth: funding process) of funding organizations in the UK: (stage 1) strategic decision-making about the focus of research, (stage 2) calls for and receipt of research proposals from researchers, and (stage 3) review of research proposals and research funding decision-making (Fig. 1).

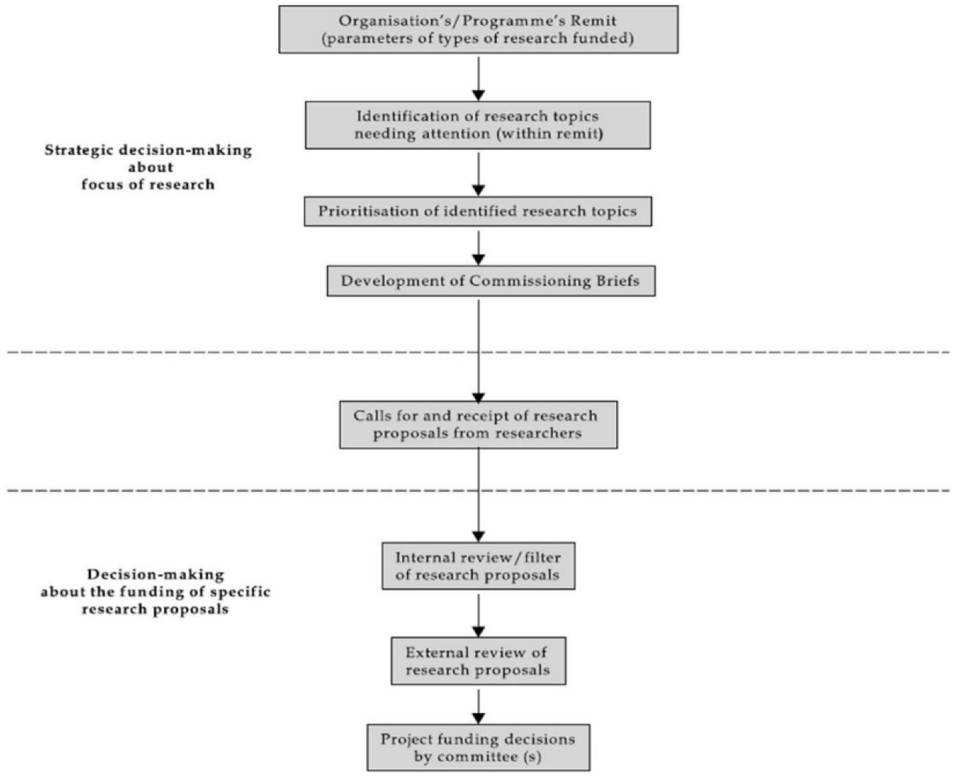

Figure 1. Stages in decision-making regarding research funding in the UK [18]

Methods

A qualitative research design was used, including (1) secondary data analysis of a questionnaire set out amongst the 19 HFs (14 responders), (2) semi-structured inter- views with HF representatives (n = 18), and then (3) a workshop with representatives of HFs, patient organizations and research organizations (n = 27).

Questionnaire

A questionnaire was developed by the PP advisory team of the SGF and distributed among all its members, before the current study was set up. Employees responsible for PP from fourteen out of nineteen HFs completed the questionnaire. It asked about embedding PP activities within the HF; how the HF stimulated PP; the challenges encountered; future plans regarding PP; and whether or not the HF desired to work together with other HFs or other (patient) organizations on PP. The data were collected during 2014 and primary analysis took place in order to answer questions regarding current PP activities. We used the results of this questionnaire as secondary data, outcomes of analysis were used as a starting point for the semi-structured interviews.

Semi-structured interviews

Between November 2015 and March 2016, semi-structured interviews were held with employees of 18 of the 19 SGF members. The remaining HF was not interviewed because it stated that no changes had taken place within its organization since the questionnaire. To prevent bias, the interviews were held by a researcher not affiliated to one of the HFs. All interviewees were involved in PP activities in their HF. The HFs differ greatly in size and in the manpower, financial resources and time allocated to PP. The interviewees therefore differed as well, ranging from CEOs and managers of research departments to policy officers of PP teams.

The goals of the semi-structured interviews were to assess: (1) whether and why PP activities take place within the specific HF; 2) when and which PP activities are carried out; and 3) what challenges or concerns are experienced. The interviews were conducted by telephone and lasted 20–60 min. Interviewees were made aware that participation was voluntary, and personal statements and individual HFs would not be identifiable when reporting the results. All interviews were audio-taped, summarised by two researchers, and later discussed and validated during the workshop.

Workshop

After all interviews were complete, a half day workshop was organized in April 2016 for all interviewees as well as other employees of the Dutch HFs and key players in PP from national patient organizations and research organizations. In total, 27 people participated. The main challenges and concerns regarding PP in the funding process expressed during the interviews were discussed in small groups. The importance of these topics was first checked with the participants to validate the findings from the interviews, and any missing challenges or concerns were added. Then the main goal of the meeting was addressed: to come up with new ideas to take on these challenges together.

Ethical approval

This study is deemed ‘non invasive’ according to Dutch law and therefore did not require approval from a formal medical ethical committee. The researchers adhered to the national Code of Ethics for Research in the Social and Behavioural Sciences involving Human Participants [19].

Data analysis

A descriptive analysis was used to interpret the data from the questionnaire. A semi-directed content analysis was used for the interviews and the workshop: predetermined codes were used based on the model of O’Donnell and Entwistle, while also open coding was carried out for a part of the analysis. Two researchers grouped the main findings under the different stages of the research funding decision-making process, by using the pre-determined codes ‘stage 1, 2, 3’. Using open coding, the challenges experienced and concerns expressed during the interviews were listed, and similar ones grouped under overarching themes. They were presented to the PP advisory team for validation and additional concerns could be added if necessary. No new concerns came up.

Results

The results are structured according to the three stages of the funding process defined by O’Donnell and Entwistle (Fig. 2): in stage 1, research topics that need attention are identified and prioritised; in stage 2, a call for research proposals is set out, often specifically for the research themes identified in stage 1, and research proposals are submitted; in stage 3, the research proposals received are reviewed, and final funding decisions are made.

HFs’ general views on the importance of PP in funding decisions

All 19 HFs acknowledge the importance of PP in one or more stages of their funding process. However, the reasons why they consider PP to be of importance differed somewhat. Three main reasons were given.

First of all, the ‘practice what you preach’ argument. Most HFs want researchers to involve patients in research (proposals); HFs believe they have an exemplary role, and therefore their own actions should convey their ideology.

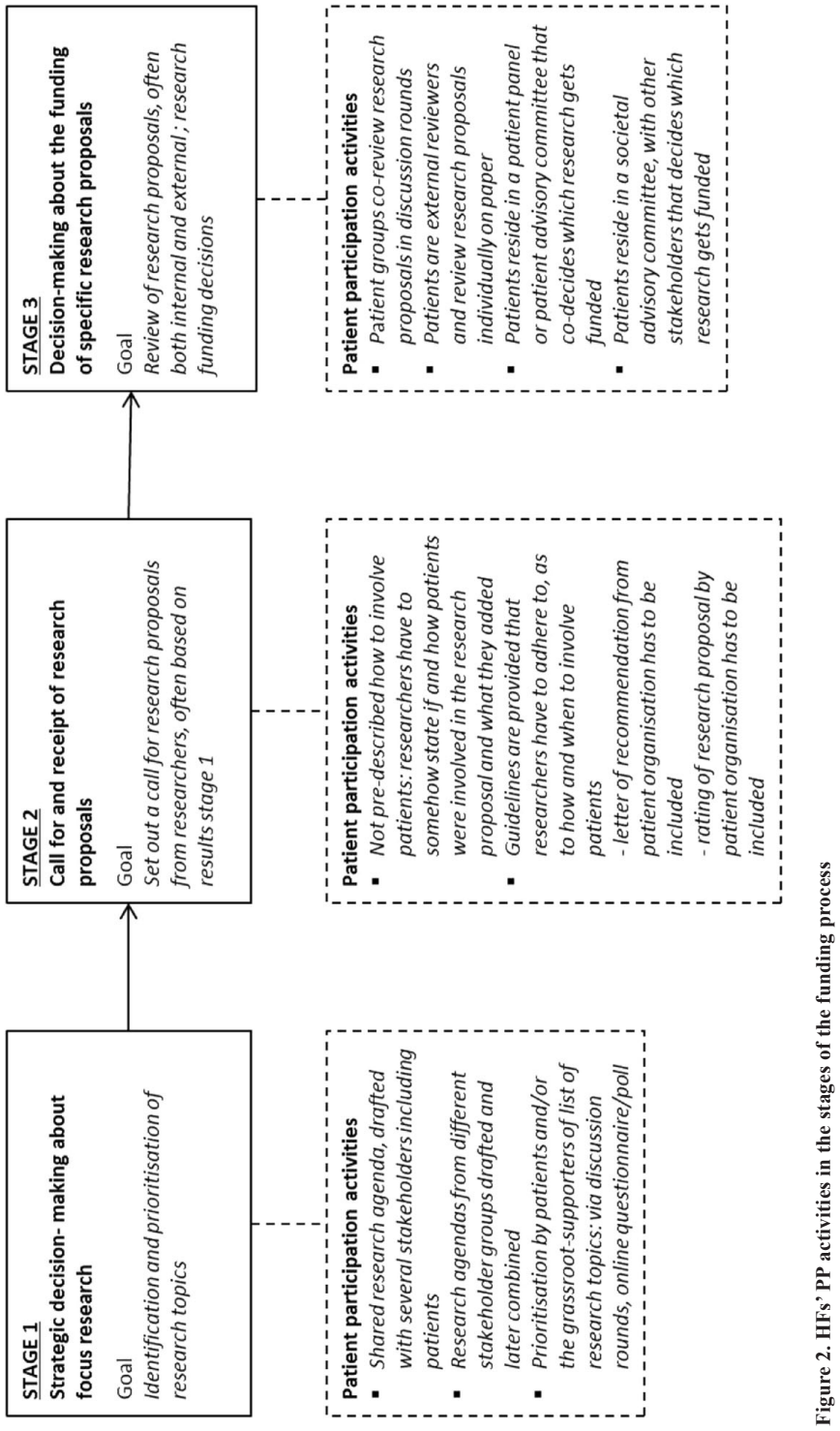

Figure 2. HFs' PP activities in the stages of the funding process

Second, the idea of 'for patients, with patients' was voiced several times. The overall goal of the HFs is to help their target population. This means that HFs work for patients and therefore should also be able to understand patients by working with patients. PP can help clarify what is important from a patient's view, which will increase the HF's understanding of the world of their target population and may lead to better decisions. This would improve the quality of research, for example because research will better fit to the needs of patients. PP in some cases may also include the participation of family caregivers or citizens, in which case this is specified.

Third, several HFs mentioned that PP is good for their legitimacy and transparency towards society. Many HFs rely on charitable donations from individuals. HFs have experienced that they can better justify their funding decisions to these donors when they work together with patients.

PP activities in the stages of the funding process

In recent years several HFs have taken action within their organizations regarding PP: in the timespan from conducting the questionnaire (2014) to conducting the interviews (November 2015–March 2016) HFs have started new PP initiatives and/or professionalised existing PP activities. Most Dutch HFs have chosen to carry out PP activities in more than one stage of the funding process (overview: Fig. 2, examples: Table 1). Stage 1 is used by ten out of nineteen HFs for PP activities, stage 2 by eight HFs and stage 3 by fourteen HFs.

Table 1. Examples of PP per stage

Example of PP in stage 1

In focus groups with patients, a list of possible research topics is created. These research topics are presented online to the grassroots constituency of the HF so they can indicate their personal priority preferences. The prioritised research agenda is aligned with research agendas drafted by clinicians and researchers. Only research that falls within the top 5 research topics is funded.

Examples of PP in stage 2

Example I

A letter of recommendation from a patient organization or other organised patient group needs to be included when submitting the research proposal. A deadline for contacting this patient group is added.

Example II

It is mandatory for the researchers or research institute to contact an organised patient group and ask them to rate their research proposal, before submitting it to the HF. The proposal will be rated on two topics: relevance of the topic and the extent to which they were involved and listened to in preparing the research proposal. The rating results need to be included when submitting the research proposal.

Example of PP in stage 3

Patients meet up to discuss a research proposal, because when reviewing only individually without a discussion, a good formulation of arguments might not be achieved. This may lead to unclear reasoning for the final judgment and decision on the proposal.

Stage 1, strategic decision-making about the focus of research

Before setting out a call for research proposals, most HFs decide on a direction or focus that researchers should adhere to in their research proposals. In deciding this direction, approximately half of the HFs specifically include the perspectives of patients. These HFs gave two reasons for including patients specifically in this stage. It justifies research funding decisions to their grassroots support. And research conducted in a direction chosen by patients is relevant by definition. A reason not to include patients in this stage is that there are too many diseases that fit the scope of the HF and therefore multiple research agendas would have to be generated, which was seen as an unattainable goal. Another argument was that the relevance of research based on the perspective of patients and other stakeholders was preferably addressed in other stages of the funding process.

Participation activities in stage 1

The main method used to decide on a direction of research with the input of patients is producing a research agenda that is co drafted by patients. HFs generally have multiple research agendas drafted with separate focus groups consisting of patients, healthcare professionals, family caregivers and researchers. Subsequently, they are combined into a final shared research agenda which is expected to be broadly supported by all the stakeholders involved. Successful examples include the research agendas for burn survivors, people with respiratory diseases and heart diseases [9, 20, 21].

HFs may combine research agendas from different stakeholder groups into one final shared research agenda themselves, or this may be done during a joint discussion between the different stakeholders.

Prioritisation of the topics on the research agenda is carried out either within the focus groups identifying the research topics or in joint discussion rounds or individually on paper. Some HFs request prioritising input from a bigger group than those who contributed to the research agenda. They conduct online questionnaires or polls, allowing grassroots supporters the opportunity to prioritise the identified research topics.

Stage 2, call for and receipt of research proposals

Seven HFs have stated that they consider it their responsibility that researchers make involvement of patients a priority when submitting research proposals for funding. This involvement starts at drafting the research proposal. HFs have articulated criteria which have to be met by researchers applying for funds. This can be that PP is an absolute condition for research proposals to be submitted, or -more often- stating that patient involvement is reviewed by the referees or advisory boards and thus an important part of the decision making process. In receiving the proposals the HFs do not perform an immediate check whether or not PP has taken place. The HFs who do review patient involvement, do so later on in stage 3. Three reasons are mentioned for participation in this stage. First, it is a good reflection of the importance and value that the HF grants to PP. Second, it gives researchers, HFs and decision makers in stage 3 insight into the relevance of the proposed research for patients. Lastly, it can help make PP a normal procedure instead of a rarity; it 'orders' researchers to actively work with patients. In the HFs' experience, this often led to researchers experiencing the importance of PP in general and, perhaps more importantly, the added value that patients can give to their research projects. No specific reasons were mentioned for not carrying out PP activities in this stage.

Participation activities in stage 2

PP in preparing the research proposal is rarely an absolute condition set by HFs for funding. How researchers should involve patients is not always predefined by the HFs either. In that case, HFs only ask researchers to state if and how patients (or patient representatives) have been involved during the preparation of the research proposal. HFs may want to consider how patients' input has changed the proposal. Because of the lack of guidelines, this often resulted in short and incomplete answers, or PP was not done at all as no patients could be found.

When a clear guideline is provided, it improves insight into the degree of input by patients and ensures that the patient input is valuable instead of a formality. Some HFs also provide a time frame, including deadlines for contacting patients, because involving patients early on improves the quality of the research proposals and allows patients more time to respond.

Stage 3, decision making about the funding of specific research proposals

Traditionally, submitted research proposals were reviewed by external expert referees and scientific advisory boards, consisting mainly of scientists and doctors. Most HFs find the approach of peer-review without patients outdated, and fifteen HFs include patient reviewers, mainly to gain insight into the relevance of the research proposals for patients. Several HFs are currently in the process of setting up a system which involves patients reviewing research proposals. HFs that have no intention to do so, explained that they have involved patients in the first or second stage of the funding process and thus already take their views regarding the relevance of the research into consideration.

Participation activities in stage 3 In almost all (15) HFs, patients co-review research proposals, either as an external referee or as a member of a patient/societal committee. Many HFs have established a patient panel or a patient advisory committee to co-decide or co-advise (differs per HF) which research finally gets funded. Moreover, there are HFs that have set up a societal advisory board consisting of patients, healthcare professionals, family caregivers and/or citizens. The number of patients in any of these settings ranges between three and twelve.

Patients can co review the research proposal, but often they are given a lay summary. Lay summaries help the patients understand medically or technically complicated proposals and the scientific jargon used. Some patients when given the original research proposal

focussed on technical, scientific details which do not fall within the scope of their review responsibilities, but rather to the responsibility of the scientific reviewers. There are various ways to review the proposals. Several HFs let patients individually review the proposal on paper, sometimes followed by a meeting where patients come together to discuss the proposal, clarify their opinion and form a consensus regarding the research proposal. Other HFs conduct the entire patient review process through a discussion, with the HF's project leader or a researcher as facilitator. The facilitator presents the research proposal, explains if and how the research has societal relevance, and answers patients' questions. The goal of these sessions is to come to a decision regarding the research proposals, agreed upon by all participating patients, and to give feedback to researchers.

The review criteria patients receive differ according to HF. For most HFs, the criteria must include the (1) relevance of the topic, for patients and for society as a whole; (2) burden for the study subjects; and (3) feasibility of the research. Only a few HFs have prepared the criteria in cooperation with patients.

Finally, if and to what extent training or coaching is provided for the patients to help them through the reviewing process differs per funding foundation, ranging from no training to several days of training.

