WORLDWIDE CLINICAL TRIALS

WHITE PAPER

ALS STUDIES AND LESSONS LEARNED FROM COVID-19

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Disruption is the hallmark of the novel coronavirus (COVID-19) pandemic. Unless one lives and works in total isolation, all aspects of life have been disrupted to a greater or lesser degree — how individuals work, study, shop, recreate, travel, and more. At the same time, there has been significant regional variability in terms of the impact of disruptions due to changing epidemiological situations and regulations.

The disruptions caused by COVID-19 have complicated both the initiation and execution of clinical trials involving therapies targeting amyotrophic lateral sclerosis (ALS). In areas where stay-at-home orders or lockdowns have been put in place, individuals participating in a clinical trial may be unable to travel to a trial center or, because of possible risk factors, may be unwilling to travel to clinics for assessments. Conversely, ALS trial centers may be constrained from allowing entry to individuals who are infected with coronavirus. The study teams may have been directed to work from home. Pharmacies may be closed or operating on a restricted schedule; delivery services may operate inconsistently or on a delayed schedule; even the health care personnel working at the trial center may have been redeployed to an emergency department (ED) or intensive care unit (ICU) in response to a surge of coronavirus patients. The FDA, NIH, and IRB promulgated new clinical trial guidelines as the pandemic evolved. The Northeast ALS Consortium (NEALS) and European Network for Cure of ALS (ENCALS) also published ALS patient recommendations that would affect how clinical trials could be conducted.

For ALS trial sponsors and CROs alike, the need to protect the health of study participants, the study team, on-site health care professionals, and the broader community in which the trial centers are located is of paramount importance. The question is, how to ensure this protection and conduct the trial? The answers lie in preemptive mitigation and adaptive processes that can be implemented flexibly as conditions evolve.

Consider Worldwide's experience with a Phase 3, randomized, placebo-controlled trial that was already underway when the coronavirus pandemic broke out in early 2020. This study involved some 300 subjects who, for 18 months, would be receiving an oral investigative medicinal product (IMP) at approximately 32 sites in 12 North American and European countries. Enrollment had been completed in 2019, and the trial was well underway when COVID-19 infections began to appear in each of the countries involved.

As the incidence of COVID-19 infection exploded, local- and country-level mandates restricting site access expanded, and many trial participants became increasingly unable or unwilling to travel to trial centers, which they were expected to do every four weeks for the first 28 weeks of the study and then every 8 weeks until the end of the trial at week 76. Though trial participants averaged only 57 years of age — so neither advanced age nor a higher incidence of comorbidities identified them as members of a highest risk population — their ALS made them acutely aware of their vulnerability if contracting any kind of serious respiratory infection. Their reluctance to travel, even when and where they were allowed to, was understandable.

IMPLICATIONS FOR STUDY CONDUCT

Trial managers and medical monitors within the CRO quickly made plans to modify the manner in which IMP would be delivered to the participants and follow-ups would be managed. The IMP in the study consisted of a capsule to be taken orally three times per day, and originally it was intended that each participant would receive a supply of the IMP during each site visit. Some countries and regions would not permit distribution of IMP from centralized repositories during the pandemic, so Worldwide made arrangements for sites to ship IMP directly to the participants. Given the possibility of

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delivery delays arising from COVID-19, an allowance was made to dispense up to four months of IMP at a time so that patients would neither need to travel for IMP nor run out before more could be shipped.

Instead of asking participants to travel to trial centers and risk infection, a decision was made to conduct clinical assessments, when possible, in the homes of trial participants. Because this was an ALS trial and ALS advances at a more rapid rate in some patients, trial planners at Worldwide had developed contingency plans for home visits before the trial commenced (anticipating that some trial participants might become unable to travel to the trial site because of their illness). Participants had already agreed to allow home visits, and the only significant change driven by the pandemic was that the home visits became the default manner of direct patient interaction rather than the exception. Ultimately, instead of fewer than 25% of patients receiving home visits (as projected in the contingency plans), as many as 60% of patients participating in the study received home visits.

