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Original Article

Speeding up access to new drugs for CF: Considerations for clinical trial design and delivery

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ABSTRACT

The last decade has witnessed developments in the CF drug pipeline which are both exciting and unprecedented, bringing with them previously unconsidered challenges. The Task Force group was brought together to consider these challenges and possible strategies to address them. Over the last 18 months, we have discussed internally and gathered views from a broad range of individuals representing patient organisations, clinical and research teams, the pharmaceutical industry and regulatory agencies. In this and the accompanying article, we discuss two main areas of focus: i) optimising trial design and delivery for speed and efficiency; ii) drug development for patients with rare CFTR mutations. We propose some strategies to tackle the challenges ahead and highlight areas where further thought is needed. We see this as the start of a process rather than the end and hope herewith to engage the wider community in seeking solutions to improved treatments for all patients with CF.

1. Current status of clinical trials pipeline

Optimal, effective care for people with cystic fibrosis has evolved over the past 3 decades. The introduction of antibiotics, mucoactive and anti-inflammatory drugs based on large randomised controlled trials, has improved important clinical outcomes such as frequency of pulmonary exacerbations, lung function and quality of life. As these therapies impact the *downstream consequences* of CFTR dysfunction in the lungs (infection, mucous hypersecretion, inflammation), the trials were conducted with people with CF and impaired lung function but were *independent of specific genotype* as the efficacy of antibiotics, anti-inflammatories and mucoactive drugs is generic in CF.

In contrast, the focus of a number of innovative drugs in the clinical development pipeline is on the *root cause* of CF, dysfunction of the CF transmembrane conductance regulator (CFTR) protein. These agents are exemplars of genotype-specific, targeted drugs. The underlying biology of particular mutations can be targeted by specific small molecules with activity directly on CFTR. Potentiators such as ivacaftor *restore protein function*; correctors, amplifiers and stabilisers *increase the amount of mutant* CFTR reaching the cell surface; *wild type* CFTR can be *generated* with gene therapy/ repair, nucleotide therapies and read-through agents. There is also increasing interest in alternative, non-CFTR directed approaches for example inhibition of the epithelial sodium channel (ENaC) and stimulation of calcium-mediated chloride secretion.

The establishment of the major CF clinical trials networks (CF Foundation's Therapeutic Development Network in N. America in 1998 [https://www.cff.org/Research/Researcher-Resources/Therapeutics-Development-Network/] and the European CF Society's Clinical Trials Network in 2008 [https://www.ecfs.eu/ctn]) intensified clinical research in the area of CF and achieved recognisable success in their missions to bring new medicines to the patients as quickly as possible with a major focus on safety and quality. In the last decade there has been an unprecedented expansion in the number of trials being conducted, although a) many of these compete for similar patient

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groups and b) the proportion of patients receiving CFTR modulators as evolving standards of care is increasing, complicating trial design.

Thus, whilst progress is extremely encouraging, there remain some major challenges for the field. In this and the accompanying article, we explore strategies to accelerate access to new treatments in the short to medium term future. We have actively sought a range of views to be incorporated into this and the companion paper (ref) from patient organisations, regulatory bodies and pharmaceutical companies developing CF drugs. We held an ECFS workshop in Nov 2017 and sought community engagement at and after the ECFS conference 2018. We would strongly encourage further correspondence from interested parties on these matters. We feel the time is right to review current challenges from clinical, economic, societal, ethical and regulatory perspectives and propose strategies to deal with these in a rare disease such as CF. We hope some of the lessons learned and approaches to this complex field will help inform further progress in CF and clinical trial programmes in other diseases.

1.1. Efficient trial delivery

44 clinical trials were either open or completed in the 12 months to May 2018 across the European Clinical Trials Network (CTN; https://www.ecfs.eu/ctn), a major aim of which is to speed up availability of new medicines. However, it is clear that drivers and priorities will likely be somewhat different for sponsors and for the trial sites themselves. A major focus for sponsors is speed, delays having significant cost implications. This frequently leads to the opening of many trial sites each expected to recruit small numbers of subjects. However, for the sites themselves, this severely limits efficiencies: the time spent in start-up, budget negotiation, contracting and close down is disproportionate for studies with small n. Furthermore, most trials are conducted in a minority of CF centres, leading to substantial inequality in patient access to trials. Concurrent conduct of trials of drugs targeting the basic defect and others treating down stream consequences may lead to a recruitment skew towards the former due to biases among clinicians and patients. In our opinion 'symptomatic' therapies will continue to be needed by the majority of the existing CF population for the foreseeable future. CFTR modulators will not 'cure' CF in people with already damaged lungs. So far, the data suggesting they substantially reduce infection or inflammation is not compelling: whilst the odds of *Pseudomonas aeruginosa* positivity were reduced after commencing ivacaftor in the GOAL study [1], Hisert et al. [2] found that reduced infective burden was not sustained in the longer term. Data on inflammation are currently limited. For these reasons, we consider it important that balance in the portfolio of trials is maintained.