Often, the balance between the voice of the patients versus the voice of the scientific advisory board and reviewers has not been precisely established and no official policy documents regarding this balance were found. Some HFs consider the patients' decision as input for further deliberations by a scientific committee. Other HFs have members of the scientific committee deliberate with patients (a delegation), comparing the judgments of both groups, in order to come to a final consensus. In that case, it is possible that no or only one patient is present when the final decision is taken. Because of the lack of policy documents, the actual influence of patients' advice as opposed to the professionals' advice cannot be deduced and often remains unclear.

Main challenges and possible solutions

HFs encounter various challenges in their PP activities. The three main issues experienced are: how to accommodate diversity; to what extent should patients receive training; and who is responsible for patient researcher dialogues. Solutions proposed by participants of the dialogue meeting are shown in Table 2, these solutions are based on their professional experience.

How to accommodate diversity?

An important challenge which is encountered by most HFs revolves around the question: 'who should participate'. This challenge is encountered in stage 1 (strategic decision-making about the focus of research) and 3 (decision making about the funding of specific research proposals). Most HFs relate to a diverse patient group, consisting of people with different diseases, social economic status (SES), ethnic minorities, and verbal and cognitive

capabilities. All HFs state that it is a challenge to include a group of patients, doing justice to this diversity and without leaving out an important target population of the HFs.

'Suitable' patients have to be recruited, who are 'capable' of participating in the decision-making process. Suitable was explained as being able to transcend individual or personal needs, i.e. participating patients are able to think beyond the boundaries of their own disease and thus can speak for a broader patient group. Capable was explained as having the ability to reason with others concerning complex topics and to learn, reflect and make decisions. HFs doubt whether they should only include patients with a higher educational level, although this would not be a fair representation of the patient body since a large group would be excluded, often the ones most in need.

Table 2. Proposed solutions to main challenges

Proposed solutions to accommodate diversity
- Diseases could be combined under broader disease domains when dealing with a patient body with a large diversity of diseases or disease types.
- Family caregivers or entrusted physicians can participate as patient advocates when participation is not possible for certain patient groups due to their disability, or when no patients willing to participate can be found because the prevalence of the disease is low.
- A participant profile can be made, including what skills are needed for specific PP activities or tasks.
- A database of patients interested in participating in the funding process can be set up, including their background, skills and interests in order to link them to the above-mentioned profiles.
Patients with different skills, background, educational level can join different PP activities.
- Training can be organised for patients who are willing to participate, before deciding whether or not they are capable of participating in certain activities.
- Cooperation can be established with local organizations that work with target groups which are harder to reach (e.g. ethnic minorities, people with low SES).
Proposed solutions for patient training
- A 'chief listening officer' can be appointed, to listen to the participatory wishes and needs of patients and to give an overview of bottlenecks experienced regarding the prerequisites for effective participation.
- It can be acknowledged that there is a limit to the willingness and capacity or workload of patients, and a central point (or person) can be set up where patients can indicate their capacity (changed) or manageable workload.
- An incentive can be provided in the form of a reward for researchers who commit to establish a dialogue with patients (on their own initiative and in their own way).
- Contact days for groups of researchers and patients can be facilitated, in order to bridge the gap between them.
- Training days for researchers can be facilitated, with possibly patients providing training sessions on 'how to meaningfully interact with patients'.
- A HF employee can be appointed to answer questions from researchers on how to contact and have a successful dialogue with patients.

To what extent should patients receive training?

Several HFs struggle with whether or not patients should receive training and what it

should consist of. This challenge is encountered in all three stages. The training should provide patients with enough information to make participation meaningful, while not professionalising them so they lose their unique perspective as a patient. HFs stress that when deciding on training and its content, it will involve making additional demands of the patients. Therefore, it is an important challenge to monitor the patients' capacity and willingness to handle the workload.

Who is responsible for patient / researcher dialogues?

HFs question who is responsible for a successful dialogue and what skills the researchers need to establish a dialogue. This challenge is encountered in stage 1 (strategic decision making about the focus of research) and 2 (call for and receipt of research proposals). HFs point out that it is sometimes difficult to decide where their responsibility ends and that of others, in this case researchers or research institutes, begins. They find that researchers often do not yet see the added value of PP or know how to accommodate PP, and therefore the HFs take it upon themselves to ensure that dialogues are established between patients and researchers. These are dialogues in stage 1, for example setting a research agenda with both researchers and patients, but also in stage 2 where researchers should work on their research proposal in cooperation with patients. They want to find effective ways to 'persuade' researchers to take on the responsibility of setting up a dialogue with the patients themselves and get the necessary training.

Discussion

The HFs agree that the time of questioning whether or not patients should be involved in the process of allocating funds to health related research is over. The focus is now on how to organise, optimise and entrench PP meaningfully in the HFs' funding processes. This process is being given active support by the Dutch government; policy documents underline the need for so called responsive research, so funding will be allocated to research with societal relevance [22]. Furthermore, a health-related research funding organization (ZonMW), funded by the Dutch government, also works with patient panels for the different calls for proposals they set out. Dutch patient advocacy groups are collaborating to combine their influence and together make recommendations for the successful involvement of patients in health-related research [16]. Similar participatory initiatives, supported by governments, are seen internationally. Exemplary is the government of the UK who funded 'INVOLVE', a national advisory group which aims to support active public (including patient) involvement in the healthcare system, public health and social care research [23].

All Dutch HFs are involving patients in at least one stage of their funding process. From the UK-based study of O'Donnell and Entwistle, we see that stages 1 and 3 are chosen as the focal points for PP activities [18]). UK activities include postal surveys or focus groups,

consumer panels, and consultation meetings with consumer representatives from voluntary organizations to identify and prioritise important research topics [18]. In the Netherlands, stage 1 is used for PP by 10 out of 19 HFs; drafting research agendas is quite common, postal/on- line surveys are carried out less often but is increasingly seen as a method with high potential.

Although only 8 of 19 Dutch HFs have PP activities in stage 2 and those activities are often less structured or in a pilot phase, most HFs voiced their intention to involve patients here in the future. If researchers include patients before submitting their research proposal, they will experience that the research proposal is improved, facilitating possible further cooperation [24].

Stage 3 is most often chosen for PP activities in the Netherlands. Approaches to involve public/patients include co reviewing research proposals and being a member of a review committee [18]. This corresponds to the situation amongst the HFs: most of them have set up a system where patients co review the proposal and do so with similar review criteria. This is also is what is to be expected of HFs, who's main task is to make funding decisions on research proposals which ultimately should benefit the patient. However, a UK-based study of ten research funding bodies by van Bekkum and Hilton showed that even though most funders find stage 3 promising for participation, only two of them involved the public in a committee and just one included them in their external review [8]. Some UK funders feared the public's opinion might be biased by emotions or a personal agenda. An Australian based study of PP activities of a funding organization for cancer research also considered stage 3 as promising for participation. They set up a patient (consumer) panel to review research proposals based on criteria of the public value of the research [3, 4].

Concerns were voiced by the Dutch HFs but also in the UK and Australia regarding the identification of 'appropriate' participants and difficulties with recruitment and deciding who should represent patient and public perspectives [17, 18]. The Dutch HFs specifically perceived a difficulty in reaching certain patient groups, due to cultural or linguistic barriers and the fact that these groups are also underrepresented in patient organizations, while the cultural diversity of the Dutch society and thus of the patient population is growing [25]. Similarly, in two UK studies, funders noted that people on committees tended to be better educated, such as retired academics or professionals, and wondered if they represent the entire patient body [8, 18]. This was also voiced by Wind, who stated that she wants to get rid of the phenomenon that mainly the 'intellectual elite' participate, and insisted that a broader patient population should be included [26]. The authors recognise that for each stage the 'appropriate participants' are different. Stage 1 would be the stage where patients with a wide range of social, economic and educational status can participate in various participatory methods, while stage 3 is more prone to the so called 'intellectual elite' where patients' representative participate.

A second prominent issue of concern is whether or not patients should receive training before they participate and what this training should consist of. Many Dutch HFs raised this issue, and it was extensively discussed during the workshop. Those in favour of training pointed

out that to participate in stage 3, participants needed insight into scientific research and the funding process to be able to make a good judgment as well as to become a helpful discussion partner for the scientific review committee and researchers. The opposite opinion entailed a worry that patients become 'proto professionals' and lose their unique patient perspective. Especially when participating in stage 1, a training was not deemed necessary. It is remarkable that in UK and Australian studies, training is provided for patients but no concerns were raised [3, 4, 8, 17, 18]. However, in literature we see academics who are and who are not in favour of the training of patients. In the UK a research awareness training programme has been developed for patients, in order for them to actively and meaningfully be involved in research, evaluations and audit projects [27]. According to Dedding and Slager [28], training is not necessary but using more creative methods might help to accommodate non- academic participants and encourage them to share their knowledge, experiences and needs [28].

The third challenge that was often mentioned by the HFs concerns the responsibility for patient-researcher dialogues. This mainly regards the dialogue needed in stage 1, for example while setting up a shared research agenda, as well as in stage 2 where researchers should work together with patients on their research proposal. HFs deem themselves, together with researchers, responsible for the establishment of this dialogue and cooperation. However, they find that in practice this task often solely falls upon them. HFs take this responsibility and facilitate contact between researchers and patients, however they hope that in the near future this will become a shared responsibility.

Limitations of the study

Several HFs have a group of people working on PP, while only one of them was interviewed per HF. It might be that other interviewees from the same HF would have given a different line of argumentation or had different experiences. The position of the interviewees within a HF varied. This might have caused a difference in the information provided: for example, a director might have different arguments and explanations regarding PP activities than the employees who carry out these activities in practice.

No patients were involved in the questionnaires and interviews, because solely HF employees were asked to participate. However patient advocates joined the PP advisory team who advised in the set-up of this study. Furthermore, three patient organizations participated in the workshop.

In recent years, many PP initiatives have been set-up within the field of health related research. We included non scientific documentation (policy documents of the UK and Dutch governments and from patient advocacy groups) on these initiatives. More grey, non scientific literature is published regarding PP initiatives than these examples. Although of importance, including these is outside the scope of this study.

Conclusion

Most Dutch HFs are committed to PP, but further broadening and optimising of patient involvement is still needed, and transparency and cooperation between funding foundations are necessary. Our proposed solutions to the experienced challenges during PP activities, could serve as inspiration for national and international foundations that want to include patients structurally in their funding process.

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Ethics approval and consent to participate

Due to the non invasive character of this study, no ethical approval was needed.

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Chapter Six

Aligning patients' needs and research priorities towards a comprehensive CF research program

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Abstract

The Dutch CF Foundation started to focus on scientific research thirteen years ago. The patient organization defined the patients perspective and unmet needs bottom-up, and through a structured process. The patients research priorities were matched with the research priorities of Dutch basic scientists and clinicians. The Dutch patient organization facilitated the process, in which mutual dependency between patients, scientists and clinicians is the keyword. The, at that time initiated dialogue, maintained. Subsequently a research program called "HIT CF" was composed and executed over five years. HIT CF was financially supported mainly by the patient community and some other stakeholders.

Introduction

The scientific research system in general has started to change over the last decade from being supply driven, towards a more needs-oriented focus [1]. The implementation and translation of research findings, into routine clinical practice can be improved by involving the people most in need of them [2]. A perspective article in the *New England Journal of Medicine* stated that academic environments often place more value on the discovery itself and less value on learning how to realize the potential benefits of its application [3]. It is, therefore, important to focus on the patients' needs, when research priorities are defined. If scientific work intends to add value to the patients' lives, the researchers' and clinicians' focus should align with the patients' priorities. Patients are experts of their disease, because they live with it and have experience with their treatment on an individual level. At the same time, they are not necessarily trained and skilled into biomedical issues. The need to consider broadening the base of the educational level of all stakeholders involved, is described by the CF Italian Patient Centered Outcomes Research Working Group (IPaCOR) [4]. With another approach from the UK through the James Lind Alliance Priority Setting Methodology [5], consensus was found about a top 10 list of clinical research questions, incorporating both the patients' and clinicians' communities. This shows how a systematical approach can be used effectively to prioritize the research agenda.

The Dutch Cystic Fibrosis Foundation (NCFS) has been working on a process for patient participation in the development, design and simple mentation of a research program, prioritized by patients. In this process the cooperation between the patient organization, clinicians and scientists, became a method in which mutual dependency is the keyword.

Start in 2007

NCFS decided to focus on research in 2007 and to prioritize a research agenda based on the patient's needs. Patients' and parents' priorities were assessed by means of an online focus group consisting of 15 patients and 15 parents. They applied for the focus group after a request was sent to Dutch patients and parents through an electronic newsletter, the NCFS website and the NCFS quarterly. The focus group was invited to suggest topics they personally and individually felt important to investigate. From the responses, a list of 150 CF-related research questions was generated and subsequently condensed by the participants to 10 research topics that were given the highest priority. We had 1400 CF patients in 2007, according to the Dutch CF Registry. They all have access to the services NCFS delivers, no membership is needed. All were then given the opportunity to rank this top ten online through online newsletters and social media. 196 people responded.

The final ranking was matched with the five research priorities of Dutch clinicians and scientists in a dialogue session organized by the NCFS (see 1st quarter Fig. 1). The priorities of the clinicians and scientists were derived from an online survey. Four topics were suggested by both patients and clinicians: insight into the basic defect, infection, inflammation, and

segregation policy. The fifth topic (psychosocial issues) was added only by patients, resulting in the top-five priorities. This topic was chosen to be incorporated in the research program by NCFS, because it was highly valued by the patients. This ultimately led to the first research agenda of NCFS, covering 2007–2011. In this period, 3 national multicenter studies, 3 PhD projects and several smaller CF-related studies were started that matched these priorities. The results were frequently communicated to the CF community, who became actively involved in fundraising; a budget of €1 million was brought together. It was the first time NCFS had a research budget.

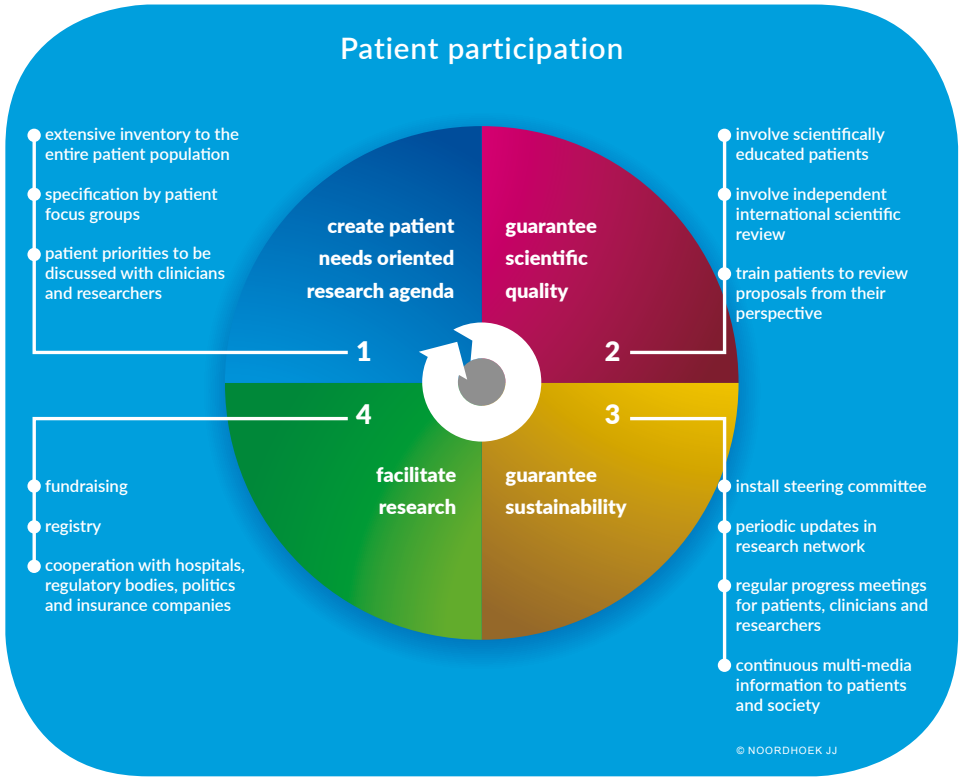

Figure 1. Patient participation in research

Updating the research program

The impact of the 2007 research agenda was disappointing in the opinion of NCFS. The topics were highly diverse, results were partly conclusive and in just a few cases suitable for follow up research. The patient priorities' list was updated in 2012, also to find out whether the set priorities had changed or if new topics were of greater interest for patients. Change was to be expected because the patient organization was communicating frequently

about developments in research worldwide. The same routine was used as in 2007, starting by online questionnaires to patients and parents and concluding with a dialogue with professionals to align research priorities. "CF disease mechanisms and treatment of the basic defect" was now given top priority by the patients and parents, followed by infection and inflammation. "Segregation policy" was removed from the top five and replaced by the topic "fatigue in CF". Following the new priorities, NCFS now opted for a programmatic approach. A group of well known scientists and clinical researchers in the Netherlands, with strong track records and a solid research infrastructure for CF in their centers and labs, was created to address the top priorities in a research program: targeting the basic defect in people with CF, infection, and inflammation. This consortium of (basic) scientists from Utrecht and Rotterdam, clinicians from Utrecht, Rotterdam and The Hague, and the patients represented by NCFS drafted a research program, called "HIT CF", consisting of four tracks with 16 projects in total. The scientific quality and the relevance of the program were extensively reviewed before the start, by foreign CF experts, clinicians and scientists. The Netherlands Organization for Health Research and Development (ZonMw) reviewed it too. All rated the program as "excellent" (see 2nd quarter Fig. 1). Researchers were convinced that cooperation is important and that their sometimes different scope could be aligned in the same, comprehensive program.

Patients were involved in reviewing the research proposals of the HIT CF program, to make sure that their perspective was incorporated and the proposal was judged as acceptable, feasible, manageable and safe for them. After an online call for participation, a patient/parent review group was installed in 2012. An academic level and English language skills were demanded. The members of this group participated in an online interactive training. Four of these patients and three parents are still successfully and regularly reviewing CF-related research proposals and study protocols at a national and international (ECFS-Clinical Trial Network) level.

