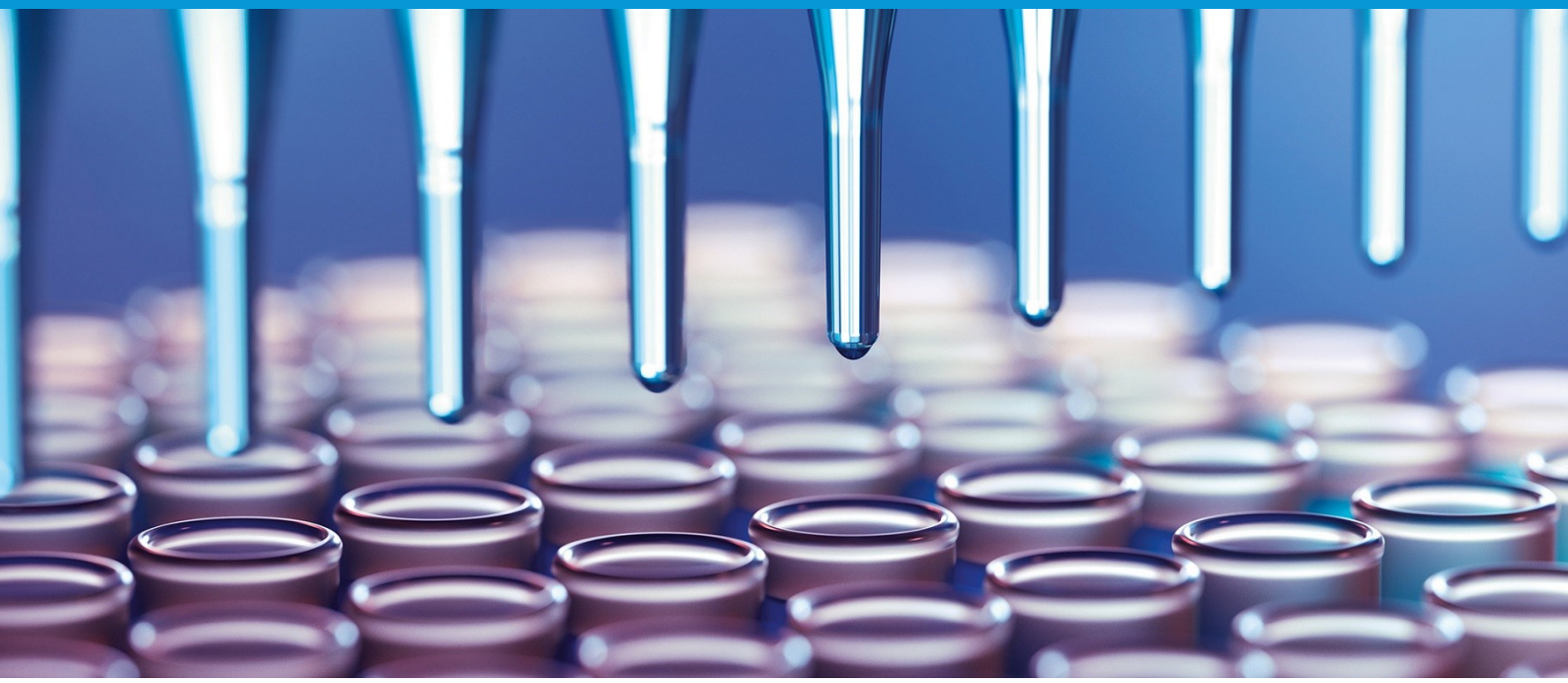
fieldfisher

Clinical trials in the midst of COVID-19

April 2021

Covid-19 – Running clinical trials during a public health crisis



Clinical trials are an essential part of getting therapeutics from lab to patient but during the COVID-19 pandemic, trials for treatments outside of COVID-19 have been heavily disrupted. However, in light of all this immediate disruption there has been speculation that the swift action taken to produce a vaccine could set a positive precedent for the future of clinical trial research.

This paper focuses on how European guidance has been concretely implemented at national level in several key European countries. We address the issues affecting ongoing trials; including data management, compliance with protocols, measures to be taken by sponsors, and the recommendations and regulations imposed by the authorities. We also look at the challenges surrounding the opening of new trials, including trials for COVID-19 treatments and vaccines.