1.1.1. Increasing participant numbers and geographical reach

In 2018, 355 new patients were enrolled into 25 CTN-supported clinical trials. This equates to only 2.0% of the European CF Society (ECFS) Clinical Trials Network (CTN) population. This rate of enrolment is likely due to several factors such as capacity of trial teams, patient awareness and geography, although allocation has a strong influence. For very 'popular' trials, there is usually a cap imposed upon centres who would be willing and able to recruit more subjects, and access to slots is often further limited by centres outside Europe having opened earlier. Specific inclusion/ exclusion criteria will apply, the majority of trials, including those which are not CFTR mutation-specific, requiring a defined range for lung function based on forced expiratory volume in the 1st second (FEV_1). Most commonly, patients with organisms such as *B. cenocepacia* and *Mycobacterium abcessus* will be excluded on the basis of 'more rapid rate of decline'. Whilst this may be true for some, it is not universal and we should encourage a fresh look at this. There are fewer trials available for younger children and there may be a reluctance on the part of some investigators to 'increase the burden' for their patients by asking them to participate. There is evidence that participation in clinical research is beneficial for patients, even those on placebo arms. *So how can we increase the number of patients participating in clinical trials* and *use our networks to their full capacity?*

1.1.2. Supporting multiple trials in limited patient populations

Positive clinical trial data from sponsors with established track records of drug development in CF has increased patient awareness and is likely to encourage their participation in future trials of the similar or new generation drugs. We recognise benefits of having a range of CFTR modulators; there may be differential advantages for particular mutations and favourable adverse event profiles/ drug-drug interactions for individual patients. It is therefore encouraging that a number of pharmaceutical companies currently have CFTR modulator programmes (https://www.ecfs.eu/ctn/clinical-trials; https://www.cff.org/Research/Developing-New-Treatments/Clinical-Trials/). Supporting newer sponsors and aiding patients' decisions about participation when several options are available is an important role of our networks and trial teams.

1.1.3. Therapies targetting the consequences of CFTR dysfunction: how their development can continue to be supported

Until full restoration of CFTR function can be achieved from early childhood (before the development of complications), and possibly even thereafter, people with CF will need anti-infectives, anti-inflammatories and mucolytics. There may be a perception that trials for such drugs are somehow less 'exciting' or transformative, resulting in recruitment challenges for these programs. Within both the CTN and TDN, drugs targeting CFTR function will likely receive higher scores in prioritisation processes, so how can we ensure that a balance of trials is available and that patient access is optimised?

1.2. Proposed solutions (Table 1)

- Clinical trials Networks should be expanded, and work more to a hub and spoke model allowing free flow of patients between centres. This will require more communication and perhaps challenge operational systems in some areas, particularly when considering cross-border referrals. In order to work optimally, it may also require increased oversight, a central role for the Networks in site selection and trial allocation, and/or new performance management systems; all of these could potentially add to sponsors' costs, although these will likely be more than offset by a reduction in start-up costs for fewer sites. Additional manpower, including for activities at local referring sites, should become an expected component of budgets. This referral system happens within parts of the UK Clinical Trials Accelerator Platform (https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-trials-accelerator-platform). Efficiency is increased, although perhaps at some expense of equity of site involvement. The pros and cons associated with such a system are listed in Table 2, although this may not be exhaustive. It is essential that trust exists between clinical teams, who may fear 'losing' patients to the trial site. In our experience this a very rare event and no more common than movement of patients between clinics for other reasons.

Table 1
Proposed solutions for improving the efficiency of trial delivery.

- Maximise participant pool
  - Expanded trial networks
  - Rational and justifiable (not repeat cut-and-paste) exclusion criteria
- Consider hub and spoke referral system (Table 2)
- Involvement of the networks in the rational allocation of trials
  - Maintain a representative portfolio including support for therapies targeting symptoms
- Centralised training and analysis systems for less common outcome measures
- Continued emphasis on patient/family awareness
  - Optimise engagement/involvement through trials trackers
  - Input into protocol design
- Research into feasibility/desirability of remote monitoring

Table 2
Envisaged pros and cons of trial networks working in a hub and spoke fashion. In this model, fewer trial sites would recruit a larger number of participants by recruiting from not only their own clinical cohort but from other CF centres within their network, which would act as 'Participant identification centres' (PICs). In the UK, this is a recognised role within the national approvals system and activites can be reimbursed.
The status of a centre does not need to be fixed. As an example, in the London Network of the UK Clinical Trials Accelerator Platform, lead trial centre is taken up by sites in rotation with others agreeing to serve as PICs, which mitigates some of the downsides.

	Pros	Cons
For sponsor/ CRO	Fewer sites to initiate and monitor - Monitoring visits more efficient - Lower start-up costs - Potential to build relationship with study team	Recruitment pace may be slower, although possibly offset by time-saving with start-up activities PIC fees/ contracts (although minimal compared with costs of opening more sites)
For participants	Managed by trial team 'expert' in fewer protocols	May require travel to 'new' CF centre: lack of familiarity, distance, time Less choice of trials at their own centre
For trial teams	Fewer trials each with more participants - Less time spent on start-up, training, close down - More familiarity with fewer protocols - Easier to build relationship with CRO - Build strong relationships with local network sites: share best practice, trial selection tailored to expertise/facilities/interests	Recruitment of participants unknown to the local team requires: - Excellent communication with home team - System for timely reporting of AEs Referring site needs confidence that clinical care will be retained
For referring centres	Access to more trials for the sites' patient cohort	Site will not be able to open for every trial they may wish

