Practical Implications of Undertaking Clinical Trials during the COVID-19 Pandemic

Faced with the coronavirus pandemic, restrictions and ever-fluctuating situations have necessitated changes to ongoing and future clinical trials. Practical and harmonised actions have been required to ensure the necessary flexibility in trial facilities, and adaptations to regular procedures have been needed to maintain the integrity of the trials, as well as ensuring the rights and safety of trial participants, and the safety of clinical trial staff.

The pandemic has seen announcements from pharma companies, clinical research organisations (CROs) and universities about delays in the enrolment of patients to trials, as well as terminations and temporary pauses of clinical trials. These effects have impacted clinical research, irrespective of indication, and could lead to implications for data collection and analysis going forward.

Phase I studies with healthy volunteers (HV) were particularly affected due to the lack of certainty in respect of the health status of the participants during the early stages of the pandemic. Additionally, with hospitals devoting their entire activities to COVID-19, access to Phase I units was severely restricted, if not impossible.

Regulatory Support

As the implications of the pandemic began to become apparent, the European Medicines Agency (EMA) published its first version of "*Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic*", which has subsequently been revised, with version 3 being the most recent (dated April 28, 2020). The guidance included the following key recommendations from the EC:

- Absolute priority should be given to clinical trials for the prevention or treatment of COVID-19 and COVID-19-related illnesses.
- The feasibility and immediate necessity of starting a new clinical trial should be critically assessed.
- Sponsors should consider in their risk assessment whether the following measures could be applied during COVID-19: conversion of physical visits into phone or video visits, temporary halt of the trial, interruption or slowing down of recruitment, closing of sites, transfer of trial participants to investigational sites away from risk zones, use of local laboratories.
- Priority is given to substantial amendment applications to existing clinical trials necessary as a result of COVID-19.
- Alternative ways of obtaining re-consent (for reasons related to COVID-19) should be considered during the pandemic.
- Changes in the distribution of the investigational medicinal products (IMP), alternative shipping and storage arrangements may be necessary.
- Cancelling or postponing of on-site monitoring visits by preferring online tools.
- On-site audits should be avoided or postponed.
- Consider *Guidance on the Implications of Coronavirus Disease (COVID-19) on Methodological Aspects of Ongoing Clinical Trials* published by the CHMP Biostatistics Working Party, dated March 25, 2020, to manage protocol deviations related to COVID-19.

At approximately the same time, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) published its own guidance, "*How Investigators and Sponsors Should Manage Clinical Trials During COVID-19*" (March 19, 2020). The FDA also released its guidance "Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency" in March 2020, which was subsequently updated on July 2.

Any guidance from the regulatory authorities will be updated depending on the evolution of the pandemic and new available scientific data.

Managing a Clinical Pharmacology Unit

As with many similar facilities, when the pandemic struck Belgium in March, the SGS Clinical Pharmacology Unit (CPU) reduced its activities to an absolute minimum. Recruitment and start-up of trials/cohorts was completely put on hold.

To safely restart clinical trial activities, a thorough risk implementation plan was put in place and was based on the instructions and guidelines from the Belgian government, local and regional regulatory authorities, the ZNA Stuivenberg Hospital to which the CPU is attached, and also SGS global policy. This allowed activities to be undertaken, with internal guidance in place to ensure measures were adopted to avoid any potential spread of the SARS-CoV-2 virus, to ensure the safety of trial participants and staff at all times, and to ensure the quality and integrity of data from the trials.