Organization

A translational approach was chosen, in which observations in patient care lead to basic scientific questions for the laboratory, and the answers from the laboratory were subsequently verified in patient care. This approach urged clinicians and scientists to interact continuously and intensively, leading to the mutual dependency of different study groups. This 'bed to bench to bed' approach stimulated profound interactions between CF patients, clinicians and scientists, and had a continuous focus on clinically and socially relevant outcomes for all research efforts within the program. The frequent interactions between patients, clinicians and scientists in working groups led to the maximal involvement of patients in clinical studies and in fundraising, and also encouraged researchers to translate and apply the study results constantly for individual patients and for the community. For example, questions from patients concerning personalized medication were addressed in studies with organoids, that resulted in clinical trials and sometimes even reimbursement of off label drugs.

A steering group, consisting of five Principal Investigators and two representatives of NCFS,

monitored the program at 3-monthly meetings; scientifically, logistically, financially and from the patients' perspective. More generally, researchers and clinicians presented their work to patients and parents during the year, through webinars, symposia, etc. The HIT CF program ran for 5 years, and the total costs amounted to €4.8 million (3rd quarter of Fig. 1). All kind of funding events by the national CF community and facilitated by NCFS, contributed to HIT CF, together with co-funding parties.

Impact

The 2012–2016 program has led to over 50 publications so far, including high impact papers in Science, Nature Medicine and Cell Stem Cell [6–8]. Several national and international awards were granted. The HIT CF program and, especially, the organoid technology program have been presented at many national and international symposia for clinicians and researchers, as well as national days for families (3rd quarter Fig. 1). This demonstrates its societal impact through presentations on radio and television and articles in newspapers. The opportunities offered by the organoid technology, aiming at precision medicine, is appreciated by the regulatory authorities and health insurance companies and will hopefully shorten the time for accessing new medication and combinations for people with CF. Several patients with ultra-rare mutations were identified as drug responsive and health insurance companies approved their continued treatment without formal clinical trials.

Update 2016

After an online survey in 2016, targeting patients and parents in the same way as before, 189 patients and parents responded; 97% were in favor of continuation of the HIT CF program, but now completely focusing on new therapies targeting the basic defect. Therefore, in line with the same procedures as the first HIT CF program, the new HIT CF 2.0 program was designed, reviewed and started in 2017. At that time 1580 Dutch patients were registered. The program consists of 17 projects with a duration of 5 years and costs summing up to € 5 million. It is aiming at final validation of organoids, developing evaluation parameters for new therapies, implementation of new therapies in patient care and innovation of technics to develop new therapies. Patients from all Dutch CF centers can participate in the projects through the Dutch CF Research Network (4th quarter of Fig. 1). HIT CF 2.0 is also reaching out to a European level via the EU Horizon 2020 granted project "HIT CF Europe".

Conclusion

This report describes in retrospective how the Dutch CF Foundation involved patients and parents of children with CF, to prioritize their research topics and develop a process in which the mutual dependency between patients, scientists and clinicians is realized. The Dutch patient organization was able to facilitate a bottom-up process of questioning the patients about their unmet needs. Parents and patients were trained in reviewing protocols; a dialogue between patients representatives, clinicians and scientists was initiated and maintained. This patient driven process led to the successful HIT CF program in which the CF community participates.

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Chapter Seven

Intestinal organoids and personalized medicine in cystic fibrosis: a successful patient-oriented research collaboration

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Purpose of review
New therapeutics have been introduced for cystic fibrosis that modulate cystic fibrosis transmembrane conductance regulator (CFTR) function in a mutation-specific fashion. Despite CFTR genotype-based stratification of treatments, treatment efficacy is variable between study participants suggesting that individual factors further contribute to drug efficacy. Moreover, these treatments are licensed for a limited amount of CFTR mutations, and study participants with rare mutations that can potentially benefit from available treatments may be missed. New approaches that better support the identification of responders to CFTR modulators are, therefore, needed.

Recent findings
We, here, review how a patient-oriented research collaboration between basic and clinical scientists and a national cystic fibrosis patient organization led to the development of a CFTR-dependent assay using primary stem cell cultures termed intestinal organoids that can measure the individual efficacy of CFTR modulators in a preclinical laboratory setting. Early observations suggest that drug responses in organoids reflect drug responses in vivo.

Summary
We particularly focus on the importance of patient-oriented research collaborations, and how such a collaboration helped to develop a personalized medicine approach for CFTR modulators. Intestinal organoids and biobanks thereof may be used to select optimal, individually tailored treatments for current and future (combinations of) CFTR modulators with only limited patient discomfort.

Introduction

The introduction of novel cystic fibrosis transmembrane conductance regulator (CFTR) mutation- specific therapies (CFTR modulators) has led to a dramatic shift in the consequence of the CFTR genotype for an individual with cystic fibrosis (CF) [1]. CF is caused by mutations in the CFTR gene and represents one of the most frequent life-shortening genetic diseases in people of western countries. In the pre-CFTR modulator era, the CFTR genotype was mainly important for diagnosis, and, less importantly, for prognosis [2]. In the current clinical practice, CFTR modulators that can have life-changing impact for individuals with CF are available for treatment, but licensing and reimbursement of these modulators is based on inclusion of CFTR mutations into industry-sponsored clinical trials [3,4,5,6–8,9]. For many study participants with rare CFTR mutations, these treatments, there- fore, remain out of reach. In addition, the strong clinical improvements observed with VX-770 (ivacaftor) treatment in study participants with CFTR gating mutations appear not to be matched by VX-770/VX-809 (ivacaftor/lumacaftor) treatment in study participants with the most common F508del (p.Phe508del) mutation, the most dominant CFTR mutation present on one allele in rv85–90% of CF study participants [3,5]. The current genotype-based stratification procedures successfully select CFTR modulator-responsive sub- groups, but associates with considerable heterogeneity in treatment suggesting that cost-effectiveness and risk–benefit ratios can further increase [3,5]. Additional stratification procedures and individual biomarkers for these treatments that act independent of the CFTR genotype may further help to improve the clinical impact of CFTR modulator treatment.

Two CFTR modulator treatments are currently available that demonstrated efficacy in placebo- controlled, double-blinded randomized clinical trials [3,5,9]. Inclusion of study participants with particular CFTR mutations for these trials was based on drug responses of CFTR mutations in in-vitro studies [10 – 12]. Much of the enthusiasm around CFTR modulators was ignited by the strong improvements across several clinical domains in trials with the first CFTR modulator VX-770 in patients with the G551D (p.Gly551Asp) gating mutation [6]. VX-770 was originally selected in vitro for restoration of gating defects in F508del [11]. Subsequent efficacy studies in vitro demonstrated large effects of VX-770 on full gating mutations such as G551D, which were then followed up by positive clinical trial data [3,6,11]. After licensing for G551D, it took approximately 3 years to extend the label of VX-770 to eight additional gating mutations targeting rv5% of CF patients [9]. For one mutation (G970R, p.Gly970Arg) that was originally selected as potential VX-770 responsive gating mutation, in-vivo efficacy could not be demonstrated [9,12]. Additional studies are currently being performed to further extend the label as to include more VX-770 responsive mutations.

A second CFTR modulator treatment consisting of a combination of a corrector VX-809 that (parti- ally) restores mutant CFTR trafficking and VX-770 is currently United States Food and Drug Administration and European Medicines Agency-approved for treatment of study

participants with F508del homozygous (F508del/F508del) mutations. Most enthusiasm surrounding VX-809/VX-770 combi- nation treatment is fueled by the ability to treat the largest group of approximately 50% of genetically 'identical' F508del/F508del CF study participants [4,5,10]. However, the overall efficacy is limited in comparison to VX-770 in study participants with gating mutations, and many study participants who receive treatment appear not to clearly benefit as suggested from pulmonary function testing and in-vivo CFTR biomarker analysis. So apart from identifying patients beyond F508del/F508del that may benefit from this treatment, risk–benefit and cost-effectiveness ratios may improve by selecting the high responders to VX-809/VX-770.

Here, we focus on the use of ex-vivo intestinal stem cell cultures or intestinal organoids for individual assessment of clinically available CFTR modulators using a recently developed CFTR- dependent swelling assay in intestinal organoids [13]. Within 4 years after the first observations that organoids swell in response to forskolin, in- vivo responders to VX-770 were selected based on preclinical CFTR modulator studies in organoids [14]. We discuss recent observations that support that intestinal organoids can help to develop personalized treatments for study participants with CF. In addition, we also focus on the importance of strong collaborations between patient organizations, basic scientists, and clinical CF researchers to set up a patient-oriented research infrastructure that promotes the translation of research into clinical impact.

Who to treat with what, and how?

What domains can academia focus on as to help bring more effective treatments to people with CF? Effective treatment depends on our ability to answer the question 'who to treat with what, and how?'. The 'what' refers to treatment interventions such as CFTR modulators. Research in this area focuses on the development of new treatments, that is, the 'what', and industries play a dominant role in this domain. The 'who' and 'how' implies that we need individual criteria that provide sufficient resolution to identify high and low responders to treatment so that clinical decision-making can be adjusted in an objective manner. Individual biomarkers of CFTR function may help to select or deselect people for treatment, and may guide fine-tuning of individual use of drugs to enhance therapeutic benefits. Academia and hospitals may lead in these domains because of their strong access to patients and samples.

A patient-oriented research collaboration

Patient organizations are becoming increasingly important to coordinate research activities for rare diseases, and can act as hubs between patients, fundraisers, researchers, and policy makers. For example, the US CF patient organization (Cystic Fibrosis Foundation) is strongly shaping CF research and impact thereof in the US and beyond. Experiences in the Netherlands also support that a collaborative and focused approach in which patient organizations directly work together with basic and clinical scientists can help to translate basic research into impact for patients. A first step was to establish a research agenda integrating the patients' perspective. The Dutch CF Foundation (NCFS) approached 30 CF patients and parents, and together prepared a list of 150 research questions and prioritized 10 research topics. Subsequently, all patients and parents in the Netherlands could rank this top 10 online so that five top priorities for research could be established. When patients' and parents' priorities were updated, the top priority shifted from 'mechanism and treatment of airway inflammation' in 2007 to 'CF disease mechanisms and treatment of the basic defect' in 2012. These nationwide surveys ensured that a patient-driven research agenda could be established, and served to prioritize research funding according to the patients' needs.

A collaborative consortium consisting of the NCFS, and clinical and basic researchers with established track records and (clinical) research infrastructures was formed to shape a research program 'HIT-CF' that aimed to translate research on the basic CF defect into impact for patients (www.ncfs.nl/bestanden/researchprogramme- hitcf.pdf). This program focuses on 'bed-to-bench' and 'bench-to-bed' approaches, leading to mutual dependency between different disciplines and ensures a tight interaction between basic and clinical researchers. Regular meetings of all project members, the NCFS, patients and parents help to maintain focus on clinically and socially relevant outcomes for all the research efforts within the program. Project management is carried out in 3-monthly meetings by representatives of the NCFS and principle investigators that collectively value research progress, as well as financial status, opportunities for shared fundraising and dissemination of findings to the public. This setup helps to facilitate a strong continuous focus on patient impact, and allocate available funds to multidisciplinary research in which basic and clinical research is fully integrated.

Intestinal organoids and cystic fibrosis transmembrane conductance regulator modulators

We decided that we could potentially complement efforts in the CFTR modulator field by focusing on the development of new individual readouts for CFTR modulators. In 2009, Sato et al. [15] published a breakthrough study showing that single leucine- rich repeat-containing G-protein coupled receptor 5 positive epithelial stem cells derived from murine intestine could grow into three-dimensional multi- cellular epithelial structures termed intestinal organoids using defined in-vitro culture conditions. The intestinal organoids recapitalized in-vivo tissue architecture in terms of cell composition and polarity, and consisted of a closed, three-dimensional single epithelial cell layer with the apical membrane facing the internal lumen [16]. In 2011, human intestinal organoid culture protocols were described by the same

group [17]. One of the important features that we realized about intestinal organoid cultures was that these cells could be greatly expanded in vitro and bio banked for future use without a need for genetic modifications. This would facilitate the generation of patient-specific data sets on in-vitro cultured cells; whereas only a single rectal biopsy procedure that causes only limited discomfort to patients was required [18]. As intestinal current measurements using rectal biopsies were included as part of an extensive diagnostic protocol starting in 2011 for newborns with CF identified through newborn screening, left- over rectal biopsies were used to generate rectal organoids from CF study participants.

We established a functional assay to monitor CFTR function and response to CFTR modulators in rectal organoids [13,19–22]. Stimulation of organoids with cyclic adenosine monophosphate (cAMP)-inducing agents such as forskolin induced rapid swelling of organoids within 1 h as a result of ion and fluid transport into the lumen. This phenotype is consistent with cAMP-dependent vectorial anion transport in Ussing chambers using fresh intestinal tissue biopsies [23,24], and with induction

secretory diarrhea in vivo by cAMP agonists such as cholera toxin [25]. Forskolin-induced swelling (FIS) can be observed in both healthy control and CF organoids, but is completely absent in organoids from CFTR knockout mice, and study participants who have two CFTR null alleles. It is partly affected in organoids derived from study participants with CFTR mutations associated with residual function, and correlates with in-vivo and ex-vivo biomarkers of CFTR function such as sweat chloride concentration and intestinal current measurements [13,14]. It is important to realize that the relation between CFTR function and FIS is not linear between 0 and 100% of wild-type CFTR function, as became apparent from analyzing FIS in a study using organoids from 71 study participants [14]. FIS is highly sensitive and at saturating forskolin conditions, organoids swelling reaches a ceiling when CFTR mutations with varying consequences such as R117H-7T (p.Arg177His-7T/c.[350G>A; 1210 –12(7)]) or the splice mutation T5TG13 (c.[1210 –12(5);1210 –34TG(13)]) are present.

Incubation of organoids with CFTR modulators restores the FIS of CF organoids, and allows the quantitation of individual drug responses [14]. Consistent with published data from bronchial air- way epithelial cells, restoration of FIS by CFTR modulators is dependent on the CFTR genotype [10,11]. The dynamic range of FIS measurements needs to be accounted for when interpreting these data. High residual function of R117H-7T prevents a clear detection of potentiator activity when organo- ids are stimulated with saturating levels of forskolin, but R117H-7T organoids are very responsive to potentiation at lower forskolin stimulation [14]. When restoration of FIS by CFTR modulators was compared with pulmonary improvement (absolute improvement in FEV1 compared with placebo) in available published clinical trial of CFTR Modulators, correlations between the in-vitro response of organoids and in-vivo response to identical treatments were identified when organoids were stimulated at lower concentrations of forskolin (0.128 mol) [14]. For this correlation, FIS in the presence of CFTR modulators was corrected for FIS in the absence of treatment (CFTR residual function). The data outlined above suggest that CFTR modulator responses in organoids can be used to identify drug responsiveness in vivo.

During standard organoid culture conditions, wild-type and CF organoids can be easily Distinguished based on their large fluid-filled lumens (Fig. 1) [14]. This steady-state lumen area (SLA) Phenotype can be quantified by determining the percentage of lumen area over the total area and typically reaches beyond 30% for healthy control organoids, whereas organoids with established CF mutations all show SLA values below 10%. The SLA phenotype thus is a CFTR-dependent readout with a dynamic range between CF and healthy controls. The limited SLA phenotype (below 10%) shows variation between the different CF organoids, and was also detected in organoids that showed no FIS response indicating that variation in SLA below 10% is not fully CFTR dependent in contrast to FIS. Over- night incubation with CFTR modulators increased the SLA of CF organoids, essentially in a similar genotype-dependent manner as observed with FIS. Correlations between in-vivo drug efficacy and the SLA phenotype of organoids could also be established. This assay is the preferred assay when efficacy of treatment is compared with healthy control organoids, and indicated that VX-809/VX-770 com- bination treatment reaches approximately 25% of the healthy control SLA (it is noted that F508del/ wild-type organoids are at rv80% SLA of wild-type/ wild-type organoids). The high SLA of healthy control organoids leads to underestimation of FIS Rates because of the prefilled lumens, and therefore, it is more suited to only compare CF conditions with the FIS assay (e.g., efficacy of treatment as compared with VX-809 in F508del/F508del). Apart from being an additional readout for FIS for quantitation of drug responses, the dynamic range between CF and healthy controls of the SLA indicate that it may further help to diagnose CF in difficult- to-diagnose cases, for example, when mutations are identified of unknown disease liability, or when biomarkers of CFTR function show borderline values.

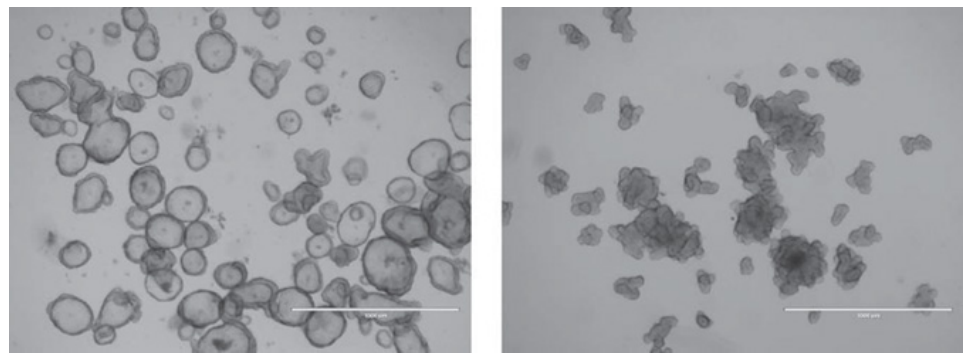

Figure 1. Rectal organoids of a healthy control and cystic fibrosis patient. Representative examples of rectal organoids from a healthy control or subject with cystic fibrosis (S1251N/F508del), grown during standard culture conditions. Healthy control organoids have large fluid-filled lumens, which are severely reduced in CF organoids. Scale bar represents 1000 mm.