- Consideration should be given to allocation of fewer trials to each site, with higher recruitment goals for each, whilst minimising any bias arising from too high a proportion of a study cohort coming from one centre. The portfolio of trials at each site could be made up of both CFTR modulator and symptomatic therapies, mirroring the current pipeline. Time and resource will be saved by sponsor/ contract research organisation (CRO) in set up and by sites themselves. Such a shift would clearly require significant co-operation between sites/investigators to achieve a balanced and expansive selection of experimental therapies for patients whilst also promoting the concept of research
- All of this will require increased engagement with patients and national patient organisation. We recognise that there may be some hesitation from trial sponsors or CRO's over reduced control in site selection, for example running trials in countries/ sites with limited experience and concerns related to time delays. These concerns could be reduced by sharing of individual site metrics with prospective sponsors, although this has not been done to date and raises understandable concerns at the Network and site level. We suggest this issue merits further discussion, taking into consideration the regional differences in access to standard care across parts of the globe.
- The CTN and TDN have developed standard operating procedures which are now implemented for routine activities such as spirometry and more specialist procedures such as nasal potential difference measurement and lung clearance index; SOPs for the latter have also been harmonised with Australasia. The establishment of central training and analysis hubs where appropriate, will impact positively on logistics and optimise data quality once sponsors are confident to work with them.
- Direct engagement between Network sites and the CF community needs to be increased. The majority of CF patients report not having been approached about clinical trials and unless they are proactive, may lack awareness of what is available. Clinical networks and country-specific initiatives such as the Clinical Trials Accelerator Platform led by the UK CF Trust with the searchable 'Trials Tracker' (https://www.cysticfibrosis.org.uk/get-involved/trialstracker) provide useful links, but we consider more could be done for example via blogs or live video streams; with increased awareness may well come improved recruitment
- Sponsors currently consider that the 'lead-in' times in many regions/ centres are prohibitively long and require complex procedures. Centralised approvals systems, established largely to streamline these processes, appear not to be fulfilling their promise consistently. We see a huge opportunity for inter-regional cross-fertilisation with sharing of best practice/ pitfalls which could be leveraged by the Networks, although changes may be challenging to implement. ECFS CTN has established 'mentoring' visits for teams to the best-performing sites, into which this could be incorporated.
- Geographical reach could be widened by the implementation of protocols incorporating remote data collection. This will clearly only be suitable in certain instances and may meet with sponsor scepticism initially, but is an approach being used in other patient populations (clinicaltrials.gov NCT02921724). It could conceivably incorporate not only clinical monitoring (eg. uploading of spirometry) but also electronic pill pack monitoring, and blood sampling such as those being developed for remote monitoring of patients with diabetes. Opinions of the regulatory agencies will clearly be of paramount importance in the future direction of travel in this regard so it is encouraging that such novel ideas are being discussed on a number of platforms including through the FDA website (https://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm535768.htm).
- People with cystic fibrosis and their families/ carers should have a clear voice on prioritisation of research and clinical trials both as individuals and through national patient organisations. An excellent start on this has been made through the James Lind Alliance (http://www.jla.nihr.ac.uk/) and further determination of patient priorities should influence the approach to clinical trial prioritisation. The community may also have innovative and creative suggestions in trial design- we have heard ideas such as trial buses staffed with research nurses to enable extended geographical reach whilst maximising participant convenience.

1.3. Optimal future trial design

Optimising trial design has become a very high priority to ensure a) efficient conduct of studies to b) meet regulatory requirements for safety and efficacy with c) the minimal numbers of patients and d) in the shortest time period possible. This will allow more trials to be conducted and translate ultimately into more rapid access to the market for more agents. However, as clinical standards of care evolve, we will require innovative alternatives to current protocols and the consideration of alternative outcome measures. There is also a need for phase 3 trials to generate data adequate for a Health Technology Assessment (HTA) in those countries which commission drugs by this process. This requires trials of sufficient length and with relevant health utility outcome measures which may not have been mandated by regulatory bodies. An excellent illustration of a collaborative approach to this issue has been recently set in the chronic disease, Duchenne muscular dystrophy, with the establishment of Project HERCULES (https://www.duchenneuk.org/project-hercules). The group of 8 pharma companies, clinical academics, qualitative researchers, health economists and patient organisations seeks to ensure that the value of new therapies is demonstrable and appropriate for HTA through careful consideration at the stage of clinical trial design. The European Medicines Agency has recently made available joint consultation with healthcare commissioners to facilitate sponsors designing phase 3 programs that address the requirements of both (https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guidance-parallel-consultation_en.pdf).

The Task Force and discussants identified the following areas as posing specific issues:

a) *Testing new CFTR modulators* in subjects already receiving such agents clinically.

For most patients with class III mutations, and a growing number with residual function mutations, ivacaftor is available and highly effective. However, lung function is not normalised in the majority of patients with this drug and exacerbations still occur, albeit at a

significantly reduced frequency [3]. It is well-accepted that a proportion of patients fail to regain lung function lost during an exacerbation [4] and the only study to have focussed on this area specifically, concluded that exacerbations experienced by patients on ivacaftor were not of a 'milder' nature with regards either their short or longer term impact on lung function [5]. Furthermore, in the longer term, lung function still declines (albeit more slowly) in patients on CFTR modulators, at least in those with already impaired lung function. Similar data exist for dual combinations although the potential of highly effective triple compounds remains to be seen.