Impact of COVID-19 on ongoing clinical trials

Some of the problems encountered in ongoing clinical trials due to COVID-19 include increased difficulties in patient recruitment, tensions between stakeholders concerning payment (including CRO/sponsor), management of participating patients who test positive for COVID-19, an increase in protocol deviations, compliance with local government regulations related to COVID-19 (e.g. protective measures), and interruptions or terminations of clinical trials.

The response from authorities concerning ongoing clinical trials has been to issue specific recommendations at both the European and national level, with the goal of providing clarity and harmonisation. Regulatory flexibility has been increased although this is not meant to be continued permanently. The driving principle when adjusting the conduct of clinical trials is the implementation of a proportionate response, based on a risk-benefit assessment, where patient safety is always the first priority.

The pandemic has also led to the increased use of digital technologies, which can be used to meet reporting requirements.

Covid-19 – Running clinical trials during a public health crisis

European guidance issued by the European Medicines Agency ("**EMA**"), the Heads of Medicines Agency ("**HMA**") and the European Commission[1] has allowed sponsors to take relaxed measures to adapt the conduct of ongoing clinical trials to overcome Coronavirus-related challenges without always having to notify or request authorisation from competent authorities.

As an overarching principle, sponsors should always strive to ensure compliance with the protocol to the highest level possible when setting up exceptional measures. All changes must:

- be documented (CT and on-site record) and justified;
- take into account the best interest of patients and sites; and
- be proportionate.

Such measures can also be taken by the investigator of a site after discussion with the sponsor.

Exceptional measures include:

- **At trial level** extension of the trial duration, temporary cessation of the clinical trial or the slowing or stopping of patient enrolment. For multi-centre trials, it is possible to replace temporarily the principal investigator (all permanent changes must be notified to the competent authority);
- **At site level** possibilities include closure of sites (without compromising patient rights and safety) or postponement of site activation.
- **At patient level** measures include the transfer of participants to existing or new sites that are less exposed or closer to home, performance of critical testing (necessary to ensure patient safety and trial integrity) at local laboratories or health centres, and patient visits being done through phone or video unless absolutely necessary that they be carried out in person. In particular, when transferring a patient to another site, it is necessary (i) to provide justification for each transferred participant, (ii) to collect consent from both the patient and the investigator, and (iii) to ensure the transfer of data collected so far (including medical records) to the new site. If patients are transferred to a new site, it is considered as an urgent safety measure, which must therefore be followed by the submission of a substantial amendment to competent authorities

[1] EMA/HMA/EC, Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic, last updated on 4 February 2021; EMA, Points to consider on implications of coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, 26 June 2020.

Covid-19 – Running clinical trials during a public health crisis

Dialogue with authorities

Communication with the authorities is another important aspect to consider with respect to ongoing clinical trials during pandemic. As a reminder, under EU law, only substantial amendments to the protocol or clinical trial dossier need to be submitted to competent authorities for validation.

A substantial amendment should be submitted to competent authorities where there is a potential impact on the safety, physical or mental integrity of the participant, or the scientific value of the clinical trial. This should be assessed by the sponsor and if the amendment is not substantial, internal documentation remains required.

Three types of situations can be distinguished:

- **Situations requiring urgent action** by the sponsor or investigator to protect the participants: in such cases, there would be no need for a prior notification. However, documentation justifying the urgent intervention is required, and competent authorities should be notified as soon as possible. This would be the case when there is an IMP shortage for instance;
- **Substantial amendments not requiring an immediate action** by the sponsor or investigator: prior submission of the amendments to the relevant local authorities is then required (e.g. when distribution of medicines to patients' homes is envisaged);
- **Other changes** (e.g. procedural or non-patient safety related amendments) should be notified to competent authorities, along with relevant information such as the risk assessment carried out by the sponsor, justification, corrective measures implemented – if any.

As regards to changes made to the informed consent forms ("**ICF**"), they usually will require prior authorisation from competent authorities prior to any change (except when the change results from the implementation of an urgent safety measure). If urgent safety measures implemented require that new consent be collected, sponsors can use a variety of means to do so (such as the use of videoconference tools along with an email confirmation).

Finally, under European guidance, any deviation must be handled by the sponsor according to standard operating procedures in place. In all cases, sponsors must (i) check whether the deviation envisaged would lead to an amendment of protocol (in which case competent authorities will have to be notified), and (ii) perform a risk assessment of all deviations, and report them in the clinical study report.