Additionally, because the trial protocol had included provisions for conducting patient visits by telephone every 8 weeks starting in week 32, the protocol was amended to allow the substitution of telephone visits for in-home visits when circumstances made it impossible for a home nurse to check on patients.

After notifying the institutional review boards (IRBs) and ethics committees (ECs) of all these changes, new guidance on patient visits and IMP distribution was released to all the active trial sites. Sites were to do the following:

- Implement home visits rather than site visits according to the established treatment schedule
- Implement telephone visits rather than home visits when necessary
- Direct patients to local labs for any required testing if a home nurse was unable to visit
- Provide guidance on safety assessments
- Provide guidance on documentation of any COVID-19–related protocol deviations that may have occurred

Because contingencies for home nursing and telephone visits had already been planned, these changes did not require any significant changes to the electronic data capture (EDC) systems used in the trial. Slight modifications were incorporated into the EDC to enable individuals to note any anomalies arising from a COVID-19 infection (whether affecting the participant or the household in which the patient lived). This particular modification to the EDC presaged subsequent regulatory guidance requesting that the same indicator variable be appended to databases to be used in subsequent analyses.[1] Additionally, a protocol amendment formally allowed the accommodation of any delays due to COVID-19 arising in the performance of required assessments.

HOME VISITS

Trial planners had anticipated in advance of the pandemic that perhaps as many as 25% of patients would need home visits before the end of the trial because the progressive nature of ALS would have precluded travel to the site. Worldwide trial managers and clinical assessment technologies (CAT) team managers had developed home nurse training programs to ensure the consistent collection of data during home visits. Third-party vendors provided training in the use of spirometers to measure respiratory function and (in France) portable ECG systems to measure cardiac performance. A third-party patient portal provider had been engaged to make training programs available if additional nurses were brought

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onboard or if nurses needed to be recertified. Through these portals, home nurses could stay abreast of any developments or changes relating to service delivery, trial protocols, or the IMP.

Bringing the trial home

Between March and August 2020, as COVID-19 lockdowns moved through all participating countries, reliance on home nursing services to complete study visits increased dramatically. Trial activities taking place during a home visit, where tasks were completed directly by home nurse or remotely by site investigator teams, included the following:

- Adverse event assessment
- Track concomitant medications
- Measure vital signs/weight
- Perform spirometry and, in France, ECG
- Collect blood/urine samples

Any other assessments that could only be conducted in-clinic were not conducted during at-home visits.

It should be noted that site personnel were expecting to use the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) and the Columbia Suicide Severity Rating Scale (C-SSRS) assessments during every on-site and telephone visit with patients. When home visits replaced on-site visits, though, the sites expanded the plan to conduct these assessments by phone rather than to train the home nursing staff to conduct the ALSFRS-R and C-SSRS in person during a home visit. Because the ALSFRS-R and C-SSRS have been validated and approved for use during a telehealth call, there was no question of whether substituting data collection over the phone rather than in-person on-site would affect the validity of the data captured, even if more responses were collected over the phone than had been anticipated originally.

Finally, it should also be noted that patient response to the increased use of home nurses varied. No patients had objected to visits by home nurses before the advent of the pandemic, but as the pandemic spread and more areas went into lockdown, the use of home nurses encountered some challenges. In France and Italy, home nurses were asked to undergo regular COVID-19 testing to minimize risk of viral transfer to homebound patients. As a consequence, home nurses encountered little resistance to home visits in those countries. Conversely, in the U.S., where nurses did not have access to regular COVID-19 testing, trial participants (or their families) in certain regions refused entry to unfamiliar home nurses for fear of contracting COVID-19.