Thus, there remains an *unmet need* and there is a realistic possibility that more effective alternatives will become available, but for certain groups, the ethical and practical implications of testing them pose a challenge. Patients on modulators are unlikely to agree to be randomised into a trial including a placebo arm of any substantial duration [6]. A washout period may be acceptable and a short duration may be sufficient to recalibrate sweat chloride, but recalibrating FEV_1 may take longer. This is currently incompletely understood and may depend on the duration of therapy pre-withdrawal. Washout certainly could carry adverse clinical consequences, a drop in FEV_1 already being apparent after a 7-day washout from ivacaftor in Galapagos' potentiator GLPG1837 study [7]. Head-to-head comparisons of drugs from different sponsors are unlikely to be feasible, particularly if (as seems likely) the onus falls upon the newer company to purchase and pay for blinding of the prior product. A pragmatic approach to this would be a *regulatory requirement* for manufacturers of comparator drugs to provide these for such trials *at nominal cost*. This would require considerable multi-agency buy-in but could substantially enhance understanding in the field whilst preserving patient safety. Variable access in different health care regions further complicates any comparisons. At the time of initiation of this Task Force, the only globally licensed CFTR modulator for homozygous F508del patients was lumacaftor/ ivacaftor (Orkambi). It is not tolerated by all subjects and the acute efficacy is at best modest [8], meaning that patients may be willing to come off treatment to participate in trial a potentially more effective compound. However, we are likely to find that this increasingly difficult; during the preparation of this article the field has already evolved with agencies approving tezacaftor/ ivacaftor (Symdeko/ Symkevi). This combination is better tolerated [9] and once established, patient willingness to stop taking the drug may be a limitation in future trials. We urgently need to consider implications of this in designing sufficiently powered, non-inferiority or superiority trials and the incorporation of adaptive designs to facillitate the study of new CFTR modulators. Adaptive design allows modifications to trial design or statistical analysis of accrued data to improve efficiency. For example this allows stopping an arm of a trial which is futile, allowing patients to be redirected into treatment arms with a higher likelihood of demonstrating efficacy. We can learn much in this area from colleagues working in oncology and related disciplines who are some way ahead with creative trial design [10].

b) *Building on efficacy* of an existing CFTR modulator with 'add-on' molecules.

The optimal approach for the majority of CF patients will be a combination of drugs targeting different aspects of CFTR dysfunction in addition to current symptomatic therapies. The results of early phase clinical trials using triple combinations suggest that at least 3 drugs will be required for optimal benefit for homozygote and heterozyote Phe508del patients [11]. Some companies are developing molecules which may be most useful as 'add-on' therapies to an existing modulator, for example CFTR amplifiers, stabilisers or ENaC inhibitors. Similarly, the potential of genetic-based therapies could be maximised by concomitant use of CFTR modulators. Translating these theoretical benefits into reality will, however, be a hugely complex undertaking. Competing drug companies are unlikely to work together. In the above scenario, the sponsor of the add-on drug trial may be unwilling or unable to fund the existing drug if it is not one of their own. Whilst the approach could simply to be recruit subjects already receiving the existing drug clinically, testing an add-on before the existing drug has a license, in different populations or regions where it is not available, will be challenging. Secondly, assessing *safety* of a new agent which is being built upon a foundation of another drug with only limited patient-years of use raises issues which have not concerned us in the past. There will be complex issues of dose and timing of multiple drugs, assessment and optimisation of PK/ PD and the potential for drug/ drug interactions both within multiple-component drugs and with other concomitantly administered therapies. We are struggling to provide solutions to this and require the experience and skills of those working in other disease areas, such as cancer, where this approach is more established and from whom we may best learn.

c) *Alternative outcome measures:* why should we consider them?

ii. Outcome measures commonly used in clinical trials today.

The commonest surrogate endpoint employed in CF is the pulmonary function measure, forced expiratory volume in the first second (FEV_1) which, measured by spirometry, has been acceptable in support of registration of chronic CF respiratory therapies to regulatory agencies. Over the last two of decades, almost all pivotal CF studies have used FEV_1 for approval of therapies for routine clinical care. Widespread implementation of these therapies has resulted in significantly improved outcomes for patients with CF with a slowing in the rate FEV_1 decline and better survival. As a result however, more patients maintain FEV_1 in the 'normal' range, which has an impact on the size of an eligible population, inclusion criteria most commonly stipulating FEV_1 40–90% of predicted values.

In most of the clinical trials of CFTR modulators, the increase in FEV_1 is observed in the first weeks of the study. Consequently, the proposed duration of a trial will not influence sample size calculations for studies employing FEV_1 difference endpoints. Indeed, the recent phase 3 clinical trials of the triple compound CFTR modulators (https://investors.vrtx.com/news-releases/news-release-details/correcting-and-replacing-two-phase-3-studies-triple-combination) used a 28 day period for primary outcome, although whether this will be acceptable to all regulatory agencies (and HTA processes) remains to be seen. In longer term studies, many of which are post-marketing phase 4, rate of lung function decline is a focus. This is highly relevant, as it relates to survival, but many such studies have (of necessity) employed suboptimal designs, for example using an observational or registry group as controls, which have led to some concern over interpretation.

Pulmonary exacerbations (PEx) are associated with lung function decline and contribute significantly to morbidity and mortality [12]. Differences in relative risk of exacerbation or median time to next exacerbation have been employed as key secondary clinical end points for clinical trials of a variety of chronic CF therapies. Studies powered for PEx need to be longer and larger than those powered for change in FEV_1, but proactive enrichment for subjects with exacerbation risk factors may reduce sample size requirements. The FDA has recently agreed to PEx rather than FEV_1 as the primary endpoint in a phase 2 program for an anti-inflammatory agent (clinicaltrials.gov NCT03451045). PEx is also being used increasingly as an outcome measure for interventional trials in CF lung disease in relatively healthy patients and children who have normal or minimally-reduced (or unmeasurable) pulmonary function. However, the relative infrequency of exacerbation in very young children and infants, and the difficulty in establishing standard diagnostic criteria, precludes its use as an end point in these age groups due to sample size requirements. It may be that once highly effective modulators are in widespread use, PEx become so infrequent that powering a study for them even in older populations will become impossible. Furthermore,

although there is a consensus that PEx represents an important outcome in CF clinical trials, the definition used in most studies has been a broad one of new or increased pulmonary and systemic symptoms, reduced FEV_1 and commencement of new antibiotic treatment. Large multicentre clinical trials that have been conducted over the past years have used some variations of physician-derived definitions. Due to the crucial importance of PEx, it is very important to have standardised, validated criteria for diagnosis and treatment for both clinical practice and in clinical trials.