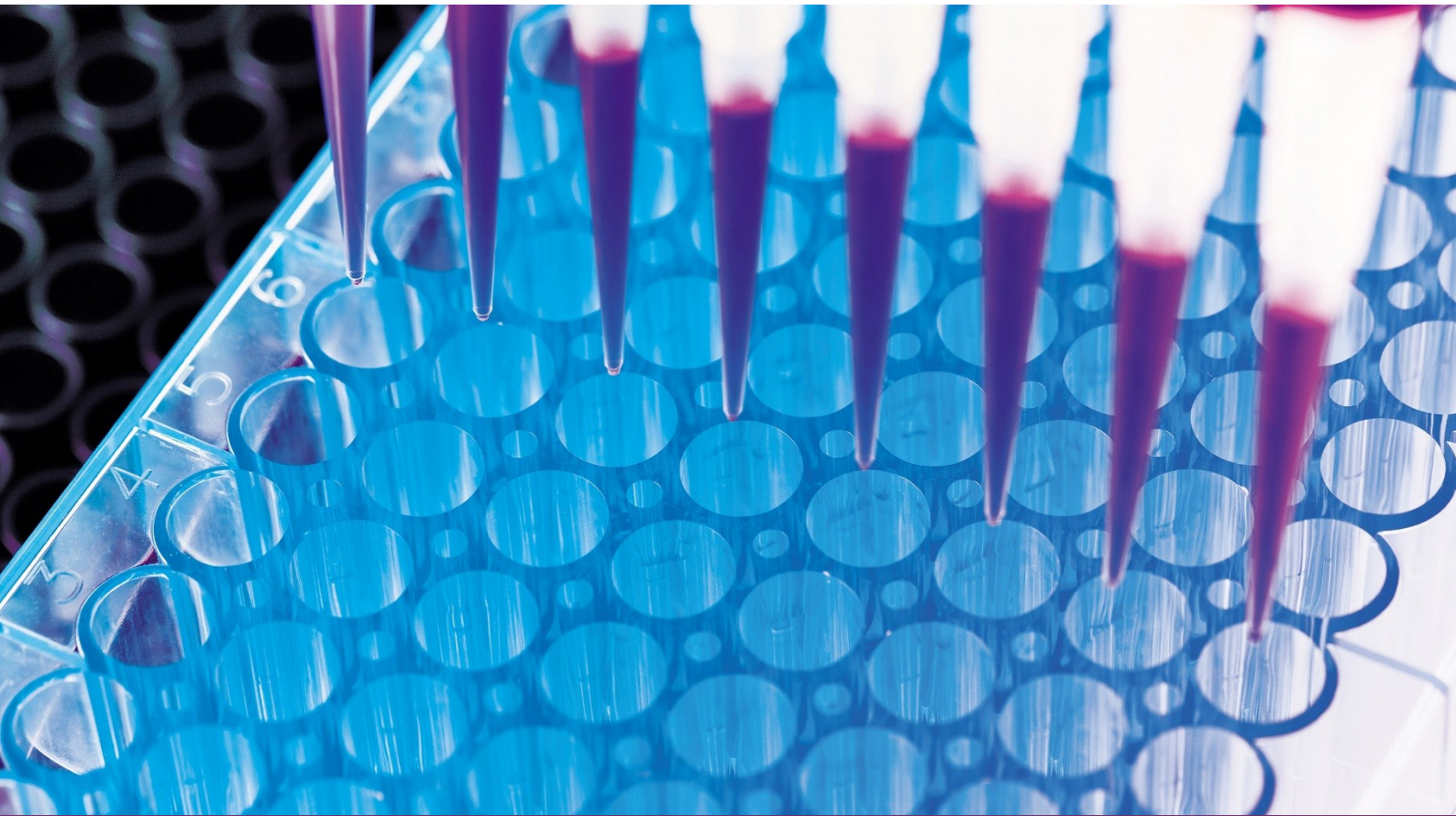
Covid-19 – Running clinical trials during a public health crisis

Distribution of investigational medicinal product

As regards investigational medicinal products ("**IMP**") as well as other medicines and medical devices distributed to patients during the course of a clinical trial, the public health crisis has led to the reorganisation of distribution, to ensure continuity of care for participants – especially when they could no longer travel to the site to pick up their IMP.

