

COVID-19 and the neurological disease therapeutic pipeline

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From the interruption of clinical trials by shelter-in-place orders to the challenges involved in safely collecting biofluid samples, drug development for neurological disease was hit hard by the COVID-19 pandemic this year. However, the field has responded with innovative solutions, and 2021 could see the therapeutic pipeline flowing again.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in late 2019 and rapidly spread across the globe, led to an almost complete worldwide shutdown of research targeting neurological diseases by mid-March¹⁻⁷. Thus, the therapeutic pipeline for neurological diseases — which had previously been rapidly expanding — came to a grinding halt. Public health measures necessary to control the spread of coronavirus disease 2019 (COVID-19), including social distancing and shelter-in-place orders, have impacted every stage of therapeutic development, from basic science discovery to the manufacturing and distribution of both approved and experimental neurological therapeutics. However, the impact of COVID-19 has been most profound in the area of active clinical trial conduct, where both the medical research workforce and clinical trial participants were substantially limited in their ability to meet the rigorous demands and tight time schedules inherent in human clinical trial activities^{1,2}.

Many experimental therapeutics require dosing via on-site administration, as well as carefully timed outcome measure assessments; thus, the interruption of clinical trials by the COVID-19 pandemic has severely damaged the implementation of the precise protocols required to obtain proof of safety and efficacy^{1,2}. For example, an article by Joseph Broderick and colleagues¹ published in June described the impact of COVID-19 on the NIH StrokeNet, a network of centres performing clinical trials in stroke. An initial complete shutdown of all trials across all centres was coordinated centrally and was followed by a phased research restart plan that took into account local situations and regulatory oversight. This approach was successful in re-engaging research activities to at least some degree within 55 days in all but one of the ongoing studies. However, the success of the restart activities and the long-term effects of the shutdown are not yet known.

The interruption of essential components of clinical trial conduct that are necessary for advancement to the next stage of therapeutic development (and/or eventual approval of the experimental therapeutics) has created challenges for both sponsors and regulatory agencies, who have been left uncertain as to how to handle these unprecedented, widespread disruptions^{2,3}. Nevertheless, solutions have been proposed and have started being implemented. Remote assessments to allow distanced trial conduct are under rapid development and include the use of telephone evaluations, video conference-assisted evaluations and other remote digital strategies^{1,6}. Indeed, Broderick et al.¹ recommended that trial sites incorporate remote assessments as

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needed, as well as simplifying and limiting participant visits.

A change in assessment modality during a trial or missing data resulting from COVID-19 related interruptions can complicate statistical analyses and might bias the results. The interpretation of adverse events is also complicated by the pandemic as neurological and cognitive outcome measures can be affected by COVID-19-associated signs and symptoms^{1,2,4}. In another key publication from this year, Suzie Cro and colleagues proposed a four-step statistical approach for handling missing outcome data³. Their approach entails clarifying the treatment estimand of interest with respect to the occurrence of the pandemic, establishing what data are missing for the selected estimator, performing primary analysis under the most plausible missing data assumptions and performing sensitivity analysis under alternative plausible assumptions. Such an approach begins to define a strategy for interpreting the results of trials interrupted by the pandemic.

Performing clinical trials in the COVID-19 era requires consideration of the risks of COVID-19 exposure during research engagement and biomarker collection. In June,

