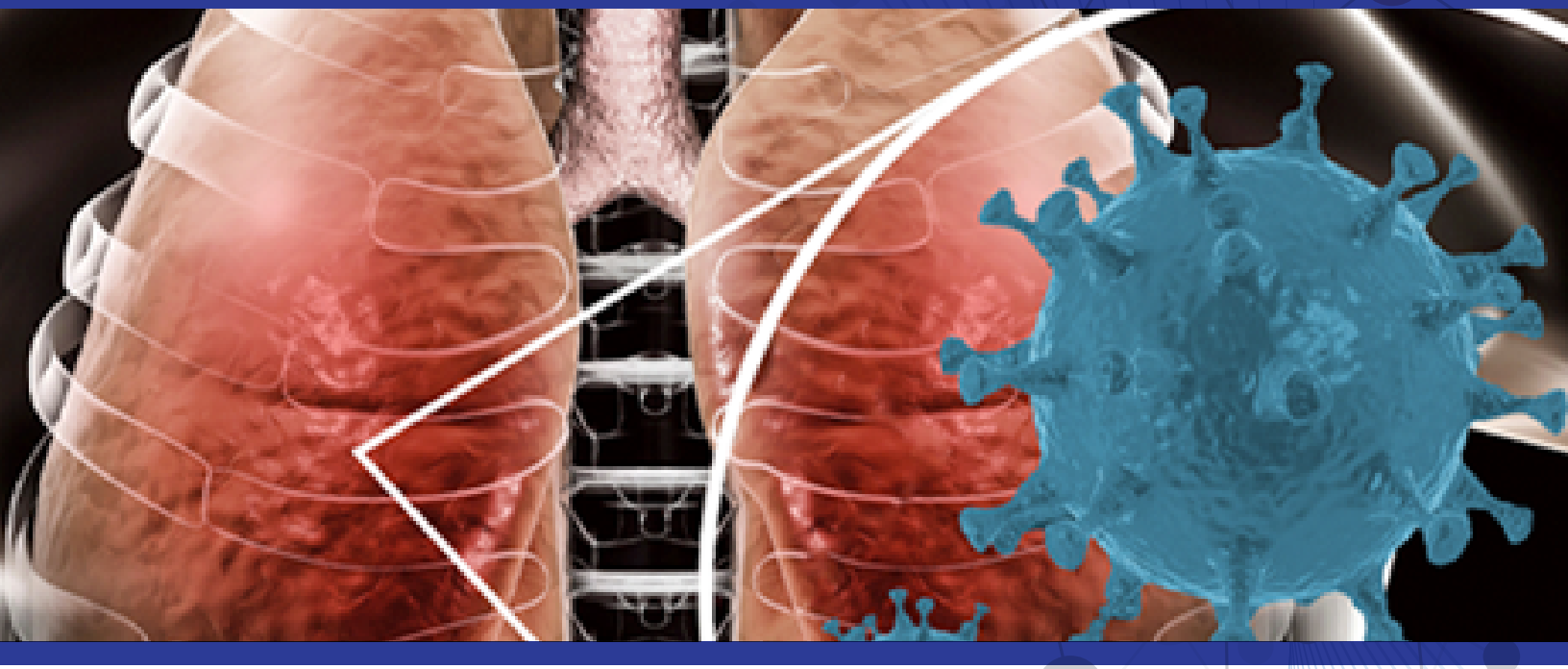
CERTARA

Considerations for Managing Clinical Trials and Regulatory Filing Strategy During COVID-19