Other outcomes include patient-reported measures of quality of life such as the CFQ-R and for systemic treatments, weight gain and change in BMI. Of recent interest are markers of gastrointestinal health [13], in particular pancreatic exocrine [14] and endocrine [15] function, which are showing promise although this may be subgroup/ disease-stage specific. These will not be covered in further detail here, where we focus on newer end-points which could either a) improve efficiency of trial delivery or b) allow assessment of efficacy in a group for whom FEV_1 is not useful. However, we would urge investigators and sponsors involved in trial design to consider the addition of a *basket of outcome measures* from which the field can learn and incorporate into future hypothesis-driven studies, even if not completely necessary for the trial in question. Consideration of alternative clinical trial outcome measures has been the focus of two workshops convened by EMA, illustrating regulatory interest in this issue (https://www.ema.europa.eu/documents/report/report-workshop-endpoints-cystic-fibrosis-clinical-trials_en.pdf; https://www.ema.europa.eu/documents/report/report-european-network-paediatric-research-european-medicines-agency-workshop-gastrointestinal-gi_en.pdf). Clearly a balance needs to be maintained with acceptability/ participant burden; striking this balance is something for which the patient voice is of enormous value.

ii. CFTR biomarkers as trial outcome measures.

Elevated chloride levels in sweat are characteristic of CF. In populations, a relationship between disease severity, degree of CFTR dysfunction and level of sweat chloride has been shown. It was therefore expected that treatment with CFTR modulators which improve CFTR function would decrease sweat chloride levels. The observation that this reduction in sweat chloride occurred rapidly, within a matter of days, led to the notion that used of this biomarker could allow shorter, more efficient trials selecting modulator compounds, combinations and doses. However, correlation with clinical outcomes is less than completely clear. In the ivacaftor phase 3 trials [3,16,17] a marked and sustained decrease in sweat chloride by approximately 50% was demonstrated which was accompanied by an ~10% absolute improvement in pulmonary function. However, on an individual patient basis, there was no correlation between the decrease in sweat chloride levels and FEV_1 improvements, nor did there appear to be a threshold level for change in sweat chloride above which an improvement in FEV_1 could be observed. We consider that more evaluation of the reasons for this apparent discordance in some individuals is required. It may partly relate to the day to day variation in both measures within subjects [18], individuals experiencing respiratory exacerbations on the day of study visits and possibly under-reported deficient concordance between the two sweat test samples obtained. Additionally, it may reflect organ-specific differences in responsiveness to a drug or to the contribution to the measurable abnormality made by CFTR dysfunction. Whereas in the sweat gland, raised sweat Cl^- is completely attributable to lack of CFTR, in the lung, decreased lung function is substantially contributed to by downstream consequences of this ion channel abnormality, infection and inflammation. Furthermore, short-term poor adherence or missed doses may impact to a much greater extent on sweat chloride measurements than on pulmonary function. In contrast to individual patient data the decrease in sweat chloride and FEV_1 improvement show a closer relationship across trials in different genotype populations and, more recently, of different CFTR modulator agents. Fidler et al studied data from 8 trials of ivacaftor monotherapy, including subjects with G551D, other gating mutations, residual function mutations and homozygous for F508del [19]. This analysis showed that *on a group basis*, changes in these two parameters correlated well. With data emerging on other molecules, we should ensure we maximise our potential to understand this biomarker better, particularly given the ease with which it can be measured. The CHEC-SC study (https://www.cff.org/Trials/Finder/details/506/Sweat-chloride-observational-study) should add to the body of knowledge accumulating around this biomarker. Sweat tests are performed on patients receiving CFTR modulators through their clinic and compared with their historical values from the time of diagnosis alongside clinical data available through the patient registry.

The nasal potential difference (NPD) test measures the transepithelial potential difference, another marker of CFTR function. It has been used as a proof of concept in phase 2 clinical studies of CFTR modulators to demonstrate CFTR activation. Again, in the ivacaftor phase 2 trials there was little to no correlation between improved NPD levels and decrease in sweat chloride or improvement in FEV_1 [20]. In the lumacaftor clinical trial in patients homozygous for F508del, there was a smaller, dose-dependent decrease in sweat chloride with no change in NPD [21]. So far, a close relationship between NPD and pulmonary function has not been demonstrated. Despite standardisation efforts jointly undertaken by both European and N. American CF trial Networks [22], the high variability and time-consuming nature of NPD means, in our opinion, it is most suitable as a marker of CFTR function in proof of concept phase I or II studies. NPD cannot be a surrogate marker of severity of lung disease or survival of patients with CF. Likewise intestinal current measurement (ICM) is a surrogate electrophysiological measurement of CFTR function in the intestinal cells. No correlation was shown with sweat chloride levels or pulmonary function or other clinical parameters of severity in CF and therefore like NPD, it may best be used in phase 1 or 2 clinical trials when proof-of-concept for a specific compound is explored.

iii. Sensitive outcomes for populations with earlier stage lung disease.