Accommodating spirometry

Spirometry features prominently in most ALS studies, and this trial was no exception. However, as a matter of public health and safety during the pandemic, the inclusion of spirometry in the patient visits (on-site or at home) presented challenges. All parties involved — including regulators, clinical staff, home nurses, and patients — agreed that spirometry presented a need for rigorous enforcement of infection control and cleaning policies as well as the use of specialist viral and bacterial filters during exhalatory measurements. Some preferred vendors of spirometry equipment provided single-use components that would eliminate the risk of one patient contracting COVID-19 from a previous equipment user. Another vendor indicated that contamination could be avoided if proper cleaning procedures were followed.

Even the European Respiratory Society offered recommendations on how best to accommodate

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spirometry safely — but, as COVID-19 cases began to spike in different areas, governments took it upon themselves to lock down the use of spirometry:

- The U.K., Italy, and Spain implemented rules prohibiting the use of spirometry at home or at a site.
- In Belgium, nurses were precluded from using a spirometer during a home visit, but clinicians at a study site could use spirometers to measure respiratory function.
- In still other areas, spirometers could be used at home but not at study sites.

From a trial management perspective, these prohibitions proved complicated to accommodate — simply because countries (and states within countries) did not update their policies on spirometry in any coordinated manner. Prohibitions went into place at different times in different places, which caused the data capture from spirometry to vary by time and location. The EDC includes a record of the countries that imposed these restrictions, and this information will be referenced in the CSR so that reviewers understand why the spirometry data is missing for these countries and these dates.

Acknowledging the influence of COVID-19

Finally, given the expanding presence of the novel coronavirus itself, the Worldwide trial team had to determine how to record the presence of COVID-19 if detected in the trial participant or the participant's immediate household.

- If a participant tested positive for COVID-19, it would be recorded as an COVID-19-related adverse event (COVID-19 AE)
- If a participant presented with suspected symptoms of COVID-19 but no PCR test confirmed infection with COVID-19 (or tests came back negative), it would be recorded as Suspected COVID-19 AE
- If a member of the participant's household tested positive or was quarantined for COVID-19, the presence of COVID-19 within the caregiving setting was noted as an Exposure to COVID-19 AE
- If a trial participant were admitted to a hospital due to COVID-19, the admission would be recorded as a severe adverse event (SAE) due to hospitalization

Testers always notified local health authorities if a participant was found to have tested positive for COVID-19. Local ethics boards were notified about participants testing positive to COVID-19 only if they requested notification.

ACCOMMODATING THE UNEXPECTED AMIDST THE UNEXPECTED

Approximately 6 months into this 18-month trial — but still before the pandemic had begun — a safety issue surfaced that needed to be addressed. Researchers noticed significantly elevated readings in liver function tests, and the protocol was modified to ensure this condition was monitored closely. One practical change was that numerous patient visits that had been scheduled to take place as phone visits were rescheduled to be site visits so that researchers could draw blood and monitor the readings associated with the safety concern.

With the onset of the pandemic, though, and the inability of patients to go to sites as scheduled, Worldwide had to make other arrangements for the lab work associated with the safety concern. While the home nurses would be able to collect a blood sample during a home visit, it could not be assumed that they would be able to take those samples to the research centers for analysis, as the centers themselves were locked down. Where circumstances prevented a home nurse from visiting the patient or collecting samples, the patient was asked to go to the lab nearest their home to provide the samples.

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Once they had received the lab results, patients would share those results with the site. Due to the oversight required for the safety issue, the medical monitor team had to adapt to review a large volume of local lab results sent by sites directly. Following this, study systems were adapted to enable the EDC to incorporate patient data from the local labs and thereby ensure that it informs final study data.

Between site visits that did occur as scheduled and the home visits that occurred when site visits were impossible, the trial teams were able to monitor the safety issue without interruption.

Accommodating changes in an Open Label Extension

The challenges presented by the pandemic and the local lockdown orders also affected an Open Label Extension (OLE) trial to the main ALS study that was commencing at the time the pandemic exploded. That trial had been designed as a separate protocol for patients who had just completed the main ALS study.