Personalized medicine with organoids

The drug responses of organoids with CFTR mutations for which clinical data have been generated can help to interpret drug responses of organo- ids with mutations for which the clinical response has not yet been determined. For example, potential clinical responders to VX-770 may be recognized by comparing the individual response of an organoid upon VX-770 treatment with average responses of organoids from study participants with gating mutations such as G551D or S1251N (p.Ser1251- Asn). Potential non responders may be identified by comparing individual organoid responses with VX-770-treated organoids with F508del/F508del for which VX-770 treatment appeared ineffective [7]. A similar methodology may be applied for VX-770/VX-809 combination treatment. Using this approach, we identified two study participants with extremely rare CFTR genotypes (G1249R (p.Gly1249Arg)/F508del) who showed essentially similar results in their organoids as compared with S1251N-expressing gating mutation organoids; that is, some residual function, high response to VX-770, and limited response to VX-809 [14]. In-vivo treatment of 4 weeks indicated the typical responses observed upon VX-770 treatment in study participants with gating mutations: strong responses in CFTR biomarkers such as sweat chloride concentration and nasal potential difference. Pulmonary responses were variable, one study participant strongly improved by 13% in percentage-predicted forced expiratory volume 1 (ppFEV1), whereas the other who had a lower baseline ppFEV1 showed no improvement. Measurements of airway resistance (RAW0.5), a response indicator reflecting airway resistance during normal breathing that shows better sensitivity to changes at low ppFEV1 values in people with asthma [26], improved more clearly in the study participant without improvement of ppFEV1. In contrast, a study participant whose organoids (R347P (p.Arg347Pro)/F508del) responded in The range of VX-770 responses of F508del/F508del organoids showed only a minor response in sweat chloride levels and no improvement in FEV1 upon in-vivo treatment. By biobanking the organoids, potential future treatments can be assessed without further discomfort to the study participant. This first data suggest that preclinical drug efficacy testing in rectal organoids may help to select potential responders to CFTR modulator treatment, even in the context of extremely rare CFTR genotypes.

The above indicated data suggest that organoids have use to identify drug-responsive or unresponsive (rare) CFTR genotypes. Studies of organoids with identical CF-causing mutations such as F508del/F508del or F508del/null also demonstrate quantitative differences in response to therapy [13,14]. These patient-specific differences are maintained upon long-term culture (6 months) or biobanking, supporting that individual genetics beyond the CF-causing mutation (including potential diversity in the CFTR gene itself) may impact the response to therapy in vivo [14]. Average drug responses in F508del/null organoids are approximately 50% of F508del/F508del organoids. At the individual level, the high drug responding F508del/ null organoids show higher responses to treatment as compared with the low drug responding F508del/ F508del organoids. These data may indicate that additional stratification for in-vivo therapeutic response is promising in study participants with identical CFTR genotypes by analysis of functional drug response in individual cell cultures such as organoids.

In addition, organoid-based measurements can also function as an outcome parameter for CFTR modulator treatments. Blood samples before and after treatment can be used to stimulate organoids, and indicate whether sufficient levels of modulators in blood are reached [27]. In this way, the pharmacokinetic properties of treatments can be assessed in an individual setting. This also helps to interpret how much drugs should be used in preclinical set- tings to ensure that organoids are stimulated with clinically relevant concentrations. We recently explored this blood assay in a study where we aimed to stimulate residual CFTR function using b2-adrenergic receptor agonists [28]. Organoid swelling can be activated by cAMP activating b2-adrenergic receptor agonists in a dose-dependent manner when organoids with mutations associated with residual function are stimulated. However, in-vivo CFTR modulation was difficult to identify upon treatment with b2-adrenergic receptor agonists, but some evidence for CFTR modulation was detected in study participants that received oral, but not inhaled, salbutamol by nasal potential difference measurements. Blood samples after oral, but not inhaled, treatment could stimulate organo- ids, consistent with detection of some CFTR activity in vivo. Concentrations in blood were in a range that associated with only limited CFTR activity when organoids were stimulated with pure salbutamol. This indicates that blood samples before and during treatment may report on pharmacokinetic proper- ties of treatments. In individual settings, the blood assay may help to identify study participants who may respond poorly to treatment because of pharmacokinetic reasons.

Intestinal organoids thus provide a possibility for the preclinical selection of CFTR modulators, and the monitoring of drugs during therapy. These individual measurements may help to select optimal treatments, aiming to achieve maximal long-term clinical benefits for individuals receiving treatment (Fig. 2).

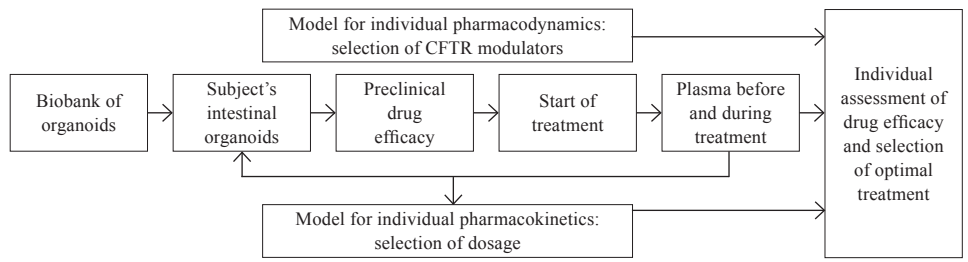

Figure 2. Personalized medicine with intestinal organoids. Individual bio banked intestinal organoids provide a resource from which individual organoids can be cultured for preclinical assessment of (combinations of) CFTR modulators. Upon in-vivo treatment, plasma before and after treatment can be incubated with organoids to monitor the level of modulators in plasma.

These measurements can inform on individual pharmacodynamic and pharmacokinetic parameters of CFTR modulator treatment, and may help to select individually tailored treatments with optimal long-term treatment outcomes.

Conclusion

The integration of patient organizations and the establishment of multidisciplinary research teams helps to facilitate the translation of basic research findings to achieve a greater impact for patients. A collaborative effort in the Netherlands between the national CF patient organization, basic and clinical scientists led to the development of a CFTR-dependent swelling assay using an in-vitro stem cell culture model that allows accurate measurements of individual CFTR function and responses to new CFTR modulators. Measurements in rectal organoids correspond with published relations of the CFTR genotype and CFTR residual function, other in-vivo biomarkers of CFTR function, and pulmonary responses of CFTR modulators in published clinical trials. Organoids measurements also led to the preclinical identification of study participants with rare CFTR mutations that demonstrated clear responses to VX-770 upon in-vivo treatment. Additional data and assays with rectal organoids suggest that this technology can help to personalize treatment for people with CF by providing a detailed understanding of individual pharmacodynamics and pharmacokinetic properties related to CFTR modulator treatments. Still, much is yet to be learned, and the early results in these proof-of- concept studies require validation in larger studies and by additional laboratories to firmly establish that rectal organoids can help to optimize personalized treatment of CF.

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7

Chapter Eight

Mini-guts in a dish: Perspectives of adult Cystic Fibrosis (CF) patients and parents of young CF patients on organoid technology

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Abstract

Background

Organoid technology enables the cultivation of human tissues in a dish. Its precision medicine potential could revolutionize the Cystic Fibrosis (CF) field. We provide a first thematic exploration of the patient perspective on organoid technology to set the further research agenda, which is necessary for responsible development of this ethically challenging technology.

Methods

23 semi-structured qualitative interviews with 14 Dutch adult CF patients and 12 parents of young CF patients to examine their experiences, opinions, and attitudes regarding organoid technology.

Results

Four themes emerged: (1) Respondents express a close as well as a distant relationship to organoids; (2) the open-endedness of organoid technology sparks hopes and concerns, (3) commercial use evokes cautiousness. (4) Respondents mention the importance of sound consent procedures, long-term patient engagement, responsible stewardship, and stringent conditions for commercial use.

Conclusions

The precision medicine potential of organoid technology can only be realized if the patient perspective is taken adequately into account.

Introduction

Organoids are 3D cell structures that can be cultured out of human pluripotent and adult stem or progenitor cells [1]. They closely recapitulate the architecture and function of real-life human tissues and they can be applied in fields ranging from disease modelling to drug development and regenerative medicine [1,2]. Organoids can be stored in so-called Living Biobanks, which enables widespread use of the technology [3–5].

Organoid technology could potentially revolutionize Cystic Fibrosis (CF) research and care as it offers a strikingly accurate and personalized model for disease [6–10]. The development of novel drugs for patients with CF, particularly for those with rare mutations, is challenging, because small sub-groups make it impossible to conduct classical trials. The intestinal organoids, derived from rectal biopsy material of patients, constitute a novel model for stratified drug development and for the prediction of individualized drug response, as they are genetically and functionally similar to patients [9,11]. Although organoid technology has been predominantly applied in the research setting, the technology starts to impact the clinical care of patients with CF [6]. The technology promises to have a far-reaching impact on the lives of patients with CF, particularly on the lives of those with rare mutations (see supplementary material, attachment 1 for more background) [6–8].

Now that organoid technology promises to thoroughly change the CF field, what do patients with CF actually think of this revolutionary technology? Earlier we showed that organoid biobanking comes with ethical challenges related among other things to the moral and legal status of organoids, consent, commercialization, return of results and governance [4,5]. These challenges are not necessarily new, but form a convergence of existing debates on the ethical aspects of genomics, biobanking, big data, and other stem cell technologies [4,5].

In related fields, such as the derivation and use of induced Pluripotent Stem Cells (iPSCs), ethical debate and empirical research on the attitudes of participants have already led to policy recommendations [12–17]. Although some common ground has been established, such as the need for patient consent, debates on the above mentioned questions are still unsettled. What is more, organoid technology is a novel type of stem cell technology that may give a new twist to ethical debates [4,5]. In this paper, we aim to provide a first thematic exploration of the patient perspective on organoid technology in order to set the further research agenda. We aimed to recruit respondents for whom organoid technology could be or could become of relevance, i.e. adult patients with CF and parents of young patients with CF, to examine their experiences, opinions, and attitudes with regard to organoid technology.

Materials and methods

We performed a qualitative interview study to identify relevant themes with regard to organoid technology as perceived by patients with CF and parents of young patients with CF [18].

Sample

We aimed to collect a wide range of experiences and viewpoints from Dutch patients for whom organoid technology could be or could become of relevance. When we conducted our qualitative interview study, particularly adult patients with CF and young patients detected in the newborn screening were eligible for participation in organoid research. Therefore, we chose to recruit adult patients with CF and parents of young patients with CF (preferably b5 years of age), that had participated in organoid research or not (see supplementary material, attachment 1 for Background on organoid technology and CF).

Adult patients with CF and parents of young patients with CF were first approached via repeated calls on the website and on other types of social media of the Dutch Cystic Fibrosis Foundation (NCFS). Since mainly adult patients responded to these calls, we additionally recruited parents of young patients via treating physicians in the Wilhelmina Children's Hospital (WKZ).

In total, we conducted 23 interviews with 26 respondents: 14 adult patients and 12 parents of young patients with CF (see Tables 1 and 2 for Characteristics of the study population). Since organoid technology was emerging in the CF field, for those respondents that had participated in organoid research the processes around retrieval of rectal biopsy material, consent, the research project, and long-term storage of organoids varied (see Tables 1 and 2, and supplementary material, attachment 1 for Background on organoid technology and CF). The time span between their variable experiences (Tables 1 and 2), including consent, and the interview varied between roughly a couple of months and two years. Due to poor recall of their experiences, we could not calculate exact time spans.

Data collection

The interviewer, SNB, conducted the interviews between June 2015 and February 2016. The interviews were held in Dutch, they lasted between 50 and 80 min, and took place at the University Medical Center (UMC) Utrecht or at the respondent's home. SNB used a semi-structured topic list to guide the interviews, which was based on literature, pilot interviews, and comments from the NCFS patients' research advisory board (see supplementary material, attachment 2 for the Interview topic list). The topics evolved following information that was obtained from completed interviews. The REC of the UMC Utrecht assessed that the study was exempt from formal review. Patients and parents provided oral informed consent for their participation.

Table 1. Characteristics of adult patients.

Patients (n = 14)	Participated in organoid research (n = 5)[a]	Did not participate in organoid research (n = 9)
Gender		
Male	3	7
Female	2	2
Age (years)		
18–30	1	2
30–50	2	3
N50	2	4
Education		
Primary, lower secondary general, or lower vocational	0	0
Higher secondary general or intermediate vocational	1	3
Higher vocational or university	4	6
Treating hospital		
University Medical Center, Utrecht	1	5
Erasmus Medical Center, Rotterdam	0	1
Haga Hospital, The Hague	4	3

[a] The participation of adult patients in organoid research was variable in terms of the processes around retrieval of the rectal biopsy material, consent, use, and long-term storage of the gut organoids (see supplementary material for background on organoid technology and CF). 3 patients participated in a specific organoid research project and had given biobank consent. 2 patients could not recall the context of their participation in organoid research.

Data analysis

The interviews were audiotaped, transcribed verbatim, and stored coded. In our data analysis we focused on identifying broad themes. We applied the constant comparative method, which means that data analysis is an iterative process in which we go back and forth to develop codes, concepts, and, lastly more interpretative themes [18]. SNB coded the full transcripts by labelling units of texts that referred to one or more topics, using NVivo 10 software [19]. The codes were developed into

higher-order concepts and themes. Reliability was ensured by continuous discussion of the codes and themes during team

Table 2. Characteristics of parents and their children.

Parents (n = 12)[a]	Whose child participated in organoid research (n = 10)[b]	Whose child did not participate in organoid research (n = 3)[c]
Gender		
Male	6	1
Female	4	2
Age (years)		
30–40	8	3
40–50	2	0
Education		
Primary, lower secondary general, or lower vocational	0	0
Higher secondary general or intermediate vocational	4	0
Higher vocational or university	6	3

Children (n = 10)	Participated in organoid research (n = 8)[b]	Did not participate in organoid research (n = 2)
Age (years)		
2–3	2	1
3–4	3	0
4–5	1	0
N5	2	1
Treating hospital		
Wilhelmina Children's Hospital, Utrecht	7	0
Sophia Children's Hospital, Rotterdam	1	1
Radboud Medical Center, Nijmegen	0	1

[a] 6 interviews were conducted with either the father or the mother of the child, 3 interviews were conducted with both parents.
[b] The participation of young patients in organoid research was variable in terms of the processes around retrieval of the rectal biopsy material, consent, use, and long-term storage of the gut organoids (see supplementary material for background on organoid technology and CF). Parents of 6 children had provided biobank consent, of whom 1 child had participated in a specific organoid research project, and 5 children participated in the monitoring program (see supplementary material, attachment 1 for Background). Parents of 2 children could not recall the context of their participation in organoid research.
[c] These 3 parents consisted of the mother and father of one child that had not (yet) participated in organoid research and one mother of 2 children, one of whom did participate and one of whom did not participate in organoid research. Therefore the number of parents does not add up.

Results

We identified four interrelated themes concerning different aspects of organoid technology that resonated among all our respondents.

Theme one: an ambiguous relationship to organoids

Most respondents see organoids as both closely and distantly related to them. Only a couple of respondents express a predominantly close or distant relationship. Respondents mention several characteristics of organoid technology that influence their thinking about organoids as closely or distantly related (Table 3).

First, respondents address the two-sidedness of the material nature of organoids. On the one hand, they reason that organoids are immortalized human cells grown out of bodily material that share unique characteristics with the donor. Therefore, most respondents regard organoids as living human materials (quotation 1 in Table 4). Some even regard organoids as living fragments of themselves. On the other hand, immortalization of organoids enables broad distribution and use, which creates a literal distance between patients and organoids. Moreover, respondents argue that organoids are just intestinal cells that have no thoughts or feelings (quotation 2 in Table 4).

Second, some respondents mention that the type of application influences their perceived relationship. The use of organoids as a personalized drug testing tool contributes to a sense of closeness. In this case organoids become an extension of the patient's body in the laboratory and testing results influence a patient's well-being (quotation 3 in Table 4). A close relationship is perceived by some if they strongly identify with the use of organoids or if, on the contrary, applications conflict with personal values (see Section 3.2 Theme 2). The use of organoids in an anonymous fashion for noncontroversial broad research purposes, however, feels as impersonal, as some say (quotation 4 in Table 4).

Third, respondents with strong motives for donation, whether personal or altruistic, mostly express a closer perceived relationship to organoids.

Fourth, imagination and language play a role in the perceived relationship to organoids. Some respondents vividly imagine organoids as organ-like structures in a dish. This image is strengthened by the term mini-gut that is sometimes used popularly (quotation 5 in Table 4). Others acknowledge that they would perceive a closer relationship to organoids if bigger organ-like structures were created. In sum, respondents perceive an ambiguous relation to organoids and they each negotiate the ambiguity of the above-mentioned characteristics in their own way (quotation 6 in Table 4).

Theme two: hopes and concerns related to the open-endedness of organoid technology

The immortalization of organoids and biobank storage combined with a broad consent procedure (see supplementary material, attachments 1, 3 and 4) create certain degrees of open-endedness. All respondents express hopes and concerns related to the open-endedness

of organoid technology.

Table 3. Characteristics of organoid technology that influence the perceived relationship of respondents to organoids in 4 different categories.

