

# Conducting Cystic Fibrosis Clinical Trials – Methodological, Practical and Ethical Considerations



## Abstract

Cystic fibrosis (CF) is a chronic, progressive, life-threatening genetic disease that primarily affects the pulmonary, gastrointestinal, endocrine and reproductive systems. It is an autosomal recessive disorder that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. To date, more than 1300 mutations have been identified in the CFTR gene. Approximately 70,000 individuals worldwide have CF, and although CF affects all racial and ethnic groups, it is more common in Caucasians of European descent. According to the Patient Registry Reports, the median age of survival for a CF patient in 2010 for the United States (US) is 38.3 years old and for 2009, 26.7 years old for Australians.

Increased participation in clinical trials for CF patients is of paramount importance in order to further clinical and scientific knowledge and the development of novel medications and therapies. As with many other chronic diseases that are of orphan status, there are many challenges and considerations when conducting CF clinical trials. This article explores methodological, practical and ethical challenges frequently experienced by study participants and research staff.

Key Words: Cystic fibrosis, CFTR, clinical trials, contract research organisation

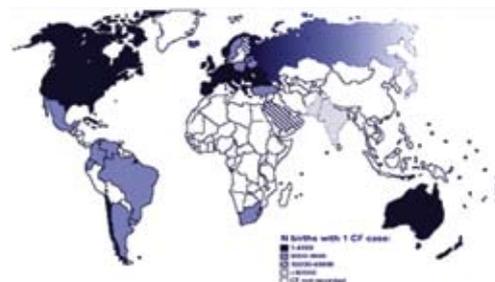
## Background

Over the past few decades, progress has been made to reduce morbidity and delay mortality for patients with cystic fibrosis (CF). The median predicted age of survival for CF patients in the US has dramatically increased over the past 20 years. In 1986, the median predicted age of survival was 27 years old compared to 38.3 years in 2010<sup>1</sup>. A similar trend

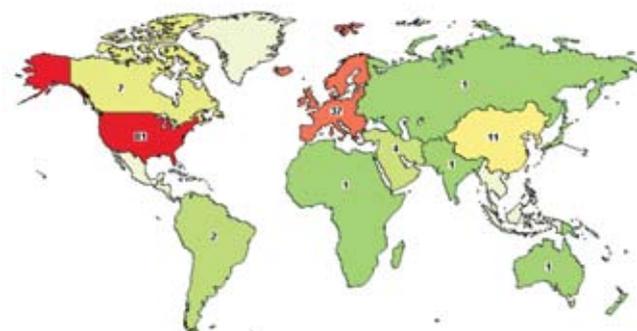
for improvement in morbidity has been observed in Europe<sup>2</sup>. However in Australia, the median age of death for CF patients decreased in 2009 compared to 2008 and 2007 (26.7 compared to 30.3 and 30.7 years old, respectively)<sup>3-4</sup>. The reason for this decline is unclear. The overall global progress is due in part to neonatal screening which has allowed for earlier diagnosis and treatment, improvement in nutrition, consensus guidelines regarding the treatment of CF patients<sup>5,6</sup> and novel medications and therapies that treat not only the symptoms of the disease but also the underlying cause of the disease.

Despite these advances, there is a continuous need for CF patients to become involved in clinical research, which will enable the development of new treatments and novel ways of managing the disease. However, as research subjects, CF patients are considered a vulnerable population and have special needs due to the relatively young age of study participants, likelihood for cross-infection, progressive nature of the disease, poly-medication use and complexity of disease due to exocrine gland dysfunction and multiple organ system involvement. As CF is considered a rare (“orphan status”) disease, there a limited patient population available for clinical research in addition to a limited number of CF centres. According to the clinicaltrials.gov website, there were a total of 143 clinical trials actively enrolling CF patients as of April 2012, as outlined below.

It has been estimated that currently less than 30% of all CF patients are potentially able to participate in clinical trials<sup>7</sup>. CF clinical trials are generally conducted at highly specialised CF centres, and therefore not only is there substantial competition for patients with this rare disease, but also for trained research sites able to conduct clinical trials to a high quality standard. It is extremely important for persons with CF to participate in clinical trials in order for new treatments to be developed. Patient advocacy organisations have done a good job to date of emphasising the need for participation in studies in addition to providing useful information on their websites about clinical trials. Development of clinical trial networks in the US and Europe has been beneficial for ensuring that CF patients have the opportunity to be involved in research. Development of similar networks in other regions such as Latin America is currently lacking, and would be advantageous. The global prevalence of CF is displayed below<sup>8</sup>.



The objective of this article is to outline key methodological, practical and ethical issues in the conduct of CF clinical trials with focus on site identification, feasibility and clinical research studies. Mitigation strategies for these challenges will also be discussed.



## CLINICAL RESEARCH

### CF Programme Considerations: Methodological Considerations

There are several unique considerations when developing a CF programme. Although animal models for CF exist, such as the transgenic and CFTR-knockout mice, there are limitations with this species and it is unclear how relevant these findings are to humans. Furthermore, it is important to note that there are currently no animal models for CF-related diabetes and hepatic disease. Due to these challenges, pig and ferrets as CF animal models have been generated, and there is hope that these novel CF models will lead to new therapeutic approaches<sup>9</sup>.