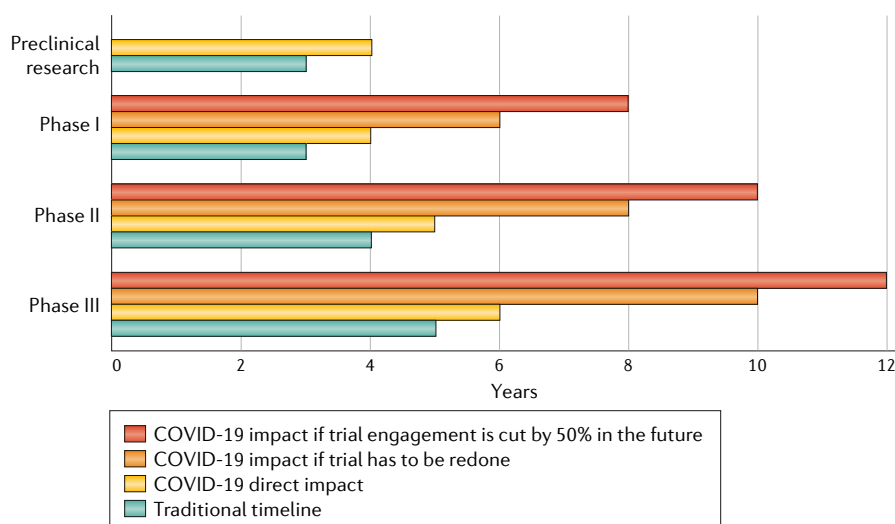


Fig. 1 | Potential delays in the pipeline for neurological therapeutic development resulting from the COVID-19 pandemic. Time required for each stage of clinical therapeutic development and the potential impact of COVID-19 on the developmental timeline based on the observed effects of the pandemic so far. Direct COVID-19 impact is a reality, and will extend the timeline for preclinical research and all phases of subsequent development for ongoing trials by a year or more, depending on the duration of the pandemic. If delays, potential need for repetition of studies and reduced likelihood of research engagement remain problematic over the longer term, an average 15-year development programme could double to more than 30 years for drugs that are currently in the early preclinical phase.

Key advances

- Understanding the impact of COVID-19 on diverse aspects of clinical trials¹.
- Development of statistical approaches to mitigate the impact of missing data³.
- Safely managing biospecimen collections that are essential for establishment of disease modification⁴.
- Overcoming site-specific barriers to safe clinical trial conduct².
- Maintaining a sufficiently large and diverse pool of research participants⁵.

Suzanne Schindler and colleagues published a set of recommendations⁴ for the collection and analysis of biofluids in Alzheimer disease research during the COVID-19 pandemic. These recommendations include adherence to universal precautions and biosafety level-1 protocols for most laboratory procedures that do not generate aerosols; use of additional safety measures if procedures have the potential to generate aerosols; clear identification of biosamples collected from individuals with known SARS-CoV-2 infection, as well as provision of this information to anyone receiving such samples; and handling all samples collected during the pandemic as if they contain SARS-CoV-2, given the high rate of asymptomatic infection.

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The COVID-19 pandemic has also had a downstream effect on the funding that allows the therapeutic pipeline to remain solvent. Maintaining a workforce skilled in clinical trial conduct has been a challenge with widespread furloughs, layoffs and economic collapse threatening not only current but also future clinical trial conduct². In addition, the need for additional personal protective equipment, COVID-19 testing of research participants and staff, implementation of

new equipment and training to facilitate biomarker collection, and the introduction of remote assessments have all contributed to an increase in the financial costs involved in running clinical trials. In an article² published in September this year, we made several recommendations for overcoming site-specific barriers to clinical trial conduct during the COVID-19 era, including the allocation of funds to standing site support with the aim of maintaining a research-ready infrastructure for future trials.

Most importantly, COVID-19 has, understandably, negatively affected the interest and willingness of many people to engage in experimental clinical trials^{2,5,7} (FIG. 1). In another key publication from 2020, Daniel Lackland and colleagues⁵ highlighted the potential for the COVID-19 pandemic to further limit the participation of historically underrepresented groups in clinical trials and recommended that the field increases efforts to recruit participants from these groups. Managing safety concerns and overcoming a growing reluctance to engage in research at this time will require innovative solutions, and implementing these solutions will require widespread efforts to educate potential research volunteers on risk reduction measures. Potential volunteers will also need to be educated on the importance of continuing to move therapeutic research forward in order to advance the development of new medicines for the treatment of neurological diseases. Without such efforts, the impact of the COVID-19 pandemic on the therapeutic pipeline for neurological diseases could extend indefinitely.

It remains uncertain as to whether effective solutions to the problems induced by the pandemic can be developed, or whether the many affected trials will be left with inconclusive results, necessitating repeat studies that would cost additional years and millions of US dollars (FIG. 1). In addition, studies scheduled to start this year have been delayed, closing the valve on our previously robust pipeline of new experimental therapeutics

even more tightly. Clearly, the impact of COVID-19 on research sites responsible for the conduct of human clinical trials has been profound^{1,2}. Nevertheless, the innovation spurred by this crisis will move the field forward in new ways, ensuring that 2021 will be a year that allows the therapeutic pipeline to resume its pre-pandemic vigorous flow. Researchers and clinicians have formed alliances to address barriers to research advancement, allowing new research into statistical techniques to handle the current disruptions to clinical trial conduct³, enabling the production of guidelines for enhanced safety of research conduct^{1,4}, and spurring on the development and validation of novel remote assessment techniques^{1,6}.

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Competing interests

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