Lung clearance index (LCI), a sensitive measure of gas mixing inhomogeneity, is abnormal early in the life of a CF patient before FEV_1 falls. Measured by multibreath washout (MBW) and based on tidal breathing, it can successfully be performed by very young children who are unable to perform forced expiratory maneuvers [23]. As a clinical trial outcome, LCI has been particularly useful in mild-moderate disease stages. In adolescents and adults with well-preserved FEV_1 (>90% predicted), ivacaftor led to a substantial improvement in LCI [24]. Although changes could also be measured in FEV_1, post-hoc analysis demonstrated that ~ 1/4 the number of patients would be needed to power a study with LCI as a primary outcome, than with FEV_1. Thus, LCI should be considered in groups with well-preserved lung function as a means to improve efficiency of trial delivery. LCI also demonstrated improvements in a trial of lumacaftor/ ivacaftor in 6–11 year olds [25] and is in use in even younger children (clinicaltrials.gov NCT02725567). standardisation, training and certification processes have taken place globally, enabling this procedure to be utilized in a uniform manner in multi-centre trials. We recognise the need to generate further data, including correlations with long term outcomes, to convince regulatory agencies to formally approve the technique as a primary outcome.

Similar standardisation efforts are also being made in lung imaging techniques, in particular CT and MRI scanning, which may also be most useful in early disease. The Standardised Chest Imaging Framework for Interventions and Personalised Medicine in CF (SCIFI CF) initiative was established to characterise image quality and radiation doses among 16 European CF centres performing chest CT [26]. Although substantial variation was found in CT protocols with respect to image quality and radiation dose usage, the performance of all scanners, based on spatial resolution and radiation dose, was very similar. The group is

now pursuing multicentre standardisation of chest CT in children/ adolescents with CF and is currently supporting a clinical trial of hypertonic saline in CF preschool children (SHIP-CT; NCT02950883). MRI is at an earlier stage, with fewer sites able to undertake lung imaging, but encouraging developments are being made which improve resolution even without the use of expensive hyperpolarised gases [27]; this may therefore be a useful modality in clinical trials of the future.

iv. Composite end points.

Composite end points have been used with success in clinical trials, for example in arthritis therapies [28] where composites of death and non-fatal cardiovascular disease (myocardial infarction and stroke) have increased power and decreased sample sizes. However, their use has also been criticized, particularly when a large number of components with differing levels of clinical importance have been included [29]. More work would be needed in CF before composites could be recommended to assess new therapies.

v. Outcome measure-led selection of trial populations.

Finally, outcome measures could also be used to select, enrich or stratify subjects ahead of trial enrolment. We already routinely use FEV_1 as an inclusion criteria- whilst the lower limit is usually a safety consideration, the upper limit generally reflects a concern that efficacy signals may be difficult to observe in those with very well-preserved lung function. Similarly, lung clearance index has been used to screen and stratify into subgroups suitable for this measure. Consideration could be given in the future to stratifying patients for anti-inflammatory drugs by sputum biomarkers, or for CFTR modulators by protein expression levels. Response to ivacaftor has been shown to be influenced by modifier gene polymorphisms [30] so with further understanding, which may arise from analysis of responders/ non-responders in ongoing and future trials, this may be a method of optimising populations for future trials.

1.3.1. Determining 'sufficient improvement' for adoption of a new drug into standards of care

The 10% absolute improvement in FEV_1 in class III mutation groups receiving ivacaftor [3,16,17] was regarded by most as highly clinically relevant. In contrast, opinion is less consistent on the clinical importance of ~3% improvement with the dual combinations of lumacaftor/ ivacaftor [8] and tezacaftor/ivacaftor [9]. Despite being licensed in Europe for several years, the former is still not reimbursed in many areas. For example in the in UK, reimbursement was declined specifically on the basis of inadequate 'cost-effectiveness' (https://www.nice.org.uk/guidance/ta398/documents/final-appraisal-determination-document). While there are well developed methods to determine cost effectiveness, these are blunt tools and are considered by some not to be fit for purpose in rare disease. For example, a drug which did not improve FEV_1 acutely, but reduced its rate of decline and pulmonary exacerbations, could be of great value if introduced at an early stage in the disease and perhaps more effective than a drug leading to large, acute FEV_1 improvement but lacking a true disease modifying effect. These are deliberately binary examples for the purposes of illustration. Restoration of CFTR function by ivacaftor in appropriate mutations leads both to acute improvements in lung function and longer term benefits including fewer exacerbations and a slowing in the slope of decline of FEV_1 [31]. However, improvement in FEV_1 is not predictive of a reduction in pulmonary exacerbations and it is intriguing that the longer term benefits of lumacaftor/ ivacaftor [32] are similar to those of ivacaftor despite the more impressive acute benefits of the latter. In addition, substantially more data (subjects and duration) are needed to demonstrate the benefits on slope of decline, making powering of such studies difficult. In patients with early stage disease, FEV_1 may be well-preserved and any improvement difficult to show. As discussed above, more sensitive measures of lung function for example using MBW are a potential solution to outcomes measures in this group of patients; the minimal clinically important difference (MCID) is yet to be determined, and may be disease-stage specific. The benefits on nutritional and metabolic measures and patient reported outcomes are also considered important by regulatory agencies and in our opinion, merit more attention. In particular, many studies employ the CFQ-R, but only list the respiratory domain as a reported outcome, meaning the potential benefits on other domains are lost. Health economists may also find such data has utility: the EQ-5D, a standardised measure of health outcomes, has been mapped to the CFQ-R by Acaster et al. using a number of models in a fashion that would allow economic evaluations of various interventions to be compared [33].