Characteristics contributing to a closer perceived relationship	Characteristics contributing to a more distant perceived relationship
1. Material nature of organoids	
Organoids relate to the human body - Grown out of human material - Unique and personal characteristics Same genetic make-up Same biological function - Related to bodily integrity Living human material - Organoids are immortalized - Organoids are 3D	Immortalization enables widespread distribution and use of organoids Organoids are just cells - Organoids have no feelings or thoughts - Intestinal tissue is not sensitive - Organoid donors have no physical connection to the organoids Organoids constitute a technology - created by researchers
2. Use of organoids	
Use of organoids can impact personal wellbeing - Improved treatment through personalized diagnosis and drug testing Use can have negative impact (e.g. a breach of confidentiality) Use of organoids can impact personal values Use of organoids can be a positive expression of personal values - Sensitive applications, e.g. reproductive cloning, growing whole organs and commercial use can conflict with personal values Use while coupled to personal information	Broad use for research is impersonal - Research only impacts future patients - Noncontroversial applications do not affect a person's values Only others can use organoids Anonymous use
3. Intention for (hypothetical) donation	
Strong motivation for and identification with donation Strong ideas about worthy use of organoids	Weak motivation for donation (e.g. 'not hindering research') Weak ideas about worthy use
4. Imagination and language	
The term mini-guts' Strong imagination of mini-guts in dish Growing bigger organs Combining organ systems	The term "organoids" No imagination of organoids, very abstract Merely growing tiny organoids

Hopes related to open-endedness

Most respondents share the impression that organoid technology could revolutionize CF drug research, which could ultimately lead to personalized treatment. This hope for personalized treatment is their main motivation to donate the organoids to a biobank. Some respondents (would) predominantly donate for the good of future patients, whereas others (would) donate in the hope of benefitting personally. Some respondents, mainly those that had not participated in organoid research or respondents for whom the purposes of future use remain somewhat unclear, have relatively high hopes for personal benefits (quotation 8 in Table 4). Others have more moderate expectations (quotation 9 in Table 4).

Table 4. Quotations from respondents.

An ambiguous relationship to organoids

1. Parent-6: 'Yes these are after all living cells and they do something, they have a function. On the screen they show that with the right medication they can grow from small to large, however small that is, so they are alive.'
2. Patient-3: 'Yes, well, it is so abstract and such a tiny piece of tissue that I don't see anything wrong with it. You spread even more tissue around through blood and urine samples and hair that falls out everywhere.'
3. Patient-11: '…so risk free…a part of myself, or a clone of myself that you can experiment on risk free…and from that you hope to get a better quality of life.'
4. Patient-4: 'If it is immediately used for research in a more generalized target group and used in large numbers, then yes it seems less personal to me, then it suddenly becomes a very different matter.'
5. Patient-10: 'In a manner of speaking, yes, mini-gut gives you the idea that you are really talking about an intestine, even if it is only a centimeter in size.'
6. Parent-2: 'It is in fact a part of him, so it is…everything that it is, is also him, so it is important that a link remains between him and the mini-gut, precisely because they could find something that could benefit him too, but it is not a part of him anymore; the way I see it they are real pieces of (son's name).'

The hopes and concerns related to the open-endedness of organoid technology

Cautiousness towards commercial use of organoids

7. Parent-7: 'Yes that is actually quite strange, something living outside your body, that's really out there, we're sitting here in Brabant and a piece of (son's name) is sitting in Utrecht or wherever it's being kept, I don't know…if you think about it it's quite strange.'
8. Parent-6: 'Because for us it is real, I feel that the mini-guts are the future for (name), that everything really depends on whether they can, well, if they can cure, or if we can turn CF into a chronic disease instead of a deadly disease.'
9. Parent-8: 'Well, in addition to the broader research I expect…that something will come of it for him, that they can do something with it. And preferably he would get a sort of tag for possible follow-up research.'
10. Patient-4: 'But maybe the creation of organs or very different purposes that have nothing to do with my disease or other diseases, and so more commercial purposes, then it becomes a more complicated story.'
11. Parent-1: 'Yes it's just that you want to be kept up to date, we are very aware that you probably get a lot of information that you can't do anything with yourself, but you still want to follow it, you want to stay informed.'
12. Parent-9: 'No, not with my child, I think. No, if I think about it, the hospital is fine, but something commercial, no. No, that makes me uncomfortable, I think.'
13. Parent-4: 'If I read something like Galapagos…that they are working on CF and they bought a license to use organoids, then I think yes, alright, we're going that much faster.'
14. Patient-2: 'Think of the pharmaceutical industry profiting from it, and it's also a piece of you. And once they start earning so much money that way, it doesn't feel so great.'

Dealing with ambiguity

15. Parent-8: 'You have to keep in mind that it will take 10, 15, maybe 20 years before there are any real results. So we are very cautious not to get our hopes up.'
16. Parent-1: '…if they say no then you don't get any research in the area of CF, then probably you will say yes.'
17. Parent-2: '…there must be somebody, a committee or something that can manage it well, good ownership. That I have the feeling that my body parts, or my personal information, are safe there. There has to be a sort of trust in that biobank that it will be handled well.'
18. Parents-6: (mother) 'Yes but I can also imagine, look, lab technicians keep everything on the basis of the unique number assigned to the organoid, so you would think that it would be quite simple to seal certain information…' (father) 'With your DigiD (Dutch government digital identification code)'… (mother) 'Or with your personal organoid code.'
19. Patient-7: 'I would find it logical that there would be some sort of compensation for the use of that material, in terms of pharmaceuticals, in the form of expedited access to drugs or something.'

Concerns related to open-endedness

Concerns mainly revolve around the uncertainty of respondents concerning whether their organoids will be used in their best interests and according to their values. Although a couple of respondents have found some reassurance in the broad consent process (see supplementary material, attachments 1, 3 and 4), most share the following concerns:

Some respondents mention the possibility that their organoids and related personal information are not being handled respectfully. Moreover, respondents mention that the open-endedness hampers a sense of contribution and identification with the aims for which their organoids are used. Most respondents wish to stay away from unworthy, trivial or unethical applications, such as growing whole organs, reproductive cloning, and purely for-profit use (quotation 10 in Table 4). This would clash with their values. Others explicitly formulate the type of research they wish to contribute to, notably CF research and care. Additionally, some respondents are uncertain as to whether their organoids will be used in ways that could positively impact their future care. Others are actively interested in organoid research and would like to get the opportunity to better comprehend the technology and its meaning for CF (quotation 11 in Table 4). Most parents wish to be able to justify and explain the storage and use of organoids to their child.

Theme three: cautiousness towards commercial use of organoids

Most respondents, including those who have given biobank consent, struggle with commercial use, e.g. by pharmaceutical or biotech companies. Some respondents, including a parent that had consented to biobank storage, even categorically reject the use of organoids by commercial parties (quotation 12 in Table 4). Others accept that we live in a society in which drug development is predominantly market-driven (quotation 13 in Table 4).

The motives that respondents give for their cautiousness seem to reflect a distrust of commercial parties. First, most respondents fear that commercial parties will not act in the best interest of patients and society. Second, the profit motive is deemed unfair or even unjust (quotation 14 in Table 4). Making money out of severely ill patients is considered to be potentially exploitative and for-profit research may result in exorbitant prices of novel drugs. Third, respondents fear a lack of oversight of the use of organoids. Fourth, some fear negative consequences of commercial use, including the sharing of sensitive information with improper stakeholders (e.g. insurance companies), or perceived unethical applications.

Theme four: dealing with ambiguity

From the previous three themes it follows that respondents have ambiguous attitudes towards organoid technology: (1) they experience a close as well as a distant relationship to organoids, (2) open-endedness of organoid technology strengthens hopes and concerns, and (3) although commercial use is deemed necessary for drug development, it evokes cautiousness. Respondents come up with different ways to deal with their variable values, interests, hopes, and concerns.

First, respondents acknowledge the importance of initial biobank consent. Respondents that have given broad biobank consent mention a couple of aspects that they experienced to be reassuring. One parent mentions that the information provided in the consent conversation helped to have realistic hopes (quotation 15 in Table 4). Other respondents mention the written information that, for instance, addressed the instalment of ethical oversight, the protection of privacy, and the return of clinically useful results (see supplementary material, attachments 3 and 4). Still, most respondents would ideally wish to restrict the scope of initial consent, although most of them had consented or would consent to the broad terms (quotation 16 in Table 4). Some would prefer to donate to CF research exclusively or to limit the sharing of their organoids. Others would like to exclude certain sensitive uses.

Second, initial consent is generally considered to be insufficient. It should, according to the respondents, be coupled with long-term engagement of participants and responsible stewardship, which includes ethical oversight, privacy protection, transparency, and the fostering of trust (quotation 17 in Table 4). Minimally, respondents share the idea that participants should be informed about major changes in governance or use and about clinically useful results. In addition, most respondents would like access to collective information concerning planned, ongoing, and finalized projects. Some respondents would ideally have access to personal information on the use of their organoids (quotation 18 in Table 4). Some only wish to be asked to re-consent to sensitive applications, whereas others wish to be asked to re-consent to each new research project. Overall, if organoids are used by commercial parties, respondents put forward more stringent conditions for long-term engagement and stewardship, including an emphasis on reciprocity (quotation 19 in Table 4).

Discussion

This is the as far as we know first study exploring the patient perspective on organoid technology. The four themes that emerge in our qualitative interview study give an impression of the experiences, attitudes, and opinions of Dutch adult patients with CF and parents of young patients with CF with regard to organoid technology. Although our respondents are generally supportive of organoid technology, the first three themes show that they have an ambivalent attitude. Respondents (1) experience a close as well as a distant relationship to organoids, (2) the open-endedness of organoid technology strengthens hopes and concerns: organoid technology is seen as a potential game changer in the treatment of CF; however, respondents express concerns about whether the organoids will be used in their best interests and according to their values; and (3) although commercial use is deemed necessary for drug development, it evokes cautiousness. In the fourth theme respondents come up with several ways to deal with their variable values, interests, hopes, and concerns. They mention the importance of a sound consent procedure, long-term engagement of patients, responsible stewardship, and stringent conditions for commercial use.

This first exploratory study gives an impression of the relevant themes to set the further research agenda, even though further research is necessary to identify differences among subgroups.

Understanding the interests of Dutch adult patients with CF and parents of young patients with CF

Like iPSCs, organoids should not be seen as a morally neutral alternative to embryonic stem cells [4,5,12]. Contrary to human embryos, intestinal organoids do not raise questions about intrinsic moral value. Nevertheless, organoids, particularly those derived from adult stem or progenitor cells, are genetically and functionally identical to the donor [11]. Therefore, donors may have a legitimate interest in managing conditions for derivation, storage, and use [4,5]. Our findings inform what the interests of donors, in this case Dutch patients with CF and parents of young patients with CF, might be.

In the first theme respondents reflect on their relationship to organoids. How can we relate their views to the moral value of organoids [4,5]? More specifically, could we regard organoids as sensitive tissue and could they give rise to sensitive applications [12,20]? This is relevant, because donors generally have more autonomy-based rights over sensitive tissues and applications and ethical oversight is more stringent [12,16,20]. Respondents do not regard the rectal biopsy material itself as sensitive. Rather, it is the transformation of the biopsy into a 3D immortalized cell line that is genetically and functionally similar to the donor that is considered meaningful, and to some extent as sensitive. What distinguishes organoids from other immortalized cell lines is their 3D structure. Some respondents do find that this feature contributes to their idea of a close relationship to organoids.

Apart from the creation of organoids itself, organoids can be used in possibly sensitive ways that are partially unforeseen. In iPSC research some types of applications have been marked as potentially sensitive, such as certain basic research procedures (e.g. large-scale genomic sequencing), transplantation into humans, and for-profit use [12,13,15]. All of these apply to organoid technology and our respondents add to this the creation of bigger organ systems. Despite these and other concerns, respondents are generally supportive of organoid technology, which is in line with other empirical studies on the attitudes of patients towards biobanking and iPSC research [13,21,22]. For our respondents the hope for personal benefit may have been a somewhat stronger motive to (hypothetically) donate organoids. Patients with CF are not mere donors of bodily materials, they are simultaneously potential end-users of organoid technology. Therefore, their interests could differ from other types of tissue donors. The fear that organoids may not be used in ways that can positively impact their healthcare indicates this personal interest.

In the third theme, respondents reflect on an area of application that raises specific concerns: commercial use of organoids. Commercial use of human samples is known to be a sensitive topic among patients, donors, and the wider public [13,23–25]. Our respondents particularly fear that their organoids might be used for developing CF drugs that will be exorbitantly priced, which may impede access to these novel therapies. This fear is not unfounded given the high prices of the latest generation of CF drugs [26].

Embedding patient perspectives in practice and policy

How should the practice and policy of organoid technology be shaped together with CF patients and their parents? In the fourth theme, respondents express that their interests and concerns could best be taken care of through sound initial consent procedures, long-term engagement, responsible stewardship, and stringent conditions for commercial use.

Donor consent for the collection, storage and use of human samples is generally recognized as an important means of protecting a donor's interests [27,28]. Explicit donor consent for the derivation and use of iPSCs is deemed indispensable and we propose extending this prerequisite to organoids [4,5,12,13,15,16]. Furthermore, several of our findings con- tribute to the idea that the initial consent procedure has its limitations. Initial consent was deemed insufficient by most of our respondents to manage their hopes and concerns, a perspective that is reflected in other work on the storage and use of human samples [12,15,29]. Besides, many respondents had flawed recall of the consent procedure, a well-known phenomenon in biomedical research in general and stem cell research in particular [30].

Therefore, we contend that initial consent should be coupled with long-term engagement of participants and responsible stewardship. For iPSC research it has already been argued that donors should be re-contacted to solicit re-consent for innovative, potentially sensitive applications, for the return of individual results, and to seek re-consent from pediatric participants once they reach an adult age [12,15,31]. We would like to add that at minimum participants should be informed about relevant collective information and major changes in governance [32]. Participatory medicine initiatives around the globe, however, show that patients can be involved more actively [33,34]. The incremental levels of involvement range from informing patients, to consultation, an advisory role, partnership, and ultimately a project in which patients have a leading role [34,35]. The desirable level of involvement is case and context dependent. A higher level of involvement may be necessary if a disease-specific biobank is set up in which participants are both donors and potential end-users, such as the CF organoid biobank, or if organoids are used for sensitive aims. The CF field in the Netherlands already sets the stage for close collaboration among patient organizations, researchers, and physicians [35].

Furthermore, public-private partnerships are needed to translate the scientific fruits of organoid technology to marketable drugs for patients with CF, as is acknowledged by our respondents. In general, for the commercial use of organoids to be ethically responsible and widely supported by patients and the public, models are needed that balance potential merits with concerns [5]. In these models, reciprocity is key [36]. For the field of CF, the ultimate goal of applying organoid technology is the realization of precision medicine. To reach this goal, pro-active negotiation of pricing is prerequisite, particularly in light of recent difficulties with reimbursement of lumacaftor/ivacaftor, a promising CF drug, in the Netherlands [37].

Limitations

First, whereas the heterogeneity of our sample allowed us to collect a wide range of viewpoints it also has limitations, particularly because the sub-groups are represented by small numbers. We, for instance, interviewed more adult male patients with CF than female patients, the experience of our respondents with organoid research was variable, and most of the parents we interviewed had a young child that had participated in organoid research. Parents without experience in organoid research were underrepresented. In this first qualitative study, however, it was not our aim to provide in-depth insight into differences among sub-groups, nor to generalize the views of our respondents to the entire population of patients with CF.

Second, due to low response rates to the open calls, we additionally recruited parents via treating physicians in the WKZ, where most children are exposed to organoid technology. The WKZ professionals have a positive overall attitude towards organoid technology, which may have influenced parents. Nevertheless, parents voiced concerns equally.

Third, it is likely that patients and parents interested in new developments in the CF field responded most readily to the open advertisements. This could influence their level of knowledge and their desire for pro-active involvement in organoid technology. The educational level of our respondents was above average and consequently they may well have been more informed and articulate.

Fourth, the timing and process of interviewing may have influenced the views of respondents. Although most respondents were primarily positive regarding organoid technology at the beginning of the interview, they gradually started to voice concerns. Those that had participated in organoid research admitted that for them it was their first opportunity to thoroughly reflect on certain sensitive topics. It remains a question whether these concerns will fade away over time.

Fifth, patients with CF constitute a distinct group. They have a direct health interest in organoid technology and they are known for their pro-active attitude in their care and in research [38].

The limitations of our explorative study clearly show the need for further future research. In order to analyze differences among sub-groups of patients with CF and to generalize findings to the entire population further empirical research is needed in which qualitative and quantitative approaches are combined and more diverse groups (in terms of e.g. educational level, disease severity, ethnicity, nationality) are included. Moreover, further empirical research should shed light on the perspective of other types of donors and organoids.

Concluding remarks

Sound governance of organoid technology in CF research and care requires considerations of consent, long-term engagement of adult patients and parents of young patients, responsible stewardship, and responsible models for commercial use. Organoid technology holds a promise for personalized therapy in CF; however, this can only be realized if the perspective of the person in question, i.e. the patient, is taken adequately into account.

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Appendix A. Supplementary data

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8

Chapter Nine

Responsible use of organoids in precision medicine: the need for active participant involvement

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Abstract

Organoids are three-dimensional multicellular structures grown in vitro from stem cells and which recapitulate some organ function. They are derivatives of living tissue that can be stored in biobanks for a multitude of research purposes. Biobank research on organoids derived from patients is highly promising for precision medicine, which aims to target treatment to individual patients. The dominant approach for protecting the interests of biobank participants emphasizes broad consent in combination with privacy protection and ex ante (predictive) ethics review. In this paradigm, participants are positioned as passive donors; however, organoid biobanking for precision medicine purposes raises challenges that we believe cannot be adequately addressed without more ongoing involvement of patient-participants. In this Spotlight, we argue why a shift from passive donation towards more active involvement is particularly crucial for biobank research on organoids aimed at precision medicine, and suggest some approaches appropriate to this context.

Key words
Stem cells, Organoids, Biobanking, Ethics, Precision medicine, Involvement, Governance

Introduction

Research on human tissues is quickly on the rise, especially with the rapid development of complex tissues such as organoids. Organoids are three-dimensional multicellular structures derived from stem cells, cultivated to self-organize into differentiated functional cell types spatially organized in a manner similar to an organ, and that are able to perform at least some organ function (Lancaster and Knoblich, 2014; Huch and Koo, 2015). Because of their characteristics, organoids have enormous potential for drug development and precision medicine, which aims to increase cost- effectiveness and risk-benefit ratios of therapies by more precisely targeting therapies to individual patients (Hewitt, 2011; Kinkorová, 2016). To illustrate, biobank research on patient-derived organoids has already led to successful personalized treatment of cystic fibrosis (Noordhoek et al., 2016; Saini, 2016).

