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Early View

Correspondence

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SARS-CoV2 disrupts clinical research - the role of a rare disease-specific trial network

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Take home message (243 characters with spaces):

Rare disease patients may suffer delayed access to new drugs as SARS-CoV-2 is disrupting clinical trials. Our survey demonstrates that the European cystic fibrosis clinical trials network is ideally placed to track and address such disruption.

Correspondence (756 words)

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has disrupted clinical trials worldwide [1]. This could delay the approval of new medicines and reduce access to investigational treatments via clinical trials. This particularly impacts patients with rare diseases such as cystic fibrosis (CF).

Here we present the results of several surveys performed within the European CF Society Clinical Trials Network (ECFS-CTN) that aimed to assess how the pandemic disrupted CF clinical trials and to rapidly share useful information about operational mitigation measures by clinical trial teams across Europe. We also monitored continued access, via trial participation, to CF transmembrane conductance regulator (CFTR) modulators as disease-modifying treatments in CF. These modulators restore CFTR transcellular chloride transport caused by pathogenic variants in the CFTR gene, demonstrating marked improvements in lung function and quality of life [2]. Licensing and reimbursement of CFTR modulators varies by country and around 450 CF patients across ECFS-CTN sites currently access CFTR modulators via clinical trials. Trial and treatment interruption could result in clinical deterioration and a reduced quality of life for these participants.

Methods

Four surveys were answered by clinical trial investigators and research coordinators in the 58 ECFS-CTN sites between March-May 2020 (Weeks 1, 2, 4 and 6). Each survey contained the same core questions; other questions were added/removed as the situation evolved. Two responses from the same site were included if they represented adult and pediatric clinics. If multiple responses were received from the same adult/pediatric clinic within a site,

consistency was checked, and the lead investigator response was included for result calculations. Following data cleaning, there were 55-63 evaluable responses for each survey (representing 40-49 sites and 12-16 countries).

Results

The Week 1 survey was performed just before initial FDA and EMA guidance in mid-March 2020 [3,4] and showed that many sites had already prohibited new enrolment into trials and onsite monitoring visits (**Table 1**). Existing trial participants could mostly continue attending onsite trial visits in person, although remote "tele-visits" were also encouraged. Patients were reluctant to attend around 25% of clinics for trial visits; other clinics reported that patients were willing to attend trial visits if precautions were implemented, or if it was to continue receiving CFTR modulators. Home delivery of study drug increased over time, which helped avoid onsite visits.

Most sites received adequate guidance from trial sponsors from Week 1 onwards. Procedures to set up new trials continued in around half of clinics, but site initiation visits were generally prohibited. Encouragingly, patient rollover from phase 3 trials of CFTR modulators to open-label extension studies was mostly possible, guaranteeing continued treatment with CFTR modulators.

In Week 4, reduced availability of clinical trial staff was reported by 41% of clinics (median [range] reduction: 50% [10-90%]), due to staff reassignment to clinical duties (50%) or COVID-19 trials (42%), or illness/quarantine (26%). Similar trends were observed at Week 6. Additionally, 42% of clinics reported that contingency measures such as shipment of medication, telephone visits and remote monitoring took longer than normal procedures.

Survey results were returned to sites several hours after the survey closed to share knowledge about how teams (both adult and pediatric) were handling trial conduct, and ensuring patient safety. We shared summary results with trial sponsors; we also surveyed sponsors about their mitigation efforts. Our aerial view of the CF clinical trial landscape in Europe did not detect any systemic issues (e.g. closure of trial sites) requiring our intervention.

Next steps

We are compiling the crowd-sourced learnings from these surveys into practical mitigation advice for future crises, that sites can adapt to their local situations. We are also following-up the various telehealth options reported by sites such as video calls, electronic consenting, home spirometry to identify and address any associated gaps in evidence, guidance or training.

Conclusions

The pandemic caused major disruption to clinical trials, which could delay therapeutic progress in CF. The enforced healthcare measures and focus on new treatments for SARS-CoV2 should not stall development of treatments for CF and other rare diseases. ECFS-CTN's mission is to intensify clinical research in CF and get new medicines to patients faster [5]. We hope that the rapid collection and sharing of information between sites facilitated by this survey helped sites deal with the myriad of challenges posed by the pandemic and will help them better prepare for future crises. We believe that disease specific CTNs are an effective way for rare disease clinical trial sites to learn from each other and overcome obstacles such as the current pandemic, while working towards the goals of effective treatments for rare diseases.

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Table 1 Key results of repeated ECFS-CTN survey to trial sites

	Week 1	Week 2	Week 4	Week 6
Dates of data collection	18-24 March	25-27 March	8-10 April	29 April – 4 May
Number of evaluable respondents	59	55	61	63
For ongoing trials, the % of clinics allowing:				
Patients to attend onsite trial visits	71%	60%	57%	74.6%
New enrolment into ongoing trials	22%	15%	NA	NA
Onsite CRA monitoring visits	16%	11%	NA	NA
Study drug to be shipped to patients	55%	66%	67%	65.1%
New trials				
Trial set-up activities to continue	57%	60%	52%	71.4%
Site initiation visits	5%	14%	NA	NA
Initiation of CFTR modulator extension open-label studies	91%	78%	NA	NA
Guidance: the % of clinics who received guidance from:				
Hospital	55%	68%	NA	NA
Ethics committee	34%	23%	NA	NA
National competent authority	20%	32%	NA	NA
Sponsor	88%	90%	97%	93.7%

CRA=clinical research associate; CFTR=cystic fibrosis transmembrane conductance regulator; NA=question not asked