When developing a CF clinical programme, it is important to review the regulatory guidance documents drafted by the Food and Drug Administration (FDA) and European Medicines Agency (EMA)<sup>10,11</sup>. When planning human CF studies, consideration needs to be given as to the strategy regarding age ranges of patients to include in the trials. Typically, an investigational product is initially studied in adolescents and adults (or only adults 18 years and older) followed by studies conducted in children. However, as CF is still mainly a paediatric disease generally diagnosed at birth, it may be advantageous to initiate trials in different age groups including children. Of course, the ability of children to successfully perform study assessments needs to be considered, such as the lack of the ability of children to successfully perform spirometry. Additionally, for early phase studies involving a nebulised investigational product, it is important to ascertain whether the manufacturer intends to revise and/or discontinue manufacturing of the current nebuliser compressor system. In addition, the potential implications and consequences need to be considered regarding the availability of novel vibrating mesh nebuliser systems such as the Pari eFlow® and Source CF™ nebulisers, should a patient use an unauthorised nebuliser system with the nebulised investigational product being studied.

For early Phase 1 CF studies, it is important to determine

whether pharmacokinetic and pharmacodynamic data from healthy volunteers is applicable or not to CF patients. Additionally for trials involving children, unique issues to consider when designing a paediatric study include parent involvement, family decision-making, issues with phlebotomy, and the total volume of blood required.

There are several additional key challenges that exist when designing pivotal Phase 2 and 3 CF studies. Randomised active-controlled trials are mandatory for confirmatory trials, even when a reference treatment exists. The decision whether to use a parallel group, crossover or cohort study design is important, due in part to the paucity of CF patients available to participate in clinical trials. Also essential is the timeframe required to obtain key data, potential for carry-over effects, potential seasonal effects, and the requirement for long-term exposure as required by regulatory authorities.

For global studies, it is crucial to determine whether or not the CF patients are relatively homogenous across regions (including standard of care, survival rates and availability of medications including off-label usage). This can be difficult to determine, as scant data regarding CF exists for some regions such as Latin America and Central Eastern Europe. In these cases, feasibility is needed to best ascertain the risk/benefit of conducting CF studies. Additional risks based on protocol-specific target populations also may be encountered e.g., if a study requires antibiotic-naïve patients, they would be difficult to recruit.

Another area that is particularly challenging is determination of appropriate endpoints. In contrast to oncology studies, survival is not a practical or ethical primary endpoint, therefore surrogate endpoints such as spirometry, pulmonary exacerbation and quality of life assessments are typically used and are deemed to be appropriate by regulatory authorities. Nonetheless, there can be a high degree in variability for endpoints such as forced expiratory volume in one second (FEV1) and typically only children older than five



or six years old are able to correctly perform spirometry. In addition, there is no global standard definition for pulmonary exacerbation, and typically studies use two to three different definitions. Standardisation of diets across study sites and geographical regions can also be difficult, and it is preferable to centralise such efforts with local input, especially because of the effect of nutrition on pulmonary function. To further complicate matters, the determination of a standardised clinically relevant effect has not been established for many endpoints, including changes in pulmonary function and nasal potential difference.



be reluctant to change their healthcare providers. Therefore, even though a clinical study might involve adults only, it is likely that many paediatric CF centres would be able to recruit eligible patients either from their own patient database or by networking with their institution's adult CF centre. In the US, approximately 67% of all CF patients are included in the CFF's National Patient Registry<sup>1</sup>. This facilitates review of each site's patient database in an effort to pre-identify patients who satisfy the protocol's entry criteria. In Europe, the ECFS are planning to strengthen their registry in the near future.

There are many study-specific challenges for CF studies, some of which are unique to CF studies. These include sputum induction, performing pulmonary function tests in infants, organising patient (and parent/care-giver) overnight visits, managing study visit impact on school or work schedules, and the hesitancy of CF patients to be involved in clinical trials, either due to misconceptions about research, and the burden of attending multiple study visits (and potential loss of income and/or identifying themselves to their employer as a CF patient). Compliance to the study schedule and patient follow-up is important for the study success. Telephone calls and text messages from sites to participants during the study would help in compliance with the study schedule. Other compliance-enhancing measures could be reimbursing patient travel for the follow-up visits as allowed by the local regulations, and flexible clinic schedule and visit windows to accommodate research patients around their school/work schedules.

Training of all study staff is key towards ensuring quality data, as is standardising processes and procedures (i.e., sputum induction) across study sites. Educating patients about clinical research is vital, and both the CFF and ECFS provide useful brochures about clinical research to help in this effort. In general, use of advertising is not warranted as CF patients are already well known by highly specialised CF centres, and patients not treated by these centres may be under-treated.