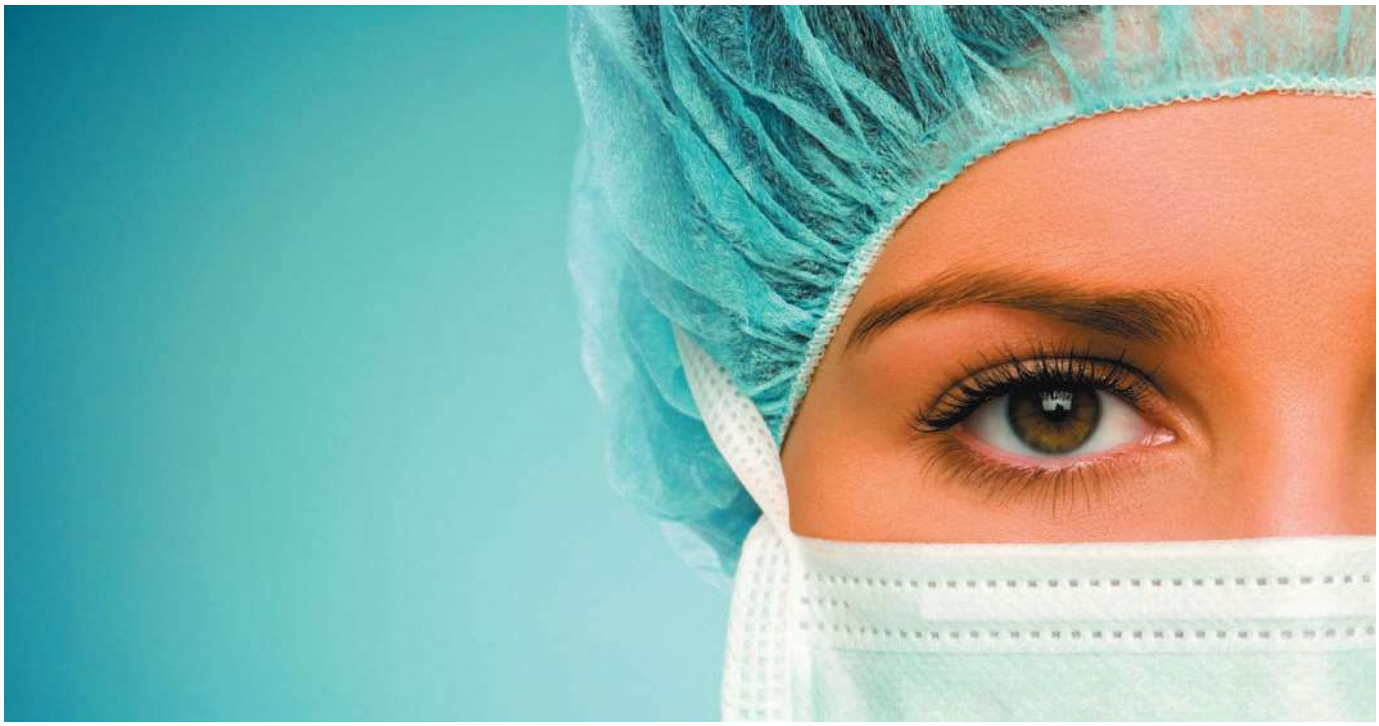
Similar to the regulatory guidance from the EMA, MHRA and FDA, this internal guidance remains adaptable to the changing effects and consequences of the pandemic.

Ensuring precautions to minimise the potential risk of SARS-CoV-2 virus infection into the unit could be implemented led to some standard activities being redesigned and additional measures being put in place.

From a practical point of view, activities and procedures have been amended for staff and visitors to the facility. Common hygienic and preventive measures were set up for the subjects and visitors, such as ensuring regular handwashing was practised, sanitising of hands with alcohol gel, face masks became compulsory at all times, and physical distancing of 1.5 metres was introduced.

To reduce the risk of potentially infected subjects accessing the site, intake interviews were conducted by telephone prior to the screening visit, using structured questionnaires. Additionally, each reception area in CPU was equipped with a device to measure the temperature of people entering the facility.

In place of the standard screening process volunteers and subjects would have normally undertaken prior to a study, all are



now provided with an informed consent form (ICF) document along with the facility COVID-19 procedure documents via email, so that they can read through them prior to arriving at the unit.

Instead of admitting all subjects of one cohort at the same time, subjects now receive individually scheduled appointments, and follow a "one-way" system at the unit, moving through the facility in a set flow to reduce the risk of encountering another subject. There is only one staff member in each interview/examination room with each participant.

During monitoring and data collection, the length of time each monitor spends in the monitoring room is limited to the minimal amount possible. The SGS unit is fully equipped with eSource monitoring and collection, allowing most relevant data to be reviewed remotely.

For the wards at the SGS Phase I unit, careful consideration was given to ensure all safety precautions were taken and the potential risk of COVID-19 infection was minimised. The wards were reorganised to reduce bed capacity by half; and specific attention was paid to toilets, bathrooms and dining/recreation rooms, to ensure the disinfection of fixed furniture and to limit simultaneous occupancy.

Where there is suspicion of COVID-19 infection or a study protocol requires testing, the SGS CPU can perform COVID-19 testing in-house or before admission, with results available within 45 minutes.

Additionally, quarantine measures were developed for handling cases with suspected COVID-19. This would involve any subject being quarantined within the CPU unit, and a nasal swab taken to test for COVID-19. They would remain quarantined until the test result is available, and if negative, the subject would be allowed to return to the rest of the group to further participate in the trial. In the case of a positive result, the subject would undergo extended quarantine within the CPU, and a mutual decision by the investigator and sponsor would need to be made to evaluate the subjects' safety and data integrity of the trial.

Clinical Activities Going Forward

Clinical trials are an essential tool in medical research, and their continuation in the future must be ensured. The COVID-19 pandemic has obliged CROs to explore ways that trials are designed and conducted, and how they could be adapted. What is clear is that lessons must be learned from the last six months, so that the highest quality of clinical trials conduct, and the safety of volunteers and research staff, are ensured.

Most sponsors have looked to restart early-phase study activities, so that product development timelines are not delayed further. Going forward, activities are looking to return to "normal", although it is expected that re-prioritisation of product pipelines by sponsors is likely, and Phase I units should be ready to welcome these trials.

What the long-term effects of this COVID-19 pandemic on clinical research will be is unclear, although COVID-19 risk assessments will likely be part of common practice for some time to come. Although these may be updated according to the most recent scientific information as and when appropriate, some general approaches such as social distancing and enhanced hygiene measures are expected to be in place for a long time.

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