To permit patient rollover to the OLE study so that existing trial patients could participate in the OLE study and receive active treatment, the Worldwide team worked closely with the sponsor to incorporate remote consent and eligibility checks into the trial protocol. Drawing on the expertise of the clinical operations and medical teams, Worldwide was able to implement robust new processes to ensure that protocol, GCP, and local IRB/EC regulations requirements were met. Along with an updated protocol, Worldwide also submitted guidelines on remote consent and remote eligibility review to the IRBs/ECs in participating countries, ensuring that sites in affected areas could implement these new processes and procedures rapidly.

Additionally, the Worldwide team quickly updated the third-party home nursing services being used for the first ALS trial to ensure that mobile nurses were trained to support this remote baseline OLE visit. Once the investigator had completed the patient consent and eligibility review (by tele/videoconferencing where appropriate), the mobile nurses were able to visit patients' homes safely, take samples, and perform other procedures such as spirometry.

By taking a dynamic approach, working closely with the sponsor, and implementing quickly, the Worldwide team was able to ensure that sites throughout North America and Europe had the critical process in place to ensure that all patients were able to join the OLE study despite COVID-19 restrictions. This made it possible for all patients to access active IMP once their participation in the main study had come to an end.

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SUMMARY

The disruption occasioned by the spread of COVID-19 — wholly unforeseen when this ALS study was initiated — occurred at an alarming rate. As the scope and complexity of lockdown mandates accelerated, individual towns, states, even whole countries hit the pause button. Trial participants were confined to their homes or other domiciliary facilities, and those who were not legally confined, as members of a vulnerable population, were understandably reluctant to travel to a study site due to heightened risk of infection. Similarly, study site staff scheduling became disrupted, as did infrastructural and logistical services on which sites depended for the delivery of IMP and other study materials. Although even the most experienced of centers had no prior experience accommodating a pandemic of this nature, all sites aggressively reoriented their operating procedures to combat the impact that the virus would otherwise have on standards of care and study conduct.

In the midst of all this disruption, these ALS trials — both the original trial and the OLE trial — continued without major interruption. While much has been written elsewhere regarding the impact of trial design on the validity of conclusions, an unanticipated pandemic could easily give rise to inconsistencies in study conduct and discontinuities in patient engagement and compliance that would have at least as forceful an impact on conclusions. For these reasons, a seasoned team and a nimble response to midstream problem solving is crucial. A sponsor needs to partner with a CRO that understands the dynamics of trial design and the portfolio of solutions that customarily might be applied to address a study's challenges, but just as important is the team's knowledge of the contingency options that can be implemented, as needs arise, throughout the life of a study.

In the case of Worldwide's response to the disruptions caused by the advent of the pandemic during an ongoing Phase 3 trial, certain options were immediately clear:

- Upscale the existing home visit contingency plans to ensure that all patients could be covered
- Recruit and train third-party health care providers to deliver at-home services using as many of the same surveillance mechanisms and assessments (as possible) as would have been used on-site
- Use telephone visits to ensure continued collection of safety and end point data when neither home nor site visits were possible
- Update study procedures to accommodate use of local labs to enable safe collection of patient samples
- Adapt study systems to allow local lab data to be collected in EDC
- Develop alternative means of ensuring that patients have uninterrupted access

Each of these options involved integrated efforts to document and train personnel, update the protocol, and coordinate with all stakeholders — from the sponsor to the regulatory boards, IRB/CAs, trial participants and their families, and more.

Ultimately, the specific actions that a CRO needs to undertake will vary from disruptive incident to disruptive incident. At its foundation, the ability to remain flexible and innovative in the course of study conduct is a prerequisite for successful trial operations. Indeed, there will be other disruptions attendant to COVID-19 before the pandemic is over and still more disruptions flaring up after COVID-19 has been contained. What remains constant is the CROs need to be creative and agile when it comes to assessing the dynamics of disruption, formulating a response that protects the health and well-being of all the people involved and drives the trial forward without compromise.

REFERENCES

1. US Department of Health and Human Services, Food and Drug Administration. Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency: Guidance for Industry 2020. Available from: https://www.fda.gov/media/139145/download.

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