Formal approval of alternative outcome measures may be possible in the future, but in our opinion, *the onus is on us* as clinical researchers to create opportunities to generate high quality datasets with which to convince the regulatory agencies of their utility. Even when/ if we do, we will need to communicate well with payers and clinical prescribers to convey the clinical implications of any change.

1.3.2. Regulatory and commissioning challenges

The approval of CFTR modulators by regulatory agencies has been straightforward. The FDA and EMA have approved ivacaftor and combinations of ivacaftor with lumacaftor or tezacaftor. In the USA these are all available, although reimbursement from insurance companies has not been automatic. In contrast, much longer processes have delayed introduction of many of these drugs in Europe, Canada, Australia and other countries where CF is common. Most of these countries assess new therapies using an HTA approach. This methodology is not well suited to rare diseases and there is significant variation between countries in Europe, for example, in how HTA is applied. Ivacaftor is useful in 5 to 8% of patients and although it has taken some time, most countries have now approved this for specific mutations though the range is restricted in many countries such as the United Kingdom. In contrast, combination therapies such as lumacaftor/ ivacaftor and tezacaftor/ ivacaftor have either not been approved or had limited approval in a number of countries with a large population of people with cystic fibrosis. In the United Kingdom (with the exception of Scotland) and in Canada, lumacaftor/ ivacaftor has not been approved despite extensive negotiations. Across Europe, there have been challenges in France for commissioning and currently no Eastern European countries have commissioned this combination. Tezacaftor/ivacaftor is now under discussion but, for example, in the UK is not even being considered due to an impasse in discussions between the sponsor and commissioning authorities. The fundamental issue is the cost of these therapies relative to their effectiveness. In rare diseases with restricted populations it is well understood that drug costs are likely to be significantly higher than in common conditions. However, most HTA assessments are made on the assumptions of common diseases which results in cost effectiveness measurements being extremely high. These may be overinflated by the assumptions in the health technology models and for example in the UK lumacaftor/ ivacaftor has not been approved despite 3 years of negotiation. Similar issues occur in countries with limited healthcare budgets.

These issues have had a substantial impact on patients who are increasingly frustrated that drugs which are available in other countries are restricted for them. It has led to tense relationships between sponsors and commissioners and has negatively impacted patients and clinicians who feel frustrated by the inequality of access to effective drugs. This is particularly challenging for centres which have delivered clinical trials and yet are unable to make these treatments available to their patients.

These are major infrastructure anomalies in drug development which are likely to recur in other rare diseases. Clinical drug development is increasingly focused on precision and personalised medicine which is likely to come at a high cost. Drug development in this context needs to be reconsidered so there is a fair price which incentivises the pharmaceutical industry to develop new drugs which are affordable to resource limited healthcare systems.

2. Testing CFTR modulators in extremely rare mutations

The use of ex-vivo predictive models for extremely rare mutations is the focus of the companion paper (ref) to this manuscript. The recent FDA approval of ivacaftor for an expanded list of residual function mutations based purely on non-clinical data (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm559212.htm) is a pragmatic solution to this issue. N of 1 trials [34], where a single patient undergoes a strict protocol of on-off drug cycles with sensitive outcomes, are also feasible, but may be more cumbersome and expensive if required for large numbers of patients. Short trials, building on safety and efficacy in larger populations with other mutations, could be conducted with the use of a CFTR biomarker, most likely sweat chloride, although the lack of correlation with clinically-meaningful outcomes in trials must be borne in mind.

3. Summary and next steps

We have highlighted major issues in the current clinical trial arena alongside several proposals to challenge the status quo that we consider will accelerate the development of, and access to, new drugs for CF. Together with our companion manuscript (ref), our intention is to stimulate multidisciplinary discussion and generate ideas to be incorporated in a formal proposal document. Acceptability to patient groups and regulatory agencies will be of paramount importance. These ideas will form the basis for the next formal workshop bringing together these stakeholders and the CF clinical trials community seeking to provide a Consensus statement on the path forward into the medium term future. To date, we have largely engaged European stakeholders, but are seeking closer involvement and consensus with global counterparts. Ultimately, we seek to maximise benefit to as many patients and in the shortest time frame possible.

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References

[1] Heltshe SL, Mayer-Hamblett N, Burns JL, Khan U, Baines A, Ramsey BW, et al. GOAL (the G551D observation-AL) investigators of the cystic fibrosis foundation therapeutics development network. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. Clin Infect Dis 1 Mar, 2015;60(5):703–12. https://doi.org/10.1093/cid/ciu944.

[2] Hisert KB, Heltshe SL, Pope C, Jorth P, Wu X, Edwards RM, et al. Restoring cystic fibrosis transmembrane conductance regulator function reduces airway Bacteria and inflammation in people with cystic fibrosis and chronic lung infections. Am J Respir Crit Care Med 15 Jun, 2017;195(12):1617–28. https://doi.org/10.1164/rccm.201609-1954OC.

[3] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. VX08-770-102 study group. a CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 3 Nov, 2011;365(18):1663–72.

[4] Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. Am J Respir Crit Care Med 2010;182(5):627–32.

[5] Flume PA, Wainwright CE, Elizabeth Tullis D, Rodriguez S, Niknian M, Higgins M, et al. Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor. J Cyst Fibros Jan, 2018;17(1):83–8.

[6] VanDevanter DR, Mayer-Hamblett N, Boyle M. Feasibility of placebo-controlled trial designs for new CFTR modulator evaluation. J Cyst Fibros Jul, 2017;16(4):496–8.

