It’s all about the patient: bringing new cystic fibrosis treatments to life

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Introduction
Cystic fibrosis (CF), an inherited genetic disorder caused by any one of around a thousand mutations in a single gene, is characterized by abnormal production of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. It is the most common genetic disorder in Caucasian children, seen in between one in 2000 and one in 3000 live births. Cystic fibrosis is a systemic disease, affecting many organs in the body, including the lungs, kidney, gastrointestinal and reproductive tracts, liver, and pancreas [1-4]. Lung function in cystic fibrosis patients inevitably declines, through build-up of mucus and repeated infections, and this is what shortens lives.

Cystic fibrosis management: Now and next
Current therapies for cystic fibrosis aim to improve lung function through eradicating and preventing lung infections by the use of antibiotics, as well as targeting symptoms in other organs. Because of this access to better treatment, disease management and access to a greater variety of drugs, patient outcomes in cystic fibrosis are improving, though there are many factors that have an influence. These include example costs of treatment and healthcare status in different countries, the progression rate of the specific mutation, and the types of bacterial infection.

The aim is to develop treatments for cystic fibrosis that are safe, effective, and patient-centric and improve outcomes and quality of life for patients. These include combinations of antibiotics to eradicate lung infections more effectively, preventing lung damage [5], and inhaled antibiotics that are easier to take, for example having shorter treatment times, using dry powder inhalers rather than nebulizers, or requiring only once-daily use. Other approaches include drugs that enhance the action of the abnormal CFTR protein [6]. However, CFTR protein potentiators only work in patients with specific mutations, which restricts their use [4].

Gene therapies, currently in preclinical and clinical trials, act by replacing the activity of the mutant gene, and therefore should work in all patients with cystic fibrosis [4]. By targeting the molecular defect, potentially at birth, gene therapy could prevent disease manifestations rather than treating symptoms, for example avoiding lung infections. By preventing damage to the lungs and other organs, this could allow patients to live healthier and longer lives, effectively ‘cured’.

Managing clinical trials in cystic fibrosis: Recruiting the patients
To create and manage a successful clinical trial in cystic fibrosis, it is important to understand the disease area, be able to find the right patients and clinical trial sites, and have an in-depth knowledge of the general and specific regulatory requirements. This can be gained by working with partners who have broad networks of researchers and physicians and prior experience in cystic fibrosis and other genetic disorders.

Cystic fibrosis is an orphan disease, and there are around 80,000 children and adults with the disease across Europe and North America. Cystic fibrosis is less common in Asia, partly due to genetic differences, and partly due to underdiagnosis, although the number of people diagnosed with cystic fibrosis in India and China is growing [1, 3, 4].

The larger population in Europe and North America, and the access to high quality treatment and study centers, has meant that many ongoing studies are based in these regions. This provides better choices for patients, parents or caregivers and physicians, but can lead to a lot of competition for a limited pool of volunteers, because
awareness within the cystic fibrosis community of cystic fibrosis drugs in development and of ongoing cystic fibrosis clinical trials is very high. At any one point in time a number of global and/or national clinical trials are being conducted so cystic fibrosis patients, and their parents or caregivers, are always in a position to ‘comparison shop’, debating the benefits, and picking and choosing the trials that they believe will be the best for their situation and stage of disease. While the environment is extremely competitive, cystic fibrosis patients and their parents or caregivers have a complex disease to manage, and they are very interested in participating in clinical trials.

Cystic fibrosis is a disease that affects both adults and children, and generally, clinical trials will need to include both to ensure the involvement of the widest possible patient population, unless specifically focusing on infection prevention in very young children with an aim to maintain their lung function for a longer period. Studies that use lung function as an inclusion or exclusion criterion can (perhaps unintentionally) dictate the age of the population that can access the study. For example, older patients will have been exposed to more infections, so are more likely to have reduced lung function compared with younger patients. Older patient groups may also have co-morbid conditions, and be taking concomitant medications, which often excludes them from a trial. Clinical trials often only include children from six years upwards, but this is likely to change as the focus on prevention, rather than treatment, increases.