In order to facilitate such research, organoids are cultivated from patient-derived stem cells and stored in tissue repositories called 'biobanks'. Biobanks facilitate multidisciplinary research aimed at a variety of purposes such as drug screening, drug development and disease modelling, as well as enabling large-scale data sharing and analysis. In biobanking, the traditional way of protecting the interests of participants is by relying on a one-off consent procedure, combined with measures to protect privacy and ex ante ethics review. However, organoid biobanking raises specific ethical and practical challenges related to the consent procedure, commercial access and commodification, privacy and ownership (Boers et al., 2016; Bredenoord et al., 2017; Munsie et al., 2017). In this Spotlight, we argue that these challenges call for a shift in focus from the paradigm of passive donation towards more active forms of participant involvement, and suggest some potential ways forward.

Limitations of the current approach in biobank-based research

At present, the dominant approach in biobank-based research can be considered a 'consent or anonymize' paradigm, in which consent for sample storage and use is viewed as a requirement only if samples are not, or cannot, be fully anonymized. In addition, emphasis is placed on measures to protect privacy and ex ante ethics review (Solbakk et al., 2009; Mostert et al., 2016). Broad consent is frequently defended as an appropriate model in the consent or anonymize-paradigm. Broad consent seeks permission for the use of stored samples for a broad range of research purposes, the specific details of which are unknown at the time of consent. Broad consent is valuable for biobank research, because demanding specific consent for each new potential use would significantly hamper research and make the use of stored samples unattractive – if not infeasible. Although broad consent is unable to provide specific details to participants, we believe it is coherent with the notion of an informed and voluntary decision (Sheehan, 2011). Broad consent therefore strikes an elegant balance, by

allowing future (re-)distribution of samples without the burden of re-contacting participants every time a sample is requested.

However, this focus on either obtaining broad consent or on full anonymization of samples is being increasingly criticized for its inability to adequately protect participants' interests (Mostert et al., 2016). For example, there is no harmonization regarding appropriate measures to protect privacy in data- and sample-based research (Knoppers et al., 2007; Zika et al., 2011; Kaye et al., 2018). In addition, whether anonymity is actually possible is being increasingly questioned because of advances in genomics and data-driven research (Lowrance and Collins, 2007; Laurie, 2011; Freeman Cook and Hoas, 2013; Kasperbauer et al., 2018). These concerns are especially relevant in the domain of rare diseases such as cystic fibrosis, because of the small number of patients. Moreover, in contrast to the common assumption that anonymity is the most important interest of biobank participants, full de-identification of samples may in fact be at odds with the needs of patients, as it rules out the possibility of diagnostics or return of results (Eriksson and Helgesson, 2005), as well as denying biobank participants any degree of control over their tissue (Gottweis and Lauss, 2010; Boers and Bredenoord, 2018).

Indeed, patients have voiced their concerns about this (Pakhale et al., 2014; Boers et al., 2018).

In addition, although we concur that broad consent is valuable for biobank research and is not problematic per se, the current emphasis on a one-off consent and privacy protection positions patient- participants as passive donors. This approach does not adequately address the challenges associated with biobank research on patient- derived organoids, nor does it sufficiently take into account the interests of patient-participants, because it does not facilitate ongoing involvement around the use of their tissue.

Why active involvement is particularly important for precision medicine research on organoids

Support for closer involvement of participants in biomedical research initially emerged as a means to increase the quality and value of clinical trials, and to facilitate efficient translation from bench to bedside by working with citizens or patients, rather than simply subjecting them to research (Ocloo and Matthews, 2016). In biobank research, this emphasis on more active forms of involvement rather than passive donation is similarly on the rise, as a way to collaborate on setting up research and governing data, to share ideas and perspectives on data and tissue use, and to improve the governance of research biobanks (Gottweis, 2008). We believe that there are a number of reasons why more involvement is important for biobank research on organoids for precision medicine purposes.

First, the specific characteristics of future research are unknown at the time of consent. At the same time, organoid technology is developing rapidly, which has already led to the

successful cultivation of many different kinds of organoids, such as stomach, liver, intestine, lung, kidney, and more recently also brain organoids, as well as gastruloids or embryoids that provide in vitro models of the early embryo (Aach et al., 2017; Huch et al., 2017; Schutgens and Clevers, 2020). These developments have raised questions about bodily integrity and identity, and what is considered ethically acceptable use (Boers et al., 2016, 2019; Bredenoord et al., 2017; Munsie et al., 2017; Boers and Bredenoord, 2018). Moreover, embryoids or gastruloids have led to discussion about whether, and to what extent, they might have moral status (Sutton, 1995; Munsie et al., 2017; Appleby and Bredenoord, 2018). Some of these applications, such as embryoids, genetic modification, chimaera research (Rowe and Daley, 2019) or brain emulation (Serruya, 2017; Trujillo et al., 2019), have already sparked public and political controversy. In fact, empirical research has demonstrated that participants in organoid biobank research experience different relationships and attribute relational value to their organoids (Boers et al., 2018). Biobank participants therefore have legitimate interests in continuous, downstream involvement around the use of their tissue (Bagley et al., 2017; Bredenoord et al., 2017; Huch et al., 2017), and participants in genomic biobanks have voiced their support for such measures (Wendler and Emanuel, 2002; Murphy et al., 2009).

Second, organoids have enormous economic value, meaning there are strong commercial interests involved (Bartfeld and Clevers, 2017; Bredenoord et al., 2017; Boers et al., 2019). The application of organoids in precision medicine brings together different stakeholders with potentially conflicting interests (Caulfield et al., 2014). Commercial parties have strong incentives to prioritize the most profitable research, but these choices will not necessarily be aligned with patients' most urgent health needs, or with academic interests. This raises the complex question of how to fairly distribute benefits. Benefits here should not be understood in a strict monetary sense, such as a share of the profits. Rather, by benefits we mean contributions to the general well-being of individuals (Hugo Ethics Committee, 2000), for example via post- trial access to drugs. Our point is not that biobank participants deserve compensation in general for their provision of tissue (Allen et al., 2018). However, contrary to healthy participants, patients depend on the activities of precision medicine organoid biobanks for treatment. To view their decision to participate as a voluntary, non-reciprocal donation would therefore be inappropriate. In our view, generating profits using tissues derived from patients is ethically contentious, if it is done without adequately taking into account their perspective on how these organoids are stored and used.

That being said, what constitutes fair distribution must also take into account the importance of financial sustainability. It is crucial to maintain an economically viable climate to attract industry investment in order to realize the most important goal of organoid biobanking in precision medicine: developing treatment. The ethical challenge here is to ensure that benefits are distributed fairly among all involved stakeholders (Caulfield et al., 2014; Mitchell et al., 2015; Boers et al., 2016; Munsie et al., 2017; Boers and Bredenoord, 2018). What fair compensation or distribution of benefits means, however, is subject to debate (Howard et al., 2011; Chalmers et al., 2015; Steinsbekk and Solberg, 2015). This discussion is highly

complex from an ethical as well as a practical perspective, and an attempt to settle it is beyond the scope of this Spotlight. However, we believe that closer involvement of patient-participants can help facilitate fair deliberation between stakeholders.

Third, the combination of organoid biobank research and precision medicine blurs the traditional boundary between the domains of biomedical research and clinical care, which are subject to different rules and standards (https://www.hhs.gov/ohrp/regulations-and- policy/belmont-report/index.html). Although doctors are legally charged with the responsibility to act in the best interests of their patients, the same obligations do not apply to researchers (Berkman et al., 2014). The convergence of research and care therefore raises the issue of to what extent the clinical duties doctors have towards patients extend to biobanks and researchers. Organoids can be a vast source of potentially clinically relevant information. However, what counts as clinically useful or in someone's best interests partly depends on the perspective of the individual, and researchers can only act in accordance with these preferences when these are known. Similar to the debate in genomics (Vos et al., 2017), we believe that biobank research on patient-derived organoids calls for a recalibration of researchers' duties around the protection of privacy, the disclosure of research findings, and data-sharing, for which we believe more active forms of involvement of patient-participants is useful (Berkman et al., 2014; Jarvik et al., 2014; Johnsson et al., 2014; Viberg et al., 2014).

Approaches to more active forms of participant involvement in biobanks

We have argued why involvement is important, which subsequently raises the question of how it can be done. An exhaustive assessment of all potentially appropriate approaches is beyond the scope of this article, but for the sake of demonstrating the merits of closer involvement, we provide some suggestions.

Biobank participants do not enrol in a specific trial; they enrol in an institution that performs certain activities, under certain terms and conditions that may change (Mongoven and Solomon, 2012). Broad consent is appropriate in this context because, contrary to specific consent, it entails a decision to permit unspecified tissue use under certain governance conditions to protect participants' interests (Boers et al., 2015; Boers and Bredenoord, 2018). The 'consent for governance' model aims to better align the consent procedure with this context, by emphasizing the creation of ongoing governance arrangements that are ethically sound, and by focusing on informing participants about (changes in) those arrangements. Without such information, it is not clear to us whether participants can make a well-considered decision to enforce their right to withdraw. In addition, the type of information provided during the consent procedure will most likely be easier to understand, which may help professionals overcome the challenge of ensuring that participants sufficiently grasp the terms of their consent (Lensink et al., 2019). The consent for governance model aims for

responsible biobank research through establishing a more continuous relationship between biobank and participant (Gainotti et al., 2016).

Another promising model is 'dynamic consent'– a model of two- way communication between biobank participants and researchers through the use of digital interfaces, allowing patient-participants to be continuously engaged in the activities of the biobank, and share preferences around data-sharing and access, agenda-setting and return of results. The use of a digital interface allows for real-time adjustments, which addresses the limitations of a one-off consent, and facilitates researchers and biobanks in their ability to act in accordance with these preferences. Empirical research into the merits of dynamic consent shows that dynamic consent may potentially provide a solution to a number of research-related challenges experienced by professionals, such as facilitation of specific research tasks, improvement of recruitment and retention, and simplification of collecting and managing consents. In addition, dynamic consent could potentially reduce costs, because transferring (some) biobank activities to the digital domain may lead to greater operability across nations and organizations, as well as provide professionals with practical tools to address changes in legislation (Budin-Ljøsne et al., 2017).

Involvement of patient-participants by providing them with some form of representative power improves their position to negotiate collective interests with other stakeholders in biobank research. We do not contend that patient-participants should be given absolute decisional authority, but rather that they should be systematically included in deliberative processes. The appropriate approach depends on the specific context of biobank and research, but in complex tissue biobanking for precision medicine, examples could be managerial involvement of patient organizations, participation in advisory board meetings, or consultation rounds to assess decisions or results https://www.bbmri.nl/sites/bbmri/files/guidelineeng_ def_0.pdf). For organoid biobanks aimed at treating a specific disease, advocacy groups such as patient organizations can be appropriate parties to engage (www.bbmri-eric.eu/wp-content/ uploads/2016/07/stakeholders-forum-report-a-step-closer-a4.pdf; Budin-Ljøsne and Harris, 2016). Patients have indicated their desire for some system of checks and balances to prevent concentration of power, and to facilitate negotiation between stakeholders to balance interests (Kraft et al., 2018).

We want to stress that meaningful representation of patient- participants implies providing them with at least a degree of leverage or control (Burton et al., 2008; O'Doherty and Burgess, 2009; Arnstein, 2019). Without any real commitment to be responsive to the input of patient-participants, such involvement would remain tokenistic (i.e. 'ticking the box'), which will do little to reduce the agency gap between stakeholders (Winickoff, 2007). A number of governance structures have been proposed to facilitate this, such as the wiki-governance model, the Every Participant is a PI (EPPI) model and the adaptive governance model (Hunter and Laurie, 2009; O'Doherty et al., 2011; Dove et al., 2012; Buyx et al., 2017). In any case, as complex tissue biobanking raises ethical challenges and patients have legitimate interests distinct from those of healthy participants, a 'social approach' in biobanking that

focuses on transparency, openness, solidarity and reciprocity between stakeholders can be valuable (Vos et al., 2017).

The cost of transitioning

Although we contend that shifting from passive donation to more active forms of involvement is needed, such a transition is not without its own set of challenges. The most important, and in our view legitimate, concern is whether the cost of such measures will have a detrimental effect on biobank sustainability and on the professional freedom of tissue researchers (Forsberg et al., 2013; Williams et al., 2015). Although the measures we propose may eventually lead to a decrease in costs – and there is evidence that suggests this (Kondylakis et al., 2017) – setting up and maintaining such a digital infrastructure implies investment of resources and coordination. Moreover, such experimental approaches to consent and governance require new forms of collaboration with research ethics committees to reach agreement on required criteria and quality (Budin-Ljøsne et al., 2017). However, as these are also changes at a broader institutional or societal level, it should not be the sole responsibility of biobanks and researchers to bear its burdens. The currently almost unanimous operationalization of ethics review and privacy protection measures can serve as an analogy: these are a significant investment of time and resources, though nevertheless crucial, and the burden of their cost is not simply placed on those working with the tissue. Moreover, European policy has already adopted involvement as a core aspect of personalized medicine (Kinkorová, 2016).

In addition, we believe these concerns may overlook the benefits of involvement of patient-participants for biobanks and research. For example, there is evidence that closer involvement of participants is an important aspect of responsible biobank research and governance, and can contribute to accountability and trust (Gottweis and Lauss, 2010; Ocloo and Matthews, 2016). Such measures not only lead to more inclusive decision-making processes, but may also result in larger tissue collections (Tutton et al., 2004; Winickoff, 2007; Blasimme and Vayena, 2016; De Vries et al., 2016; Noordhoek et al., 2019). In addition, involvement may also improve the quality and efficacy of translation from the bench to the clinic (Kirwan et al., 2017; van der Scheer et al., 2017; Noordhoek et al., 2019), which may be especially valuable for organoids, considering their potential for precision medicine (Drost and Clevers, 2017). Biobanking is an expensive endeavour, and ensuring its sustainability is crucial. A shift towards more customized, virtual approaches to biobanking with a stronger emphasis on involvement is likely to improve sustainability (Chalmers et al., 2016).

Final remarks

Further research is necessary to assess which specific conceptualizations for the involvement of patient-participants will be most fitting in the context of complex tissue biobanks aimed at precision medicine (Levitt, 2011). In assessing this, it will be crucial to find an appropriate balance between meaningful involvement and a feasible research climate. Involving biobank participants in decisional processes and governance can increase fairness, but in particular situations or by using certain approaches, it may very well turn out to be practically unfeasible and pose an unjustified barrier to research. We do not contend that involving patient-participants should be maximized at all costs; feasibility considerations should be given due respect, for the sake of all stakeholders. It is also important from a moral perspective to minimize the barriers to developing treatment. This is precisely why ensuring a responsible future for biobanking should be a priority, especially as many facets of society are currently undergoing changes in the wake of rapid biotechnological developments. Closer involvement of patient-participants can help reach these goals, and is therefore a morally important step towards safeguarding the longevity and sustainability of complex tissue biobanking.

Competing interests
The authors declare no competing or financial interests.

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Chapter 10

Summary and general discussion

Dutch patient organizations traditionally focus on patient advocacy, the spread of disease related information for patients and peers contact. Some patient organizations, like the Dutch CF Foundation (NCFS), have extended that focus to involvement in research and quality of care. In this thesis the use of the patient organizations biggest asset, the patients' perspective is studied. The two main questions are:

1. How can quality of care be improved when the patient perspective is taken into account?
2. How can we close the gap between the patients' unmet needs and outcomes of relevant research?

1. How can quality of care be improved when the patient perspective is taken into account?

Quality of care can be defined in different ways. It can be defined in terms of clinical thresholds or endpoints that have to be met; in that case it will depend on the creator of the definition to decide when these criteria are met. Definitions in healthcare can work out one of both ways: a healthcare provider can formally decide on what is seen as good quality of care and which standards have to be met. The medical specialist analyses from his own professional, evidence based viewpoint and wants to meet a certain standard in order to get or retain accreditation. This type of setting the standard for a certain degree in quality of care however, does not take into account the experience and expertise of the patient, thus leaving out what a specific, patient expert insight contributes to a definition of quality of care. In this thesis, the patients' expertise and perspective is explicitly part of the golden standard for diagnosis and care. So the focus is not only on the clinical endpoints, but also on the way communication towards the patient is organized, how care can be organized in a way it disrupts daily life as little as possible and how unmet needs of the person with CF can be addressed. Through the creation of the standards of care together with patient representatives, with the assessment of quality of care with patient experts and through an assessment of specific unmet needs of the people with CF, quality of care can be improved.

In the introduction we discussed that involvement by patient representatives in the development of standards of care (chapter two), is an important condition to ensure that the patients' perspective is taken into account. In order to make this specific input embedded in the process efficiently and effectively, some aspects have to be taken into consideration. For decades, guidelines for diagnosis and treatment of a disease were seen as an expertise reserved for medical experts, leaving out the experiences or opinion of the end users of health care. It wasn't unusual that the question 'What do *they* know about care?' was raised, when patient representatives were introduced as members of the guideline committee. It is a cultural change for the medical health care providers to acknowledge and appreciate what can be learned from the patient perspective, with the purpose to improve quality of care even with regard to clinical outcomes.

When patient representatives participate in guideline development committees, a helicopter view from their side is required. Ideally their input should be based on a systematic assessment of the patients' perspective with regard to all aspects of care. At the other end of the spectrum of patient involvement, the patient representative is reflecting on what health care professionals see as important.

The input of the patient representatives in chapter two is based on years of experience, working as patient representatives with academic backgrounds, capable of performing from a helicopter view. Their work however, was not based on a structured assessment of the patients' view on quality of care and patients recommendations to improve it.