The European guidance allows such reorganisation, so long as it takes into account product specificities (e.g. storage conditions). Several ways of reorganising supply to patients has been foreseen:

- Distribution of more doses to the participant
- Redistribution of the IMP between sites (e.g., if patients are transferred), in which case sponsors must set up a written procedure and specific documentation on the transfer;
- Distribution of products to the patient's home: if that is the case, European guidance has highlighted the fact that several measures must be implemented to ensure a delivery in conditions guaranteeing product integrity and traceability. For instance, training actions should be developed if necessary; delivery should be carried out from the site to the patient's home, at the expense of the sponsor, and through dedicated delivery services (allowing for a direct delivery to the patient's hands).



Covid-19 – Running clinical trials during a public health crisis

Monitoring and audit

Monitoring and quality assurance plans for ongoing trials have had to be adapted as well, due to COVID-19, to avoid on-site visits when possible. In such cases, European guidance recommends that a risk-based approach be implemented, always to ensure the rights, safety and well-being of participants, with adequate documentation of changes (e.g. in monitoring reports), and planning of follow-up actions for when the situation returns to normal (e.g. more frequent on-site visits).

Possible modifications concerning monitoring and auditing actions may include:

- Cancellation of, postponement of or extension of time between on-site. On-site visits which are maintained must comply with applicable local regulations ;
- Use of centralized data monitoring and review (on a temporary basis only);
- Off-site monitoring (e.g. use of calls, video visits, online tools for information exchange with site staff);
- Remote source data verification ("**rSDV**"), to be done only if absolutely necessary and permitted by local law, with a focus on quality control of critical data.

As regards data management, the objective remains to guarantee the quality of the data collected as far as possible. In order to do so, European guidance recommends that context-related systemic deviations be anticipated to the extent possible, to allow evaluation of the impact of the epidemic on the outcomes of the clinical trial. In order to do so, sponsors can implement a log of local measures taken, which could be used later on as a "reading tool" for data collected, to explain potential discrepancies.

Sponsors should also carry out a risk assessment of the impact of COVID-19 on data integrity and interpretability (through blind assessment of data). Based on the results obtained, some measures may have to be implemented, such as the taking into account of identified potential biases, the adjustment of population size, the implementation of recommendations on stopping, interrupting or restarting the trial, or that of actions to be taken when the situation returns to normal.

Clarifications on use of remote source data verification

The EMA, HMA and European Commission very recently updated their guidance, to include further specifications as to when rSDV can and should be used.

Initially, under European guidance, rSDV could be used only (i) for trials on treatment or prevention of COVID-19, or (ii) for trials on serious diseases without no satisfactory treatment option. However, as the pandemic has continued over time, the EMA, HMA and European Commission updated their guidance to expand the scope of use of rSDV – which can only be used as long as the COVID-19 pandemic lasts.

Under the updated guidance, rSDV can now also be used (iii) in pivotal trials, (iv) in trials involving patients who are vulnerable or unable to give their consent (e.g. children), and (v) in trials where the lack of source data verification could threaten patients' safety or the reliability and integrity of results, in addition to the two situations in initially provided for.

The updated guidance also reminds sponsors that rSDV can only be setup with the investigator's agreement and if adequate data protection is ensured when using this method.