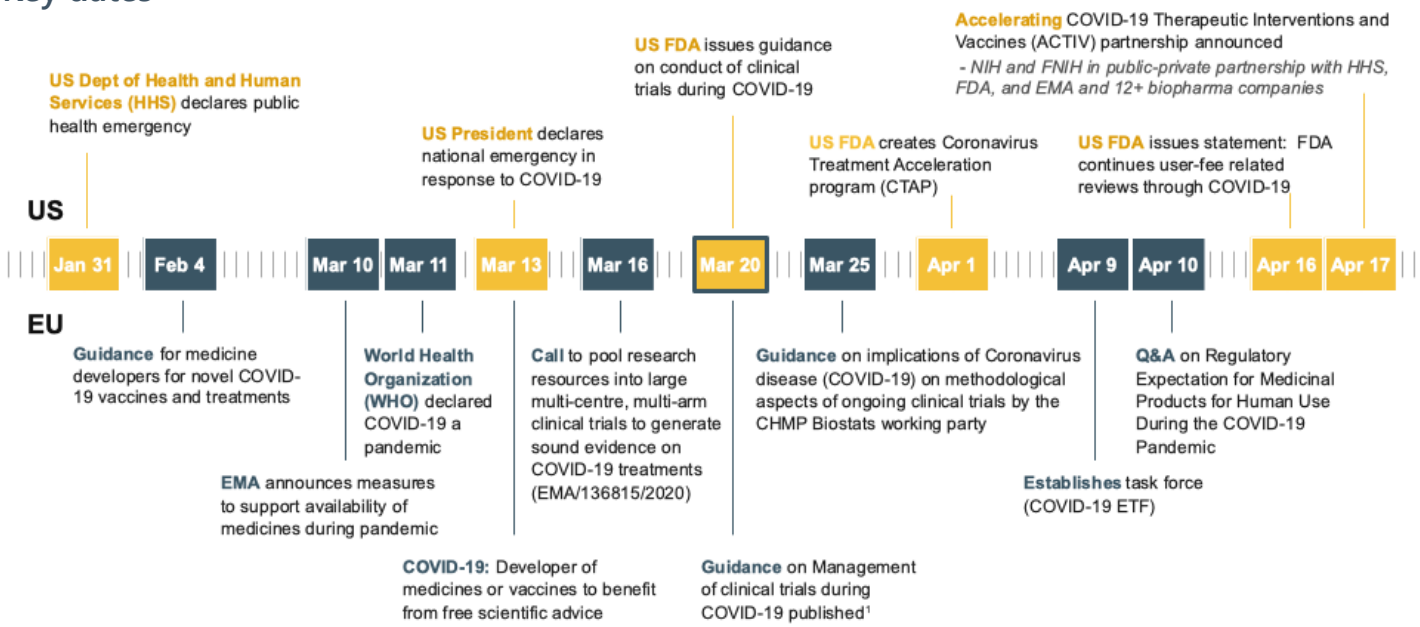
By Elaine B. Taylor
Vice President, Regulatory Strategy and Policy,
Synchrogenix, a Certara company

Mitigate the impact of COVID-19 on your clinical trials and regulatory filing strategy

Regulatory Agencies across the world have quickly responded to the COVID-19 pandemic. Your approach to ongoing and new clinical trials and regulatory filing during COVID-19 requires adaptation and new strategies, such as following recommendations and using the fast-track COVID-19 programs recently instituted by Regulatory Agencies.

In this white paper, we will focus on the reactions and programs put in place by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) and considerations for submissions to these Agencies.

Figure 1. Timeline of COVID-19 Regulatory and Government Responses During First Few Months of COVID-19 Crisis



[1] *This guidance is agreed by the Clinical Trials Expert Group (CTEG) of the European Commission supported by the EMA, the Clinical Trials Facilitation and Coordination Group (CTFG) of the Heads of Medicines Agencies (HMA) and the GCP Inspectors' Working Group coordinated by the EMA*

Other Agencies across the world are also announcing their approach for fast-tracking COVID-19 studies.

Patient safety

As with any clinical trial, the participants' safety is the most important aspect. One way to achieve this is to have an ongoing evaluation of the risks and document your assessment of them. You may postpone starting a trial or continuing a trial based on the risk assessment. However, stopping or delaying some trials may pose a greater risk to patients, for example, studies with life-saving oncology agents. It is very important that you inform your participants of any changes that are made to the clinical trial.

Regulatory recommendations

Both the FDA and EMA have asked sponsors to aggregate submissions. As much as possible, consolidate your protocol modifications into one protocol amendment, to reduce the number of touch points, thus saving valuable regulatory resources. The FDA and EMA have acknowledged that there will be more protocol deviations than normal but try to minimize these deviations.

Deciding to pause patient screening or enrollment will not generally require a protocol amendment if it does not affect the safety, scope, or scientific quality of the study. Due to the COVID-19 crisis, local authorities may require additional procedures. The FDA stated that these additional procedures do not need to be recorded as an amendment unless you are incorporating the data from these procedures as part of your study objectives.

The EMA has stated that, during this time, you should avoid or postpone audits. For COVID-19 trials, the Committee for Medicinal Products in Europe has asked that sponsors pool research resources and conduct large multi-center, multi-arm trials because larger trials are more likely to generate conclusive evidence.

Our advice

Be as unbiased as possible and transparent with the Regulatory Agency. Point out and discuss any issues or concerns, rather than have them come to their own conclusions.