[7] Davies JC, Van de Steen O, van Koningsbruggen-Rietschel S, Drevinek P, Derichs N, McKone EF, Kanters D, Allamassey L, Namour F, de Kock H, Conrath K. GLPG1837, a CFTR potentiator, in p.Gly551Asp (G551D)-CF patients: An open-label, single-arm, phase 2a study (SAPHIRA1). J Cyst Fibros May 27 2019;16(Supplement 1):S24–5. https://doi.org/10.1016/S1569-1993(17)30236-9 (pii: S1569-1993(19)30111-0. [Epub ahead of print]).

[8] Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Traffic study group; transport study group. Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 16 Jul, 2015;373(3):220–31.

[9] Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med 23 Nov, 2017;377(21):2013–23.

[10] Garralda E, Dienstmann R, Piris-Giménez A, Braña I, Rodon J, Tabernero J. New clinical trial designs in the era of precision medicine. Mol Oncol Mar, 2019;13(3):549–57. https://doi.org/10.1002/1878-0261.12465 [Epub 2019 Feb 22].

[11] Tullis E, Colombo C, Davies JC, et al. Preliminary safety and efficacy of triple combination CFTR modulator regimens in cystic fibrosis. Pediatr Pulmonol 2017;52(S47):#246.

[12] Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. Pediatr Pulmonol Apr, 2011;46(4):393–400.

[13] Bodewes FA, Verkade HJ, Taminiau JA, Borowitz D, Wilschanski M. Working group cystic fibrosis and pancreatic disease of the European society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). Cystic fibrosis and the role of gastrointestinal outcome measures in the new era of therapeutic CFTR modulation. J Cyst Fibros Mar, 2015;14(2):169–77.

[14] Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. KIWI study group. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. Lancet Respir Med Feb, 2016;4(2):107–15.

[15] Kelly A, De Leon DD, Sheikh S, Camburn D, Kubrak C, Peleckis AJ, et al. Islet hormone and Incretin secretion in cystic fibrosis following 4-months of ivacaftor therapy. Am J Respir Crit Care Med Feb 1 2019;199(3):342–51.

[16] Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. VX08-770-103 (ENVISION) study group. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med 1 Jun, 2013;187(11):1219–25.

[17] De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros Dec, 2014;13(6):674–80.

[18] Vermeulen F, Le Camus C, Davies JC, Bilton D, Milenković D, De Boeck K. Variability of sweat chloride concentration in subjects with cystic fibrosis and G551D mutations. J Cyst Fibros Jan, 2017;16(1):36–40.

[19] Fidler MC, Beusmans J, Panorchan P, Van Goor F. Correlation of sweat chloride and percent predicted FEV_1 in cystic fibrosis patients treated with ivacaftor. J Cyst Fibros Jan, 2017;16(1):41–4.

[20] Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med 18 Nov, 2010;363(21):1991–2003.

[21] Clancy JP, Rowe SM, Accurso FJ, Aitken ML, Amin RS, Ashlock MA, et al. Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation. Thorax Jan, 2012;67(1):12–8.

[22] Solomon GM, Bronsveld I, Hayes K, Wilschanski M, Melotti P, Rowe SM. Sermet-Gaudelus, I. standardized measurement of nasal membrane Transepithelial potential difference (NPD). J Vis Exp 2018;139:e57006. https://doi.org/10.3791/57006.

[23] Stocks J, Thia LP, Sonnappa S. Evaluation and use of childhood lung function tests in cystic fibrosis. Curr Opin Pulm Med Nov, 2012;18(6):602–8.

[24] Davies J, Sheridan H, Bell N, Cunningham S, Davis SD, Elborn JS, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med Oct, 2013;1(8):630–8.

[25] Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, et al. VX14-809-109 investigator group. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med Jul, 2017;5(7):557–67.

[26] Kuo W. Kemner-van de Corput MP, Perez-Rovira a, de Bruijne M, Fajac I, Tiddens HA, van Straten M; ECFS-CTN/SCIFI CF study group. Multicentre chest computed tomography standardisation in children and adolescents with cystic fibrosis: the way forward. Eur Respir J Jun, 2016;47(6):1706–17.

[27] Mall MA, Stahl M, Graeber SY, Sommerburg O, Kauczor HU, Wielpütz MO. Early detection and sensitive monitoring of CF lung disease: prospects of improved and safer imaging. Pediatr Pulmonol Oct, 2016;51(S44):S49–60. https://doi.org/10.1002/ppul.23537.

[28] Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, et al. Precision trial investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 29 Dec, 2016;375(26):2519–29.

[29] Tan NS, Ali SH, Lebovic G, Mamdani M, Laupacis A, Yan AT. Temporal trends in use of composite end points in major cardiovascular randomized clinical trials in prominent medical journals. Circ Cardiovasc Qual Outcomes Oct 2017;10(10).

[30] Strug LJ, Gonska T, He G, Keenan K, Ip W, Boëlle PY, et al. Cystic fibrosis gene modifier SLC26A9 modulates airway response to CFTR-directed therapeutics. Hum Mol Genet 15 Oct, 2016;25(20):4590–600.

[31] Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. Am J Respir Crit Care Med 1 Oct, 2015;192(7):836–42.
[32] Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med Feb, 2017;5(2):107–18.
[33] Acaster S, Pinder B, Mukuria C, Copans A. Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. Health Qual Life Outcomes 12 Mar, 2015;13:33.
[34] McGarry ME, Illek B, Ly NP, Zlock L, Olshansky S, Moreno C, et al. In vivo and in vitro ivacaftor response in cystic fibrosis patients with residual CFTR function: N-of-[1] studies. Pediatr Pulmonol Apr, 2017;52(4):472–9.