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


Published in:
European Respiratory Journal

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
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SARS-CoV-2 disrupts clinical research: the role of a rare disease-specific trial network

To the Editor:

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 Cystic Fibrosis 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.

Four surveys were answered by clinical trial investigators and research coordinators in the 58 ECFS-CTN sites between March and 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 paediatric clinics. If multiple responses were received from the same adult/paediatric 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).

The week 1 survey was performed just before initial US Food and Drug Administration and European Medicines Agency 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 reduction 50%, range 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.

Rare disease patients may suffer delayed access to new drugs as SARS-CoV-2 is disrupting clinical trials. This survey demonstrates that the European Cystic Fibrosis Clinical Trials Network is ideally placed to track and address such disruption. https://bit.ly/3hCw5dq

Survey results were returned to sites several hours after each survey closed to share knowledge about how teams (both adult and paediatric) 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.

For the next steps in this research, 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 and home spirometry to identify and address any associated gaps in evidence, guidance or training.

In conclusion, 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-CoV-2 should not stall development of treatments for CF and other rare diseases. The mission of the ECFS-CTN 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 clinical trial networks 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 goal of effective treatments for rare diseases.

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Received: 2 June 2020 | Accepted after revision: 20 July 2020

Conflict of interest: S. van Koningsbruggen-Rietschel reports grants from Algipharma (HORIZON2020), personal fees from Deutsches Zentrum für Infektionsforschung, Antabio, Proteostasis Therapeutics, Roche and Vertex Pharmaceuticals, outside the submitted work. F. Dunlevy has nothing to disclose. V. Bulteel has nothing to disclose. D.G. Downey reports grants and personal fees from Vertex, Proteostasis and Chiesi, outside the submitted work. L. Dupont has nothing to disclose.

References

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TABLE 1 Key results of repeated European Cystic Fibrosis Society Clinical Trials Network survey to trial sites

<table>
<thead>
<tr>
<th>Dates of data collection</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–24 March</td>
<td>59</td>
<td>55</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Number of evaluable respondents</td>
<td>59</td>
<td>55</td>
<td>61</td>
<td>63</td>
</tr>
</tbody>
</table>

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 clinical research associate 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:
- 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%

CFTR: cystic fibrosis transmembrane conductance regulator; NA: question not asked.


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