Changes to clinical trials

What are the anticipated changes to clinical trials due to COVID-19? In general, they are the same as always, but there are some exceptions, and the regulatory authorities have provided more explicit directions. Any changes that have been made to eliminate hazards and protect the wellbeing of participants can be implemented prior to the ethics committee and regulatory authority notification. However, you must subsequently report them to the Regulatory Agencies. The FDA will consider changes made prior to approval or submission to be protocol deviations.

Missing information

Missing clinical trial information is an important issue that requires planning. For example, patients may not be able to show up for visits, assessments may not be taken at the planned time points, or patients may drop out of the study. This information must be documented in the case report form (CRF) and in the clinical study report (CSR). You may be unable to complete the number of patients you've planned which may affect the power of the study to demonstrate efficacy or provide sufficient safety information. Prospectively address these issues in the study protocol and statistical analysis plan (SAP). Changes to efficacy and safety assessments, data management, or the SAP should be discussed with the Regulatory Agency prior to database lock.

Clinical study report

The CSR must discuss the impact on efficacy, safety, data management, or changes to the SAP, regarding potential effects to the data, results, or study conclusions. Be as unbiased as possible and transparent with the Regulatory Agency. Point out and discuss any issues or concerns, rather than have them come to their own conclusions.

Fast-track programs for COVID-19

On April 1st, the FDA created the CTAP (Coronavirus Treatment Acceleration Program) to provide fast review of programs and study protocols for drugs and vaccines for the treatment of COVID-19. Under this program, the FDA will triage requests within 24 hours, and in certain cases, review a protocol within 24 hours. These requests are prioritized based on scientific merit and the stage of drug development. As of April 16th, there have been more than 950 requests for CTAP review.

Under the CTAP program, you should submit a pre-IND meeting request and the meeting package. The FDA will review these requests and try to respond within 2 weeks. There are also emergency Investigational New Drugs and expanded use access programs for patients that cannot participate in clinical trials. The FDA may authorize the use of some investigative drugs by telephone, within hours, if needed.

As of April 19th, the CTAP has 72 active trials, with 211 in the planning stage. As of April 24th, 902 COVID-19 studies were registered on clinicaltrials.gov, with 25 completed and 400 actively recruiting.

The EMA COVID-ETF program provides for review of data, identification of promising candidates, engagement with sponsors, and scientific advice to quickly get clinical trials underway. In addition, they will provide feedback when formal scientific advice is not feasible. The EMA also has a Compassionate Use Program for patients who are not eligible for clinical trials. Remdesivir was made available for compassionate use on April 3rd. As of April 24th, 122 COVID-19 research trials were listed in the EU database.

COVID-19 related challenges

- Sponsors are facing interruptions to the clinical supply chain and distribution that may cause further delays.
- Regulatory Agencies may have delayed review and response times.

Impact of COVID-19 on current applications

On April 1st, the FDA announced that it reduced some of their operations, including on-site inspections and some advisory committee meetings. In addition, they canceled or postponed all non-essential meetings. For example, advisory meetings were postponed for Intercept's NASH drug for steatohepatits, GlaxoSmithKline's Trelegy Eliipta for chronic obstructive pulmonary disease, and DBV's peanut allergy patch.

On April 16th, the FDA stated that user-fee funded reviews were on schedule. However, FDA Commissioner Hahn advised that they may not be able to continue at the current pace, considering all the programs that they are reviewing. Currently, it appears that the approvals are on target, but some of our clients' Type B meeting requests have been scheduled 3 or 4 months later than the expected 60-day meeting date.

We expect that the EMA will prioritize their work as they did when they moved from London to Amsterdam. For example, keeping their Marketing Authorisation Applications (MAAs), new indications, and risk assessments at the top of the agenda, while deprioritizing anything less essential. In reaction to the COVID-19 crisis, the EMA is holding all committee and project meetings virtually. In addition, a measure was put into place to provide for continued availability of medicines, and they are allowing more flexibility in product manufacturing and distribution.

On April 10th, European agencies released a Q&A for Expectations for Medicinal Products for Human Use, which provides a lot of information. For example, marketing authorization holders may request a delay for renewing their application, but this request must be made before the deadline. If the Sunset Clause is applicable, it's possible to request an exemption for this. The Sunset Clause is a provision to monitor the marketing status of centrally authorized medicinal products within the European Union and European Economic Area.