The distance of trial sites from patient populations is an important factor, as the time taken to get to and from sites, as well as the length of a site visit, has an impact on patients’ ability to take part, especially those who are working or studying. As the lifespan of people with cystic fibrosis continues to extend, this will become more of an issue. For more severe patients with reduced mobility, or who depend on parents or caregivers, the impact of travel also needs to be taken into consideration.

Sponsors and clinical research organizations (CROs) need to be aware of these factors when they are choosing countries and sites for clinical trials, perhaps balancing out sites that are likely to struggle to recruit patients with those where recruitment will be easier, and ensuring a wide spread of sites across the area. Site choice and subsequent data analysis also needs to take into account the likelihood of treatment experience and naivety in different patient populations, and any differences in standard clinical practices and treatment guidelines, as these can have an impact on country, and even site, effects.

Clinical trials: Knowledge and networks
As well as a knowledge of the local and global population, the key to selecting the best sites for clinical trials in cystic fibrosis is access to an extensive network of physicians, researchers and key opinion leaders (KOLs), as well as previous experience of preferred sites. Patient associations and advocacy groups are becoming increasingly important in many different disease areas, especially orphan genetic diseases like cystic fibrosis. These groups provide important support for patients and their parents or caregivers, validation for clinical trials, access to patients and study centers, and sources of experience and expertise. Examples of associations and advocacy groups include the Cystic Fibrosis Foundation in the US, and Cystic Fibrosis Europe.

KNOW THE FACTS:

- About 30,000 people are living with cystic fibrosis (70,000 worldwide).
- Approximately 1,000 new cases of CF are diagnosed each year.
- More than 75 percent of people with CF are diagnosed by age 2.
- Nearly half of the CF population is age 18 or older.

Source: www.cff.org/What-is-CF/About-Cystic-Fibrosis
In Europe, many clinical trials are run via the European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN), which provides access to 43 large and experienced CF centres, located in 15 different countries throughout Europe, as well as connections to patients willing to be involved in studies, and links with researchers and patient organizations. Clinical trials carried out under the auspices of the network are reviewed, with advice provided for protocols, along with access to standardized research procedures and outcome parameters. Training is also provided for site staff.

Cystic fibrosis and regulatory issues
While the basic regulatory requirements for studies in cystic fibrosis are the same as those for other therapeutic drugs, devices and gene therapies, these will still vary around the world, and so it is vital to have a grasp of the regulatory and ethical frameworks in different markets and for different age groups, or work with an expert partner.

Cystic fibrosis is a lifelong disorder, and so the knowledge of regulatory and ethical issues is particularly important when working with the pediatric segment of the population. One aspect of this is understanding the pediatric investigation plan (PIP), required for approval in Europe since 2007. Drug approvals that include results from PIP studies gain an additional six months patent protection. As cystic fibrosis is an orphan disease, this means an additional two years of market exclusivity [7]. The Food and Drug Administration in the USA requires submission of a Pediatric Study Plan (PSP) early in the drug development process, in return for extra time of market exclusivity [8].

As one of the key aims in cystic fibrosis is to prevent lung infections, clinical trials are likely to involve younger and younger children, which adds additional challenges for the ethics of the trial, for example not including a placebo arm. Studies that include a wide range of age groups will need to have materials, such as patient diaries, that differ in language, content and emphasis for parents of infants, as well as for different age groups (for example, 6 to 10 years, 10 to 13 years, 13 to 18 years, and adults). Consent forms will also need to take into account the differences in ability to give consent in younger and older children and adults. Parents or guardians also need to give written consent for children and young people under 18.

Progress brings new questions
Because of these improving outcomes, physicians will have to learn to manage patients and their treatment through different life stages. Whereas in the 1960s, most children with cystic fibrosis died before the age of 5 years, the median age of survival now is 33.4 years, and many patients will reach their fifties and sixties [2, 3].

This progress will bring to light new questions for physicians managing patients, such as managing infertility issues in male cystic fibrosis patients, dealing with genetic counselling issues and pregnancies, and managing conditions associated with middle and later life. These need to be anticipated, and both physicians and patients will need to be educated in these areas. However, considering the damaging and life-limiting disease that is cystic fibrosis, these additional issues and concerns are minor compared with the great leaps forward in its management.

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References