Covid-19 – Running clinical trials during a public health crisis

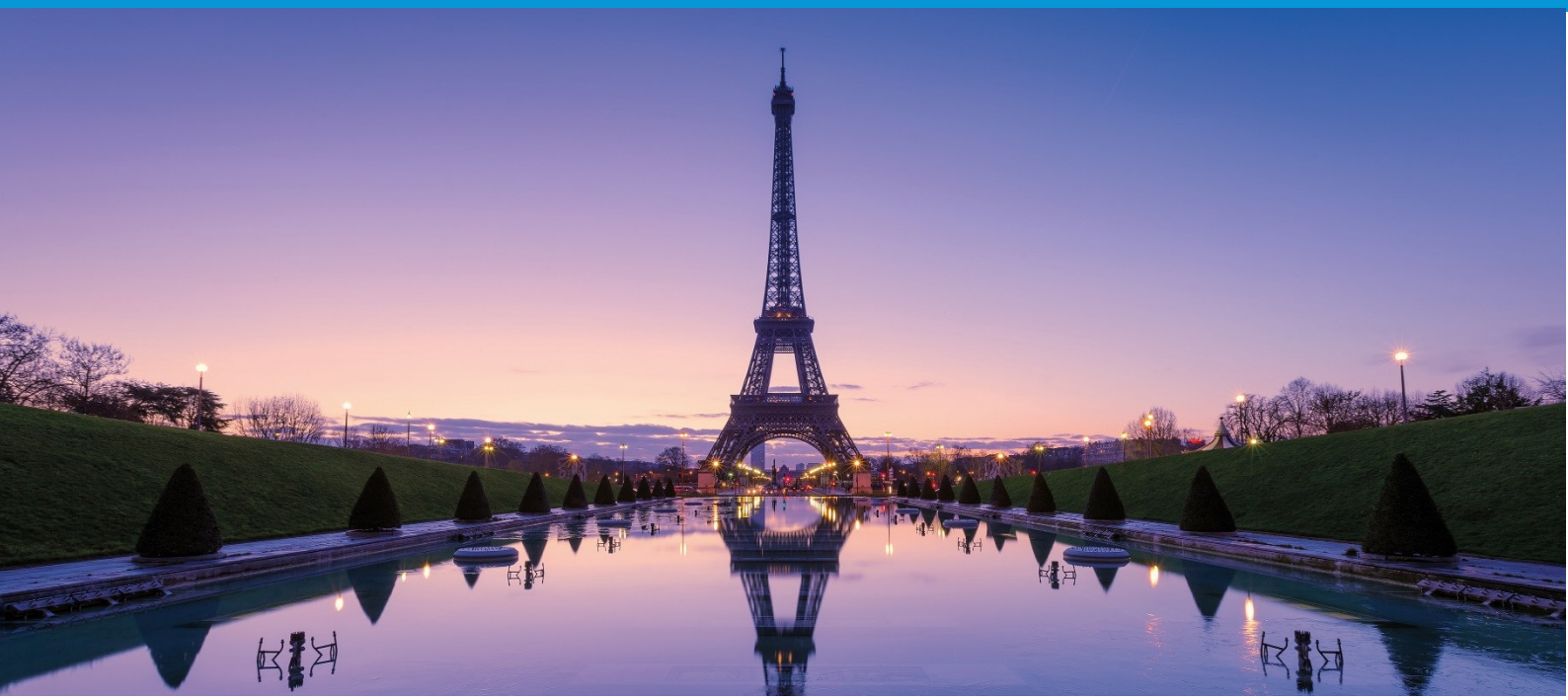
What about new clinical trials?

Under European guidance, it is still possible to open new clinical trials. However, these new trials should only be initiated if the sponsor has deemed it feasible, and if there is a need for the trial to be completed as soon as possible. Additional risks related to COVID-19 must of course be taken into account for participating patients (benefit/risk section of the protocol)

Most competent authorities, in line with European guidance, have announced they would give priority to trials on treatment or prevention of COVID-19, or on serious diseases without satisfactory treatment options (unmet medical needs). It is true for example in France where the Ministry of Health has put pressure on Ethics Committees to deal quickly with COVID-19 trials what they have done.

In order to facilitate the launch of clinical trials relating to COVID-19, authorities have allowed enhanced communication with them, as well as expedited authorisation procedures for initial assessment of authorisation requests. Regulatory flexibility with regards the collection of patients' consent has also been allowed (e.g. oral consent with a witness, electronic signature, etc.).

Country focus



France

On 22 April 2021, the French Data Protection Authority (CNIL) issued temporary recommendations for the remote monitoring of clinical trials during the Covid-19 pandemic.

In some cases, onsite monitoring activities are rendered impossible by the pandemic, these activities can now be carried out remotely.

Under European guidance, it's possible to implement remove source data verification, in specific cases and only if adequate measures are taken to ensure the protection of personal data. The CNIL has specified that the implementation of source data verification does not require a request for authorisation from the CNIL, to the extent:

(i) its implementation is the only deviation from the guidelines applicable to the processing of personal data in the clinical trial (méthodologie de référence).