Strategies to mitigate impact on trials

Let's start with timelines

For sponsors, there are going to be interruptions to the clinical supply chain and distribution that may cause further delays. There will be potential delays from Regulatory Agencies in review and response times. To plan for these effects, we must be aware of what is happening in the Regulatory Agencies, monitor them for potential delays, prepare for those delays with contingency plans, and identify critical path items.

Triage critical path items to maintain or recover your timeline

- ☐ Work with the data and the information available to accelerate the overall process at the end when that last piece of information is going to come in. In addition, factor in your own staffing limitations that may be affected by upstream delays.

There's also going to be the need for additional documentation

- ☐ Prepare your trials and submission documents that you may need to update due to COVID-19, such as protocol amendments, CSRs, SAPs, planned meeting packages, and marketing applications. In your marketing applications, provide a critical assessment of all study changes. Start drafting documents now to reduce turnaround time later.
- ☐ As suggested by the EMA and FDA, combine protocol amendments and reduce the touch points needed, making sure that your documentation is clear, concise, and accurate, to reduce reviewer questions.

Discuss any study changes with Regulatory Agencies and gain agreement on the actions that you've taken or plan to take

- ☐ Schedule your regularly planned meetings for the particular stages of your product development.
- ☐ Preplan your meeting packages in anticipation of agency discussions. Evaluate the robustness of your clinical data in light of the changes you may have had to make. Prepare a critical assessment of study changes.
- ☐ Submit your requests for meetings earlier than usual to get on the schedule and receive timely responses; and make sure your meeting requests and meeting packages are well written.

These steps will aid in the overall efficiency and success of your program

In this paper, we have covered information up to the end of April 2020. The Agencies continue to provide additional information and updates to their recommendations and guidelines. Please ensure that you stay abreast of this fast moving situation and that you are following the most up to date recommendations.

References

EMA

Links to national recommendations can be found at CTFG website: hma.eu/ctfg.html

- ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials

Clinical Trials guidelines: ec.europa.eu/health/documents/eudralex/vol-10_en

Call to pool resources: ema.europa.eu/en/news/call-pool-research-resources-large-multi-centre-multi-arm-clinical-trials-generate-sound-evidence

Q&A for medicinal products: ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf

Guidance for Voluntary Harmonisation Procedure for multinational CTAs: hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf

COVID-19 vaccine developers: ema.europa.eu/en/news/covid-19-developers-medicines-vaccines-benefit-free-scientific-advice

EMA COVID-19 information: ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19

UK withdrawal: ec.europa.eu/info/sites/info/files/notice_to_stakeholders_medicinal_products.pdf

EU COVID-19 trials: clinicaltrialsregister.eu/ctr-search/search?query=covid-19&page=2

EU treatments and vaccines: ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19#potential-treatments-under-investigation-section

FDA

Questions on clinical trial conduct during the COVID-19 pandemic: fda.gov/media/136238/download

Contact information for FDA's review divisions is as follows:

- CDER: fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder
- CBER: fda.gov/about-fda/fda-organization/center-biologics-evaluation-and-research-cber

FDA COVID-19 hub: covid19.reaganudall.org/covid-19-hub

ACTIV: nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options?utm_campaign=041720_PR_Coronavirus%20%28COVID-19%29%20Update%3A%20Daily%20Roundup%20April%2017%2C%202020&utm_medium=email&utm_source=Eloqua

Drug approvals by month: accessdata.fda.gov/scripts/cder/daf/index.cfm?event=reportsSearch.process

Advisory committee: da.gov/advisory-committees/advisory-committee-calendar

About the Author

Elaine B. Taylor
Vice President, Regulatory Strategy and Policy,
Synchrogenix, a Certara company

Elaine Taylor has more than 30 years of experience in the pharmaceutical industry and has extensive experience developing and providing strategic guidance and regulatory advice at all stages of product development. Currently, Elaine is Vice President of Regulatory Strategy and Policy at Synchrogenix, a Certara company, where she leads the Regulatory Strategy group. Her group provides global regulatory strategy, consulting, and submission support from early stage (preclinical) to post-marketing.

CERTARA

About Certara

Certara optimizes R&D productivity, commercial value and patient outcomes through its unique portfolio of model-informed drug development, regulatory science, and market access solutions. In fact, 90+% of all novel drugs approved by the US FDA in the past six years were supported by Certara software or services. Its clients include 1,600 global biopharmaceutical companies, leading academic institutions, and key regulatory agencies across 60 countries.

For more information, visit **www.certara.com**.