

The top left portion of the page features a stylized map of Europe in a light blue color, overlaid on a dark blue background. The map is surrounded by twelve yellow stars, arranged in a circle, which are the stars of the European Union flag.

Interacting with competent authorities during COVID-19 – A European

By Anna Baran, MD and Stephanie Geiger, PhD

This article covers direct interaction with various European authorities in regard to initial and amendment submissions and notifications related to urgent safety measures in response to the COVID-19 pandemic. The authors contacted selected European authorities to solicit data on submission events during 1 March and 30 June 2020. They found that the first 6-12 weeks of the pandemic presented challenges to numerous stakeholders but, after adjustments, the number of trials submitted and reviewed over the second quarter of 2020 did not differ substantially from 2019. The authors emphasize the importance of trial partners and authorities remaining connected so that they can exchange information on limitations, discuss solutions, and support guidelines that will allow studies to go live.

Introduction

The ongoing COVID-19 pandemic has had a severe impact on key stakeholders in the clinical trial operation process. These stakeholders include healthcare facilities, physicians, governmental authorities designated to review and approve study applications, and eventually, the entire biopharmaceutical and healthcare industry. The industry was presumably best designed and equipped to maintain pre-pandemic working patterns. Regarding the other stakeholders,

one could envision national health care systems being placed under continuously increasing pressure because of the pandemic, and governmental institutions not necessarily having adequate resources to enable staff to immediately switch to remote working models.

In the case of COVID-19, European regulators have made every effort to protect healthcare institutions and competent authorities from unreasonable pressure, appealing to the industry for critical assessment of the feasibility and immediate necessity of starting any new clinical trial.¹ This led to several truly conservative approaches from national competent authorities, noted in the first weeks of the pandemic, and discouraging all new submissions unrelated to COVID-19 vaccines and treatment modalities.

Pandemic, months 0-3

The challenge of working within the European environment has always been related to nuances in verbatims applied by the European Medicines Agency (EMA) and the corresponding implementations or transposition to the local environments of individual countries. This is one of the key reasons the European environment is impatiently expecting adoption of its new Clinical Trial Regulation² to better harmonize the environment of new filings and maintenance regulatory activities.

After the World Health Organization declared COVID-19 a pandemic,³ all stakeholders of clinical trial delivery processes were forced to react. Failure to do so would have demonstrated inadequate risk mitigation and management procedures. Uncertainty dominated the environment, and all parties needed weeks – or months – to understand the adaptation mechanism.

The governments, like other stakeholders, had reasons to share the fears of unpredictability. This led to an early wave of limiting industry access to the authority resources, with initial warnings on extensions of review cycle time and discouragement of any new submissions.

When scientific evidence indicated that paper may be a vehicle in the spread of the novel coronavirus, the submission process was demobilized, even though a considerable number of European countries, particularly in the Central and Eastern Europe, still use paper submission. Any documents submitted on paper were quarantined, and there was no way of obtaining documented acknowledgment of their receipt. The pandemic became a catalyst for change in mid- to late April, when formerly paper-based authorities started issuing guidance on e-signatures and electronic applications. It became clear to the industry that officials were looking to change local processes to facilitate COVID-19–related research as well as all other research.

An important development was the recent release of an EMA document on the implications of COVID-19 on the methodological aspects of ongoing clinical trials.⁴ The safety of study participants is always critical, regardless of potential consequences for an ongoing trial. However, the EMA also acknowledged the

ethical mandate to proceed with ongoing trials in a secondary setting, so that the efforts by participants and physicians could benefit drug development.

Before release of the EMA document, there was no clear initiative for the continuity of ongoing trials. A case in point involves direct experience by the authors who received a recommendation from a European local agency, acting on behalf of a national ethics committee, to terminate a pivotal phase 3 study. The study had been ongoing for nearly 2 years and was nearing the follow-up phase, yet early termination was recommended rather than applying a number of protective measures for patients and site personnel. The case was closed to mutual agreement between the two parties, and the authority reconsidered its initial viewpoint in line with the applicant’s proposed strategy. However, the issue had remained open for a number of weeks from the date of notification, and it caused considerable confusion to the local stakeholders.

Review of available statistics

To understand the impact of COVID-19 on new research and development (R&D) projects, selected European authorities were contacted to solicit data on the actual submission events performed between 1 March and 30 June 2020.

The data collection period started mid-June 2020 and lasted for 4 weeks. The table below summarizes the outcomes from a sample of countries often selected for clinical trial execution in Europe. Countries are presented in alphabetical order.