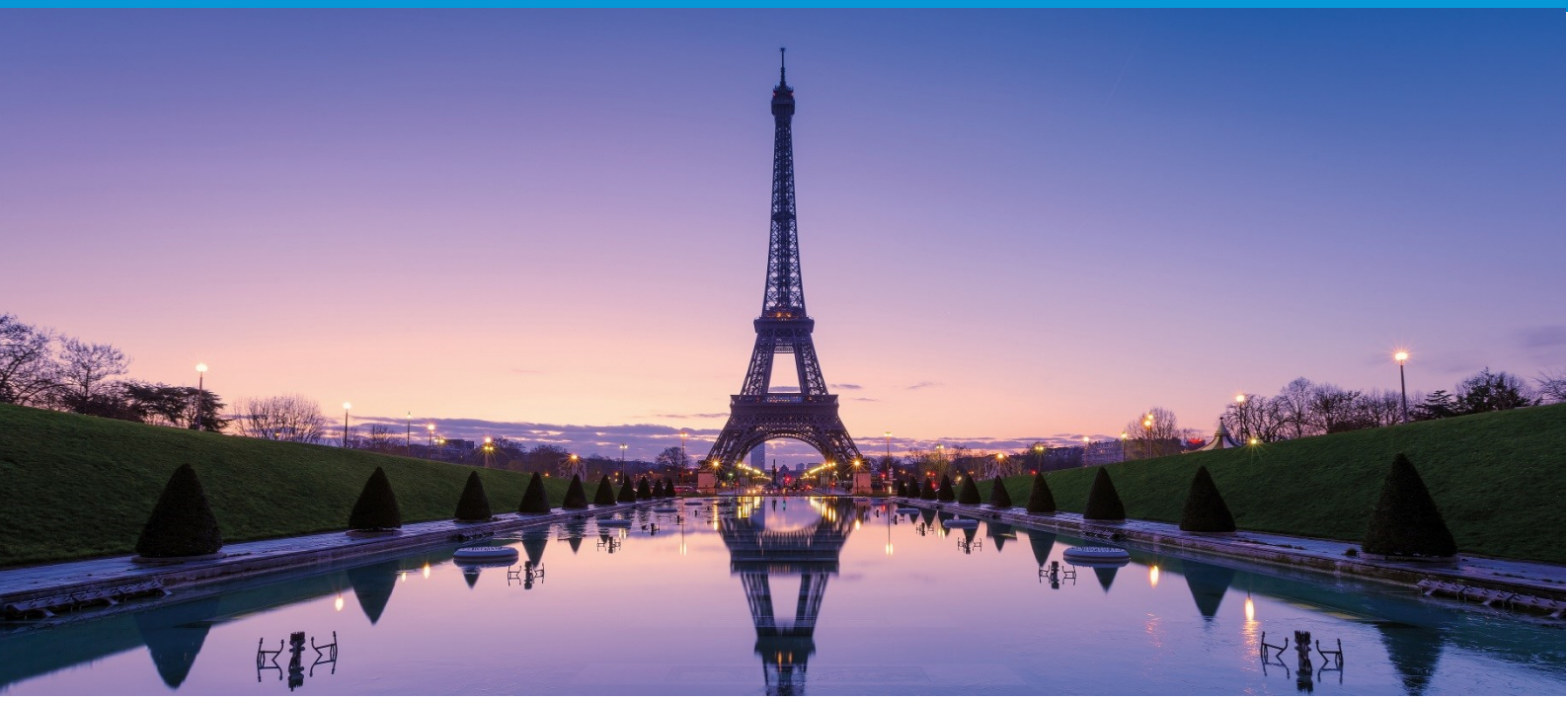
(ii) compliant with the safety measures described in the recommendation is ensured. Such safety measures include; informing concerned persons of the implementation of this measure through the ICF (which should be updated where necessary); consulting with the sponsor's and the site's DPO, who must be enabled to check the detailed specifications of the measure envisaged, and the implementation of an additional confidentiality agreement with the monitors, which covers the use of remote tools.

Additional specifications are included, depending on the way remote monitoring is implemented (i.e. monitoring through videoconference tools, use of secure platforms for the transfer of data, direct remote access from the monitor to medical records).

These measures, should they be implemented, can only last until the end of the pandemic, and if onsite monitoring is absolutely impossible.

The National Agency for Medicines and Healthcare Products safety (ANSM) issued guidance in line with European recommendations, giving sponsors the ability to implement temporary measures. During the summer

Country focus Continued



France

of 2020, the public health situation was deemed satisfactory enough that such temporary measures could be suspended and "normal" activities could resume where possible, as of 10 August 2020.

When clinical trials had been interrupted, they were encouraged to resume, so long as it did not affect patient safety. If the protocol had to be amended in order for the trial to resume, the ANSM and the competent ethics committee (CPP) were to be informed of such amendment.

Sponsors which have taken temporary measures and wish to revoke them must inform the relevant CPP as well as the ANSM that the trial is resuming according to the last approved version of the protocol. If, however, the sponsor wants to make the temporary measures permanent, submission of a substantial amendment is required.