Patient involvement in the establishment of standards of care is meaningful, if the individual experiences of people with CF can be summarized into useful insights that, merged with the expertise of medical experts, contribute to the golden standard for diagnosis and care of the disease.

When the patients' perspective is embedded in standards of care, this increases the chance that care received by a patient is optimal and efficient at the same time. This will create more space to address individual unmet needs. We expect also more willingness to explore minimization of the impact of care in daily life, when the patients' perspective is described in the standards.

Especially on an international level, an assessment of the patients' perspective is a challenge, because quality of care differs per country – and even per region in many countries - and so does the patient perspective. There are also big differences in the level of professionalisation of all patient organizations across Europe. Organizations like CF Europe do focus on professionalization of national patient organizations, but their focus could be more decisive and thorough. When more professionalization is guaranteed, the assessment of the patients' perspective can be much more impactful and less noncommittal than it is nowadays.

In chapter three we have described the assessment of quality of CF care, based on the patients' perspective by the Dutch CF Foundation. Not only is it possible to assess quality of care in a structured and effective way; we have described that quality of care also improves when the patients' perspective is taken into account and the recommendations based on their perspective, are implemented.

This way of quality assessment however, is subject to criticism in The Netherlands from time to time, from the side of professional health care providers and key opinion leaders in healthcare. The general assumption is that it will take a lot of time for each and every center and thus for professional health care workers, to participate in such an assessment [1].

To make this kind of assessment feasible for CF centers in terms of time, the patient organization needs to be able and willing to organize the procedure, thereby having access to

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own staff that has expertise in this area. If the patient organization is not able to deliver such expertise and cannot facilitate the centers in this way, the exercise is doomed to fail.
In the case of the Dutch CF centers we have seen that it is possible to organize the assessment in an agile way, taking a minimum of time from the hospitals themselves; an aspect that was investigated specifically and confirmed by the CF centers.
There are more patient organizations in The Netherlands, who are advocating diseases like colon cancer, breast cancer, or care for premature babies who need incubation, that offer hospitals or centers of expertise a quality mark, after assessment and meeting a core set of criteria. In most cases these patient organizations ask a fee for the assessment procedure they enroll. The Dutch CF Foundation did choose not to charge for the quality assessment, in order to guarantee independence.
In the run-up to the quality of care assessment process of the Dutch CF Foundation, some centers expressed hesitations whether patients or their representatives, have the expertise to judge the level of quality of the received CF care. So the introduction of the project obviously started with the explanation from the patient organization that peer to peer review processes, setting standards from a medical point of view, are not necessarily the same as the experienced quality of care from the patients' perspective.
Within this context we conclude that time investment for the centers was minimal, no fee was charged and the quality of care improved in a concrete, measurable way. The nowadays overall image of the quality mark assessment however, is a complicating factor when addressing centers for participation. We expect this to be an obstacle when the second round will be announced.
The assessment of quality of care was completed with recommendations for each CF center. Most recommendations were related to communicational issues. All centers were given the formal quality mark after the assessment, although two of them needed extra time to meet the lower limit of the core set of criteria. After two years, over 75 % of the recommendations given to the centers were fully or partly implemented, showing a high efficacy of the program. The program and the results of the assessment show, that quality of care will improve when using the patient perspective in the assessment procedures. A patient organization is capable to develop criteria of quality of care in a standardized way. It is recommended however, this type of assessment is free of charge, comes with a minimum of administrative burden for the CF centers and recommendations are taken seriously by the board of directors of the hospital. Insurance companies should take this kind of assessment into account, when they contract disease specific care in hospitals.
Chapter four is describing another example of patient involvement with regard to a specific kind of knowledge that is characteristic for a patient organization. Since patient organizations are very sensitive to and aware of the (unmet) needs of the members of the CF community, they need to systematically describe what those needs are, when they appear and at what time they have to be addressed to maximize the effect of the intervention.
The Dutch patient organization is aware of, amongst others, the difficulties that parents almost always experience, soon after the diagnosis of their child. Their perception of and coping with the diagnosis of their child can lead to mental health issues that prevent them from necessary bonding with the child.
The Dutch CF patient organization, cherishing its most important asset, namely the perspective of the people with CF and their parents, wanted to address this problem and reach out to parents in this particular situation. It is an example of the way the patients' perspective with regard to a specified problem is described as an unmet need, a problem that must be addressed in a way that is helpful for both parents and child.
By offering the coaching program, the organization was able to reach out at an early stage, providing the parents with basic psychological care. Some parents felt they needed this approach right at the start of their journey with CF; others asked for support at a later stage. The pilot shows that parents felt very comforted and supported by this project. It was also supported by mental health professionals at the CF centers. The program is extended nowadays to all people that have CF or are related to a family member with CF. The most important lesson learnt here was: initiate a mental health program that is easy to organize, accessible, at low costs. At this moment around 40 people access the program every year, sometimes on their own, sometimes with a partner or relative. The costs of the program are covered by the patient organization, that has to organize a fair amount of fundraising in order to be able to deliver good mental health support by qualified mental health workers.
This kind of professional help however, should be covered by health insurance companies. This is work in progress. In order to make health insurance companies willing to cover the costs, the coaching program has to be qualified and accredited according to the rules of the health insurance companies. That raises the question whether a patient organization will be able to secure this kind of early and helpful intervention. Intervention programs, how (cost-) effective and efficient they might be, bring an administrative burden that is hard to tackle by any patient organization.
Overall patient organizations should assess the unmet needs of the people they represent in a much more standardized way. In doing so, they can provide tailor made support and create awareness for professional health care workers.

2. How can we close the gap between the patients' unmet needs and outcomes of relevant research

There is huge variation in the way health care funds and patient organizations in The Netherlands cooperate to assess the patients' perspective as a point of departure for research projects and research agenda's. In chapter five, three stages were identified in the funding process in which health care funds carry out patient involvement activities, namely:

- Patient involvement in strategic decision-making about focus of research, like shared research agendas;
- Involvement in calls for and receipt of research proposals (e.g. mandatory

inclusion of letter of recommendation from patient organization);
- Involvement in decision-making about the funding of research proposals (e.g. patients reside in a patient panel to co-review research proposals).

Clearly most Dutch healthcare funds are committed to patient participation and are working on further broadening and optimizing patient involvement in order to optimize the impact. The Dutch CF Foundation is very active with regard to patient involvement in these processes, being one of the rare cross overs between a patient organization and a health care fund. Its success can be explained by the fact that NCFS was not the product of a merger between a patient organization and a healthcare fund; it started initially as a patient organization and gradually grew towards the hybrid position of a health care fund and patient organization. Its position was strengthened even more when NCFS became responsible for the national CF Registry. Nowadays we would call such an organization a center of expertise.
As a center of expertise, NCFS is also capable to develop a patient driven research program. In chapter six it is described how the patients' unmet needs were collected in the community and summarized into a patient driven research program that is nationally and internationally acknowledged. This way of working ensures that the patients' perspective is leading, at the start of the program and during its execution. A steering committee is installed for regular updates on progress of the program and regular update meetings are organized for people with CF, clinicians and researchers who participate in the program. This way of working seems to be sustainable. NCFS facilitates the research projects by financial support, by owning the CF Registry and by close cooperation with all CF centers and other stakeholders. By working along those lines, the Dutch patient organization facilitated a process, in which mutual dependency between patients, scientists and clinicians is the keyword. The dialogue between stakeholders, initiated at the start of HIT CF in 2012, maintained. The third round of this patient prioritized research program, called HIT CF, has just started in 2022. In Chapter seven an example is described of a patient oriented research collaboration between the Dutch CF Foundation as a patient organization and stakeholders like basic and clinical scientists. At first sight a collaboration between these kind of stakeholders might seem unusual. A CFTR-dependent assay using intestinal organoids appeared to be able to measure individual efficacy of CFTR modulators in a laboratory setting; an outcome that is of huge importance for people with CF. The development of this assay was substantially funded by NCFS. It shows that this kind of collaboration is effective and highly focused to what is important to people with CF.
Chapter eight is related to the perspective of people with CF with regard to the organoid technology. Patients have an individual benefit, when their organoids are used to screen which compounds may be working best for them. At the same time, patients organoids are important for further research for the whole population. A shift from the current 'consent or anonymize' paradigm is required, if we want to involve patients in research, asking them for rectal tissue: it is important to explain properly the research itself, and to know what

perception people with CF have towards the procedure and the use of their body materials. It helps us to find a balance between meaningful involvement of people with CF and feasible research. The 'consent or anonymize paradigm is' criticized for not defending the patients interest appropriately. A change towards more active forms of involvement from the side of the patient is needed. In this research it is shown that research and care become intertwined; through research on the patients body materials, decisions on his treatment are being taken. Acting in the best interest of the patient is no longer the ultimate starting point for doctors, but also for researchers. This implies much more cooperation between researchers and patient representatives in order to be able to work from the patient perspective.
Chapter nine discusses another aspect of the organoid technology: people with CF who donate their tissue for research have to be aware of and give informed consent for their tissue to be stored in a biobank. Biobank research on patient-derived organoids has led to successful personalised treatment of CF as mentioned before. Involvement of patients in biobanking is case and context dependent. If patients are both donors of tissue and end users, a situation that occurs when setting up a CF organoid biobank, a higher level of involvement from the side of the patient is needed. I.e. the often used initial consent should be paired to long-term engagement. Only this way difficult ethical issues, like the commercial use of biobank materials, can be addressed.

Concluding remarks

Improving quality of CF care, based on the patients' perspective is possible, doable and effective. Bridging the gap between patients' unmet needs and meaningful outcomes of relevant research is possible, doable and can be organized in an effective way. However, a patient organization needs to own skilled staff to create added value to care and research. The impact and added value of the use of the patients' perspective got more recognition in the areas of quality of care and research. Patient involvement in the area of patient oriented research and quality of care is not yet a natural process and the way to obtain standardized input from the patient perspective is full of hurdles.
Patients' input to improvement of care and research is not as obvious as the input from clinicians, researchers and key opinion leaders is. Secondly, the quality of the patients input is dependent on the professional skills of the national patient organization. Their commitment is evident, yet they not always share a common (medical) language with other stakeholders, such as clinicians and researchers.
It is of huge importance to standardize the patients' input when reflecting on or redefining standards of care. As an effect of the patients' role in the creation of standards of care, the implementation of endpoints in PROMS (Patient Reported Outcome Measurements) based on their evaluation, should also at least partly be directed by the patients' perspective. In standards of care it should not only be described what the maximum achievable level of

care is; it should also be described what is feasible for a patient to undergo. Especially when it is about a condition that has an immense impact on daily life, not only with regard to the disease itself, but also with regard to its treatment.
Further broadening and optimizing patient involvement by using the patients' perspective is still needed.

References

[1] https://www.skipr.nl/blog/keurmerken-voor-de-zorg-vloek-of-zegen/

10

Addenda

Dutch Summary - Nederlandse samenvatting

De toegevoegde waarde van patiëntenparticipatie bij de totstandkoming van wetenschappelijke projecten, onderzoeksprogramma's en –agenda's wordt ook wetenschappelijk steeds meer onderkend. Hetzelfde kan gezegd worden van de toegevoegde waarde die verkregen wordt, wanneer de eindgebruikers van zorg, vanuit hun eigen perspectief reflecteren op de gegeven zorg en er een systeem ontwikkeld kan worden, waarmee en waardoor de kwaliteit van de zorg verbeterd kan worden op een meetbare en navolgbare wijze.
Dit proefschrift onderzoekt de wijze waarop de Nederlandse Cystic Fibrosis Stichting (NCFS) als patiëntenorganisatie vorm heeft gegeven aan patiëntenparticipatie. Door onder andere in retrospectief te beschrijven hoe aan diverse projecten vorm is gegeven, werden voorwaarden en criteria blootgelegd, die belangrijk zijn voor het verder ontwikkelen van patiëntenparticipatie bij wetenschappelijk onderzoek en zorg. Het doel is te komen tot een transparante theoretische basis, die dient om vervolgstappen te kunnen zetten. Zo kan een onderzoeksagenda voor een specifiek ziektebeeld op basis van de noden en behoeften van patiënten worden geprioriteerd en er ook voor zorgen dat alle uitkomsten van onderzoek zo snel mogelijk ten bate van de patiënt geïmplementeerd kunnen worden.
Voor de zorg geldt, dat de kwaliteit ervan meestal alleen door zorgprofessionals gemeten wordt, waarmee een belangrijke belanghebbende uit het oog verloren wordt. Door het perspectief van de patiënt als uitgangspunt te nemen en criteria te hanteren die door de patiënt zelf zijn geselecteerd, kunnen (vaak relatief eenvoudige) maatregelen genomen worden, die zeer effectief kunnen bijdragen aan verbetering van de zorg.
Met betrekking tot de kwaliteit van zorg zijn drie aspecten onderzocht: de effectiviteit van de inbreng van patiënten bij de totstandkoming van (internationale) richtlijnen voor de behandeling en diagnostiek van CF; vervolgens een door de patiëntenorganisatie ontwikkeld verbeteringsprogramma van de kwaliteit van CF zorg in Nederland en tot slot een voorbeeld van een door de patiëntenorganisatie ontwikkeld ondersteuningsprogramma voor ouders van net gediagnosticeerde kinderen, dat is opgezet op basis van de specifieke behoefte van deze oudergroep op een zeer specifiek moment.
Ten aanzien van wetenschappelijk onderzoek is in kaart gebracht hoe in Nederland patiëntenorganisaties en gezondheidsfondsen zich verhouden tot het begrip patiëntenparticipatie en in hoeverre patiëntenparticipatie in hun werk leidend is. Daarnaast wordt beschreven hoe de NCFS een vijfjarig onderzoeksprogramma vorm geeft, op basis van primair de behoeften van patiënten; de wetenschappelijke kwaliteit van de projecten is wel geborgd. Ook wordt in dit proefschrift onderzocht hoe, op het oog zeer verschillende stakeholders, zoals basaal onderzoekers en patiëntvertegenwoordigers, effectief en doelmatig samen kunnen werken. Tot slot is verkend hoe het perspectief van mensen met CF effectief en duurzaam betrokken kan worden bij innovatieve technologieën, zoals de organoid technologie. In het verlengde daarvan is ook onderzocht hoe dat patiëntenperspectief benut kan worden, als het gaat om opslag en gebruik van lichaamsweefsel.

In hoofdstuk 2 wordt de tendens beschreven dat mensen die aan een aandoening lijden (of hun vertegenwoordigers), steeds vaker betrokken worden bij het opstellen van richtlijnen voor de diagnostiek en de behandeling van de betreffende aandoening. In het geval van Cystic Fibrosis kan het volgende worden geconcludeerd: in de Europese richtlijn voor de diagnostiek en behandeling van CF is een heel hoofdstuk geschreven door vertegenwoordigers van de Federatie van Europese patiëntenorganisaties voor CF, CF Europe. Deze bijdrage, die stoelt op jarenlange ervaring met en grondige kennis van de patiëntenpopulatie van de auteurs, is echter niet gebaseerd op een gestructureerde uitvraag onder Europese mensen met CF. Juist omdat de populatie van mensen met CF en de kwaliteit van zorg per land zo kunnen verschillen, is het van belang dat in de toekomst wel te doen. Dat geldt ook voor de Nederlandse situatie, waar de NCFS nauw samenwerkt met de andere stakeholders in dit proces.

Een keurmerk voor de kwaliteit van de CF-zorg kan een indicator zijn voor kwalitatief goede zorg, zo lezen we in hoofdstuk 3. Zeker wanneer de toetsing van de kwaliteit van zorg is gedaan aan de hand van criteria die in nauwe samenwerking met mensen met CF zelf zijn vastgesteld. Het keurmerk zelf is het resultaat van een strak geregisseerd proces, waarbij achtereenvolgens de voor mensen met CF belangrijke criteria worden geformuleerd; deze worden vervolgens in de CF-centra gemeten; er is een rapport opgesteld dat aan ieder CF-centrum handvatten biedt om de kwaliteit van zorg te verbeteren; na twee jaar wordt gemeten hoeveel van de aanbevelingen zijn geïmplementeerd. Communicatie blijkt een belangrijk onderwerp te zijn voor mensen met CF, of ouders van kinderen met CF, als het gaat om de kwaliteit van de zorg. Het keurmerk – vaak uitgereikt door patiëntenorganisaties - is in Nederland onderwerp van discussie, waarbij het feit dat vaak betaald moet worden voor de toetsing en de administratieve belasting voor de ziekenhuizen een terechte bezwaren zijn. In het geval van het CF Keurmerk heeft de NCFS geen fee gerekend voor de toetsing of de uitreiking van het keurmerk. Daarnaast is onderzocht hoe de CF-centra het tijdsbeslag en de administratieve belasting hebben ervaren: de CF-centra waren tevreden met het minimale tijdsbeslag die de procedure van hen vergde en zouden een volgende ronde weer mee doen. Daarnaast heeft de toetsing meetbaar en controleerbaar de kwaliteit van zorg verhoogd, op basis van door patiënten gegenereerde kwaliteitscriteria. Een patiëntenorganisatie die een dergelijke toetsingsprocedure wil uitvoeren, moet echter beschikken over expertise ten aanzien van kwaliteit van zorg en verbeteringsprocessen. Het past in de lijn van de ontwikkeling die de NCFS doormaakt, begonnen als patiëntenorganisatie, daarnaast ook gezondheidsfonds geworden, zich nu als expertise instituut voor CF te ontwikkelen en de CF-centra periodiek te toetsen op kwaliteit van de zorg, op basis van het patiëntenperspectief.