TABLE Country-level impact on COVID-19 new research and development projects

Country	Is data on initial and amendment submissions disclosed?	Comments
Bulgaria	No	Lack of readiness to disclose the data on demand. Statistics are to be published under 2020 annual reports at later stage.
Germany	No	Lack of readiness to disclose the data on demand. Statistics are to be published under 2020 annual reports at later stage.
Poland	Yes	General statistics on number of initial and amendment submissions.
Ukraine	No	Formal inquiry with justification required, not executed due to expected turnaround time exceeding the release of the publication.
United Kingdom	Yes	Information published quarterly, limited to first quarter of 2020.

After drawing conclusions from the sampling, competent authorities remained unwilling to disclose the data on demand. Despite certain unfavorable changes

in COVID-19-triggered laws – for example, elimination of the rule of implicit approval within 60 days of submission), the Polish authority was willing to disclose the data. In the period sampled, the Polish authority reported, as follows:

- 154 initial clinical trial application submitted (6 related to COVID-19),
- 1,290 substantial amendments, and
- 157 clinical trials approved.

There had been about 450-500 new filings from the previous year, which suggests the industry remained active and continued to implement new clinical studies, even during the disruption of the pandemic.

Data obtained from the British agency, limited to the first calendar quarter of 2020, makes it more difficult to draw conclusions for the key months of pandemic state. The data for the month of March indicate no early impact. However, the UK increased its pandemic response stringency index slightly later than a number of other European jurisdictions.

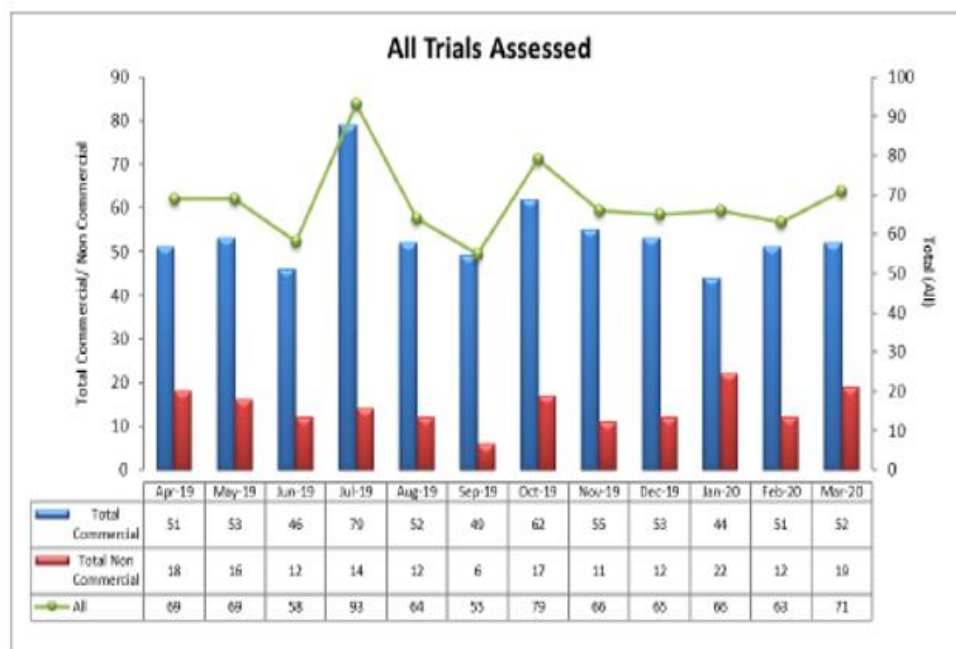


FIGURE Clinical trials for medicines in the UK: Authorization assessment performance

Source: Medicines and Healthcare Products Regulatory Agency⁵

Conclusions

COVID-19 was – and will – remain a major threat for clinical R&D efforts initiated by both commercial and noncommercial sponsors. The first 6 to 12 weeks of the pandemic presented challenges to numerous stakeholders, including the European competent authorities. The adjustments of formal procedures and interactions with scientific reviewers took time. Still, based on the limited data available to the authors, it seems the number of trials

submitted and reviewed over the second quarter of 2020 does not differ substantially from the previous year's statistics. The industry is now awaiting the implementation of EU Clinical Trial Regulation,² which is expected to further harmonize the European R&D space, remove the peculiarities of specific member states, and increase predictability of study initiation.

The restrictions the pandemic brought to critical stakeholders of clinical research will not disappear and may arise again with the occurrence of new waves of COVID-19. The formal elements of clinical trial authorization already seem to be controlled as the authorities and sponsors learn how to adapt. These parties will need to stay connected so that they can exchange information on limitations, discuss solutions and support guidelines which enable studies to go live. Physicians and study participants will remain the most vulnerable stakeholders as their roles cannot be delivered entirely remotely. These limitations will have to be respected by the drug developers, but also considered by regulators who must state realistic expectations for new study design, endpoint selection and associated sample sizes.

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