There is not a universal solution to address all of the aforementioned study programme challenges, however, it is imperative to consider these key issues and make evidence-based decisions considering the context of CF patients and the variability in disease severity. Recent experience is important so that one is kept abreast of issues and lessons learned to effectively mitigate these challenges.

### Practical Considerations

CF studies are unique in that many study sites are affiliated with patient advocacy groups such as the US CF Foundation (CFF) and European

Cystic Fibrosis Society (ECFS). Both organisations have the ability to review the protocol, vet the protocol with their network of research sites, and provide the sponsor and/or contract research organisation (CRO) a shortlist of interested sites. These networks of sites include the premier CF centres that are very experienced in clinical research and generally have an extensive database of patients that can be utilised for pre-identifying patients for a study.

When selecting sites, one must consider the mix of paediatric and adult centres to use. CF is distinctive in that many adults are still followed by paediatric CF centres, as patients can

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### Ethical Considerations

There are several ethical challenges facing CF clinical research, especially as the majority of the clinical trials involve children and adolescents, and/or utilise a placebo-control study design. Informed consent forms for CF studies can be extremely lengthy and difficult to comprehend, despite using readability statistics to ensure the document is no higher than a fifth-grade reading level. Ideally, both parents should sign the informed consent; however, some ethics committees (ECs) permit only one parent to sign the form. The precise age at which a child should be involved in the consent and assent process has not been fully elucidated. Ensuring that ECs and all study site personnel follow the tenets of good clinical practice (GCP) is key to protecting the safety of the patient.

Other ethical considerations include conducting a clinical trial in a country in which the sponsor does not ultimately intend to market the medication. The intent of the sponsor to eventually market the drug in some regions can be questioned by regulatory authorities when submitting the clinical trial application. Additionally, non-Caucasians may be under-represented in CF clinical trials. Therefore, it is important to discuss this with study site personnel and provide support if needed to reach out to minority patients who might be eligible for a study. In addition, the need to provide patient-related documents in languages other than English would potentially help facilitate enrolment of non-English-speaking patients.

Another interesting aspect is the length of time it takes for completion of a CF trial and publication of the study results in a peer-reviewed journal. It was determined that the median time is 3.25 years between completion of a CF trial and publication. Additionally, a large proportion of studies fail to report study results within five years of study completion<sup>11</sup>. This has potential negative consequences, especially as guidelines are based on evidence-based data, and patients who participated in these studies do not readily have access to study results and therefore cannot make

informed decisions about future study participation.

### Summary

Although conducting clinical trials in CF is challenging, the roadblocks experienced (such as those summarised in this article) can be anticipated and mitigation strategies can be implemented when specific trigger points are experienced. The overall goal must be kept in mind – to provide novel medications and therapies which improve life expectancy and the quality of life of CF patients worldwide. Recent experience is key in order to understand the processes of CF advocacy organisations, and identify the most experienced research sites and develop mitigation strategies proactively to address considerations and challenges.

### References

1. Cystic Fibrosis Foundation patient registry annual report 2010. Bethesda, Maryland, USA: Cystic Fibrosis Foundation.
2. Meha G, Macek M, Mehat A. Cystic fibrosis across Europe: EuroCare CF analysis of demographic data from 35 countries. *J Cyst Fibros* 2010 Dec; Suppl 9; S5-S21.
3. Reid D, Blizzard C, Shugg D, et al. Changes in cystic fibrosis mortality in Australia, 1979-2005. *Med J Aust* 2011; 195(7): 392-395.
4. Cystic fibrosis in Australia 2009 – 12th annual report from the Australian cystic fibrosis data registry. Accessed online: <http://www.cysticfibrosis.org.au/projects/dataregistry/>.
5. Flume P, Mogayzel P, Robinson K, et al. Cystic fibrosis pulmonary guidelines – treatment of pulmonary exacerbation. *Am J Respir Crit Care Med* 2009; 180:802-808.
6. Stallings V, Stark L, Robinson K, et al. Evidence-based practice recommendation for nutrition-related management of cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc* 2008; 108:832-839.
7. Goss CH, Rubenfeld GD, Ramsey BW, Aitken ML. Clinical trial participants compared with

nonparticipants in cystic fibrosis. *Am J Respir Crit Care Med* 2006; 173:98-104.

8. The molecular genetic epidemiology of cystic fibrosis; Report of a joint meeting of WHO/ECFTN, ICF(M)A/ECFS. Genoa, Italy, 19 June 2002. Accessed on 12 April 2011 at [http://www.cfw.org/docs/who/2002/who\\_hgn\\_cf\\_wg.04d02.pdf](http://www.cfw.org/docs/who/2002/who_hgn_cf_wg.04d02.pdf).
9. Fisher JT, Zhang Y, Engelhardt JF. Comparative biology of cystic fibrosis animal models. *Methods Mol Biol* 2011; 742:311-334.
10. Guidance for Industry – Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); April 2006.
11. Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis. European Medicines Agency. London, 22 October 2009.
12. Hurley MN, Prayle AP, Smyth AR. Delayed publication of clinical trials in cystic fibrosis, *J Cyst Fibros* 2011;11(1): 14-17.

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