In hoofdstuk 4 wordt beschreven waarom de NCFS het zogenaamde coaching project ontwikkelde en hoe effectief dit was. Er was aanleiding te veronderstellen, dat ouders van een kind dat recent gediagnosticeerd is met CF, door de bank genomen door allemaal door

dezelfde fases gaan en direct, bij hen thuis, passende hulp nodig hebben. Ouders kunnen deze hulp aanvragen bij de NCFS, het programma is laagdrempelig en wordt geheel door de NCFS gefinancierd. Het programma werd zeer goed door de deelnemende ouders gewaardeerd en hun aanvankelijke klachten en problemen zijn in bijna alle gevallen sterk gereduceerd. Het is hulp die in een zeer vroeg stadium aangereikt kan worden, die bijzonder effectief is gebleken en door de CF-centra ook als waardevol wordt gezien; de CF-centra verwijzen naar het programma van de NCFS. Feitelijk zouden de (relatief lage) kosten van een dergelijk programma door de verzekeraar moeten worden gedragen. Het gaat hier om effectieve zorg op maat. De juiste zorg op de juiste plaats.

Hoofdstuk 5 beschrijft een kwalitatief onderzoek naar de mate waarin 19 Nederlandse Gezondheidsfondsen (zoals de NCFS, Longfonds, Hartstichting, etc.) vorm geven aan patiëntenparticipatie bij het financieren van onderzoek of het opstellen van een onderzoeksagenda. Bij de strategische besluitvorming over de focus van het onderzoek van een gezondheidsfonds, werden drie vormen gevonden, die niet noodzakelijkerwijs opeenvolgend zijn. De eerst beschreven vorm kenmerkt zich door een patiëntengroep die systematisch bevraagd wordt over de focus van te financieren onderzoek; aan de hand van de respons komt men middels een gestructureerde werkwijze tot een onderzoeksagenda, die door de patiënt geprioriteerd is. Deze vorm wordt overigens door de NCFS gehanteerd, zie hoofdstuk 6.
Een tweede vorm kenmerkt zich door het feit dat in de aanvraagprocedure voor financiering van een onderzoeksvoorstel is opgenomen, dat een aanbevelingsbrief van de patiëntenorganisatie moet worden aangeleverd. We weten dat in de praktijk deze werkwijze door patiëntenorganisaties kan worden ervaren als ‘tekenen bij het kruisje’. Een derde vorm wordt gekenmerkt doordat de definitieve besluitvorming over een financieringsaanvraag voor een specifiek onderzoek op basis van inbreng van patiënten plaatsvindt. Alle gezondheidsfondsen realiseren zich, dat zij het perspectief van patiënten moeten laten meewegen; de máte waarin dat gebeurt is niet eenduidig en gelijk bij de alle gezondheidsfondsen. Het totale proces kan behoorlijk geoptimaliseerd worden. Uit het onderzoek blijkt dat er een grote variëteit bestaat in de mate waarin gezondheidsfondsen en patiëntenorganisaties in Nederland samenwerken, om het patiëntenperspectief als vertrekpunt te kunnen nemen bij hun onderzoeksagenda ’s en onderzoeksprojecten.

De werkwijze van de NCFS om tot een door patiënten geprioriteerde onderzoeksagenda te komen, is in retrospectief beschreven. In hoofdstuk 6 wordt de totstandkoming van de onderzoeksagenda beschreven, met een uitvraag aan alle mensen met CF of ouders van kinderen met CF, naar de problemen waarvoor nog geen oplossing bestaat en die zij belangrijk vinden voor de onderzoeksagenda van de NCFS. Door middel van focusgroepen wordt het aantal genoemde onderwerpen verdeeld over de diverse onderzoekterreinen. De prioriteiten van de mensen met CF worden vervolgens besproken met clinici en onderzoekers. Is op basis

van dat traject de onderzoeksagenda tot stand gekomen, dan worden, om de wetenschappelijke kwaliteit te garanderen, achtereenvolgens patiënten met een wetenschappelijke achtergrond betrokken; worden projectvoorstellen door internationale wetenschappers gereviewd en worden patiënten getraind om onderzoeksvoorstellen te reviewen vanuit hun eigen perspectief. Een stuurgroep wordt geïnstalleerd en regelmatig worden updates over de voortgang van het onderzoek gepresenteerd. De NCFS initieert bijeenkomsten met patiënten, clinici en onderzoekers om de stand van zaken in het lopend onderzoek te monitoren. Tot slot: de CF Registratie wordt door de NCFS onderhouden, een ziekte specifieke registratie waar veel onderzoek op gebaseerd is of gebruik van maakt. De samenwerking met de CF-centra, regulatoire organisaties, verzekeraars en soms ook de politiek, is van groot belang. Hiermee is een groot aantal voorwaarden beschreven die aanwezig moeten zijn, om een patiënt geprioriteerde onderzoeksagenda op te kunnen stellen, en projectmatig tot uitvoering van die onderzoeksagenda over te kunnen gaan. Inmiddels is eind 2022 de derde, door patiënten geprioriteerde onderzoeksagenda opgesteld door de NCFS, een onderzoeksplan bestaande uit 20 deelprojecten, verdeeld over drie onderzoeksterreinen, dat in vijf jaar moet worden uitgevoerd (HIT CF 3.0). Er is een bedrag van ongeveer 6 miljoen euro mee gemoeid.

Hoofdstuk 7 beschrijft vanuit het perspectief van de basaal onderzoeker hoe een onderzoeksproject, waarin samengewerkt werd door basale onderzoekers, clinici en de NCFS, leidde tot de ontwikkeling van personalized medicine voor CFTR modulatoren. Deze samenwerking heeft de translatie van basaal onderzoek naar grotere impact voor de patiënt, bewerkstelligd en versneld.

Vervolgens wordt in hoofdstuk 8, waarschijnlijk voor het eerst, het perspectief van mensen met CF of ouders van kinderen met CF met betrekking tot de organoid technologie in kaart gebracht. De meeste mensen in de doelgroep staan positief tegenover deze technologie en zijn zich bewust van het gegeven dat door het afstaan van een rectumbiopt (‘minidarmpjes’) er een enorme positieve impact kan ontstaan ten aanzien van de behandeling die zij ondergaan (‘personalized medicine’). De respondenten voelen zich dan ook zeer betrokken bij de gevolgen die deze technologie voor hen en voor patiënten in het algemeen, kan hebben. Toch kleven er in de ogen van respondenten ook zorgelijke aspecten aan het afstand doen van lichaamsweefsel. Ten aanzien van commercieel gebruik zijn de meeste respondenten terughoudend en vragen zij om duidelijke, voorwaardelijke condities voor de persoon die zijn weefsel afstaat. Door de respondenten wordt gepleit voor goede consent procedures en het vinden van een vorm om de lange termijn betrokkenheid van patiënten te onderhouden. Het is belangrijk om, in het kader van een zo belangrijke technologie, goede communicatie te ontwikkelen in het kader van de consent.

Tot slot wordt in hoofdstuk 9 beschreven dat participanten, mensen die hun weefsel afstaan ten behoeve van een biobank, gezien worden als passieve deelnemers. De consent

protocollen zijn daar op afgestemd. Juist omdat de technologie zo veelbelovend is gebleken en in de nabije toekomst nog meer zal worden, moet aan het consent protocol een meer betekenisvolle invulling worden gegeven, waardoor de participant een zeker controle kan krijgen over deelname aan een dergelijk traject. Bovendien is de technologie kostbaar, en meer betrokkenheid van participanten zal leiden tot duurzaamheid van de technologie.

Aknowledgements - Dankwoord

Ik was een jaar of vijf en lag ziek op de bank in de woonkamer. De dorpsdokter kwam op die late zaterdagavond naar onze afgelegen boerderij. Hij ging zitten op de rand van de bank en precíes op dat moment begon ik te huilen.
De dokter verrichtte zonder acht te slaan op mijn snikken en tranen zijn onderzoek en stelde een longontsteking vast. Toen hij van de bank opstond, stopte ik metéén met huilen. De dokter verliet het huis en mijn moeder vroeg: 'Waarom huilde je nou zo?'
'Hij zat op mijn voet!!!', zei ik verlegen.

'Waarom zei je dat dan niet?', vroeg ze. Mijn antwoord weet ik niet meer.
Door het werken aan dit proefschrift, is me decennia later duidelijk geworden, wat het antwoord moet zijn geweest: 'Hij vróeg niet wat er was!!!'
Stel dat deze dokter, ik zie hem nog voor me, had gevraagd waarom ik zo moest huilen. Stel, dat hij me even onderzoekend aan had gekeken, op zoek naar de oorzaak van mijn verdriet? Hij zou er achter zijn gekomen, dat hij op mijn voet zat. Hij zou glimlachend hebben begrepen en gaan verzitten, daarmee mijn voet bevrijdend. Mijn verdriet zou gestopt zijn. Ik zou me begrepen hebben gevoeld en niet meer verlegen. De kwaliteit van *zijn* zorg zou toegenomen zijn, door *mij* iets te vragen.
Vragen stellen aan een kind dat ziek is, aan een mens die ergens aan lijdt, aan 'de patiënt'; ik denk dat hier mijn belangstelling voor patiëntenparticipatie ontstaan is. Al noemde ik dat toen nog niet zo. Gelukkig maar. Eerst nog een tijdje spelen.
De anekdote is nog decennia lang verteld tijdens verjaardagsfeestjes.
"En toen zei ze: 'Hij zat op mijn voet!'"

Het schijnt dat het dankwoord het best gelezen deel van een dissertatie is. Ik heb er dus mijn best op gedaan.
~~Allereerst wil ik graag mijn lief bedanken, Cees, die ik nu al meer dan 32 jaar naast me weet, verbonden door een ring, die 'als een dijk om de polder van ons samenleven ligt'.~~
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was over het fenomeen patiëntenparticipatie en die nieuwsgierig was naar de wijze waarop je het patiëntenperspectief kunt gebruiken om de kwaliteit van de zorg te verbeteren. Zo werd het Keurmerk voor CF zorg geboren. Maar los daarvan hebben jullie beiden het werk van de Nederlandse Cystic Fibrosis Stichting (NCFS), onze ambities en resultaten, altijd ondersteund en aangemoedigd. Bedankt voor deze fijne samenwerking. Ik wil Vincent graag bedanken, voor het feit dat hij mijn copromotor werd en me aan de praat heeft gehouden waar ik stil viel, of me het zwijgen oplegde, waar ik rebbelde. Je hebt me enorm geholpen, al die tijd en niet alleen als copromotor. De NCFS heeft veel aan jou te danken. Je hebt de onderzoeksagenda – geprioriteerd door mensen met CF - op de kaart helpen zetten, je hebt de kwaliteit van zorg vanuit het patiëntenperspectief helpen doorgronden en bent de naamgever van HIT CF. Het was een voorrecht om 16 jaar lang met je samen te mogen werken voor mensen met CF.

Zo'n 25 jaar geleden werkte ik bij de Vrije Universiteit aan een onderzoek op het gebied van kindermishandeling. Graag wil ik Herman Baartman, emeritus-hoogleraar Preventie en Hulpverlening inzake Kindermishandeling, hier bedanken voor het feit dat hij mij een nationaal en ambitieus onderzoek toevertrouwde. De data over 2300 kinderen had ik rond. Het veldwerk was gedaan. Herman, jij hebt me als student orthopedagogiek al begeleid met mijn scriptie. Het leren schrijven, presenteren, papers insturen naar internationale congressen: ik heb het allemaal onder jouw hoede geleerd. Mijn master Pedagogische Wetenschappen kreeg ik uit jouw handen. Je veerde enorm mee met alle aspecten die er kleven aan het opvoeden van kinderen. Of ze nou een aandoening hebben of niet. Ik kijk terug op vele gezellige avonden bij jullie thuis, samen met Cees en genietend van maaltijden door jullie bereid, de laatste nog heel recent. Ik hoop op nog veel van dat soort avonden!

Toen kwam CF in ons leven en veranderde ik radicaal van koers. De NCFS wilde professionaliseren en hier kwam mijn ondernemerslust tot wasdom. Binnen deze organisatie kon ik het lotgenotencontact, de belangenbehartiging en de informatievoorziening gaan optimaliseren. Vanaf 2006 werd de wens tot betrokkenheid bij CF onderzoek een realiteit en natuurlijk ook de kwaliteit van de zorg – getoetst op basis van het perspectief van mensen met CF.

De NCFS is vanouds een patiëntenorganisatie: de *core business* bestaat uit lotgenotencontact, informatievoorziening en belangenbehartiging. Toen we ons meer met wetenschappelijk onderzoek gingen bezighouden, ook in de vorm van financiering, werden we daarmee een gezondheidsfonds. Dat zijn organisaties die opgericht zijn om wetenschappelijk onderzoek op een ziekte specifiek terrein te financieren. Inmiddels bewegen we ons ook op het terrein van de kwaliteit van zorg en beheren we de CF Registratie. Daarmee is de volgende fase aangebroken: de NCFS is een expertise instituut, een onderzoeksbureau. Een instituut dat zowel ten behoeve van mensen met CF (en hun omgeving) haar werkzaamheden verricht,

maar ook ten behoeve van de professionals in de zorg en in de academie. Ik zie in de nabije toekomst meer mogelijkheden om als expertise instituut met betrekking tot CF positie in te nemen, bijvoorbeeld door het data management voor de zorg te faciliteren, de bijscholing voor (para-)medici naar een hoog niveau te tillen en wetenschappelijke bijeenkomsten te initiëren en te faciliteren.

Dat de NCFS zo hard heeft kunnen groeien, is vooral te danken aan een bevlogen en ambitieus team. Alleen met zo'n team kun je jaar op jaar tussen de één de twee miljoen euro werven, een financieel gezonde organisatie zijn, je communicatie informatief en boeiend houden, een goede lobby voeren voor inclusie van CF in de hielprikscreening en de lobby voor vergoeding van innovatieve medicatie organiseren. Graag wil ik Ad, Alex, Cindy, Domenique, Jacinta, Johanna, Mirjam, Renate, Tom en Vincent bedanken voor de enorme inzet, de goede ideeën, de toewijding. Het is een top team! We hebben samen bewogen tijden doorgemaakt, zoals de periode dat we veel in het nieuws waren door die dure pillen, maar we kwamen er altijd uit. Domenique, dank je wel voor jouw aandeel in de follow up van het Keurmerk traject en je waardevolle aandeel als co auteur. Geen moeite teveel en prachtige tabellen maak je.

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Mijn grootste woord van dank gaat uit naar alle ouders van kinderen met CF en alle mensen die CF hebben en die met mij en met mijn organisatie hebben gedeeld en nog delen, wat hen beweegt, wat hen drijft, wat hun vragen zijn, maar vooral ook: wat hun antwoorden zijn. Ik hoop dat wij hen genoeg vragen stellen en vooral ook dat het de juiste vragen zijn.

Thijske, oudste dochter van me. Ik schrijf dit dankwoord in je mooie huisje in Värmland,

Zweden. Een week rust, prachtige herfst, bossen en meren, lange wandelingen. Jammer genoeg werd één van je kippen deze week gepakt door een vos, of was het een hermelijn, maar de Noorse boskatjes Hubert en Hampus maken alles goed. Deze plek is een parel; wel héél fijn dat je weer wat dichterbij komt wonen. Alles wat we als ouder moesten leren om pap & mam te worden, is op jou geoefend. Dat is best goed gegaan. Ik ben erg trots op je.
Dan Lucas, die de laatste tijd wel zegt: 'Je mag het best wat rustiger aan doen, mam'. De zorgen die we destijds om je hadden, gaan nooit weg, maar je vooruitzichten zijn zoveel beter dankzij de wetenschap en de zorg – en dankzij de inbreng van mensen met CF zelf. De veelzijdige en verrassende muzikant die je bent geworden, de soms tegendraadse, maar altijd zeer beredeneerde en fundamentele keuzes die je maakt in je leven, daar heb ik van geleerd en daar geniet ik van. Ik ben erg trots op je.
Jillis, je liet ons zien dat een studiekeuze ook exact kan zijn, dat elektrotechniek en ruimtevaart dichterbij zijn dan je denkt, je leerde ons dat iedereen uit zijn comfort zone kan komen en dat je jezelf piano kunt leren spelen. Exact en creatief gaan bij jou samen. Even aan de laptop, dan weer achter de piano. De afgelopen maanden was ons contact vooral digitaal. Dat dat kan, gewoon vanaf de bank thuis of uit Zweden, zo verbonden te zijn met jou, nu in New York en daarna…? Ik ben erg trots op je.

Verbonden door een ring, die als een dijk om de polder van ons samenleven ligt. Zo kan alleen jij het zeggen, Cees. Mijn dichter en mijn organist, mijn klavecimbelist en filosoof, die iedere avond voor me kookt en nooit moe wordt van mij. Dank je wel. Trotser kan ik niet zijn.

Ik doe nog een blokje hout in de kachel,

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Norra Treskog, Värmland
Jacquelien Noordhoek

About the author

Jacquelien J. Noordhoek-van der Staay
Jacquelien is born in Heemstede in 1961, grew up in the countryside, moved to Amsterdam when she started university. She is married and has three children. Currently she lives in Almere.
She has a Master in Social Sciences and in Business Administration.
Since 1998 she is the executive director of the Dutch CF Foundation (NCFS). She started her work for NCFS when the organization was small, with limited capacity in fundraising, patient advocacy, financing research and so on. Nowadays 10 professionals are working for the organization and hundreds of volunteers; fundraising and communication developed to a professional level. The impact of the organization on the quality of CF health care has grown substantially. The Dutch CF Foundation partly sets the agenda in CF research in The Netherlands, with a research program that is prioritized by the patients themselves (HIT CF). This program is acknowledged internationally. Jacquelien is chairwoman of the Dutch CF Registry.
In 2015 she was elected as president of CF Europe, the European federation of CF organizations from 41 countries. She's serving her third term now.
She has an expert reputation in representing the patients' perspective and gives talks on this topic regularly. Jacquelien has a national and international experience in giving speeches, presentations and workshops about CF and health related topics. She has accurate networks, admission to social media, she is media-trained. She's involved in discussions concerning access to innovative medicine, precision medicine, access to care, big data, (social) innovation, and technology, and 'science in transition'.