Finally, it remains possible for sponsors to "reactivate" relaxed measures which had already been taken since the beginning of the pandemic. If that is the case, the

Country focus Continued

Germany

In Germany, the BfArM (national competent authority) indicated that they would exempt entities from paying fees when requesting its counsel for questions in relation to COVID-19, or when making an application to initiate a clinical trial for treatment or prevention of COVID-19.

Country focus Continued

Italy

In Italy, the AIFA (national competent authority) issued guidance on how to deal with the impact of COVID-19 on ongoing clinical trials, as the closure of experimental centres for lockdown measures implies the need to assess whether it is feasible to guarantee the continuity of the trial, with the possibility, alternatively, of suspending the study or transferring patients to the nearest centre.

In particular, the AIFA communication invites sponsors to:

- draw up a risk assessment plan; and
- implement an action plan taking into account the need to reduce unnecessary contacts in the face of the epidemic.

A first evaluation concerns the monitoring visits. In this case, the sponsor should evaluate:

- whether *in situ* (on site) monitoring visits could be replaced by enhanced centralised monitoring, or
- if such local visits can be postponed.

The choice to centralize the monitoring can be supported by exceptional modalities such as telephone contacts or videoconferences with the staff of the experimental site aimed at source data verification.

The sponsor or the CRO must describe these modalities in a Standard Operating Procedure to be submitted for approval to the DPO of the test facility.

Any alternative methods of data processing that involve a higher risk, especially for particular patient data, must always be agreed with the DPO of the hospital. This includes, for example, video recording of source documents or making the original documents available to monitors in shared electronic areas.

The AIFA communication also recalls the opportunity to obtain on this point a "specific opinion of the Guarantor", with probable reference to the prior consultation as per art. 36 of EU Regulation 679/2016, as a result of the preparation of a data protection impact assessment.

Country focus

Spain

In Spain, the Spanish Agency of Medicines and Medical Devices (AEMPS) issued a Note on 16 March 2020 accepting that Sponsors adopt the following relaxed measures without the previous approval from the AEMPS (in line with European guidance):

- Possible postponement of on-site visits (phone calls can be organised instead);
- Interruption of recruiting of new patients to avoid unnecessary risks;
- Possible provision of the medicinal product in larger quantities, or delivery of the medicine at the patient's home;
- Possibility to have the informed consent given orally, preferably in front of a witness, documented in the patient's clinical documentation and ratified in writing;
- Set-up of centralized and remote monitoring visits;
- Possibility to transfer patients to different sites, as long as there is an agreement between the centres and there is an appropriate transfer of the patient's documentation.

If any of the measures described above were taken, the sponsor had to document them and inform the AEMPS within 4 months after the state of emergency finished in Spain (21 June 2020).

If any of these measures are taken currently (after the state of emergency has finished), the sponsor must notify the AEMPS and CEIm (national Ethics Committee on investigations on medicines) in a complementary report.

Country focus Continued

Netherlands

In the Netherlands, the Central Committee on Research involving Human Subjects (CCMO) formulated several recommendations on her website in addition to the European guidance discussed above, indicated that for some measures taken, investigators and sponsors had to inform the review committee (CCMO or MREC/IEC):

- HYCI emphasized that national legislation (like the WMO and Medicines Act) sometimes prevails over the European Guidance. Points to be considered are related to situations such as not complying with the study protocol, the informed consent process, the protection of personal privacy as a result of replacing physical visits by telephone, email and/or app.
- HYCI highlighted the fact that the development safety update report might be at risk to be incomplete;
- It gave the possibility for trial subjects to receive their medicine directly form the (hospital) pharmacy.
- HYCI indicated that they expected investigators and sponsors would take good notice of the Guidance and any deviation in procedures related to the clinical trial due to the COVID-19 pandemic would be documented adequately. A proportionate approach would be taken by the GCP inspectors when such deviations are reviewed during inspections.

Country focus Continued

United Kingdom

In the UK, the National Health Institute (NHS) and National Institute for Health and Research (NIHR) paused some non-COVID-19 research for nationally prioritised COVID-19 studies. The NIHR then issued guidance in May 2020, on how to restart trials which had been paused due to COVID-19 . A set of conditions had to have been met in order for the trial to restart, relating to the following matters:

- Study viability
- Safety of research participants and personnel
- Capacity and site readiness
- Prioritisation on the basis of 'study urgency'
- Local level roles

Country focus Continued

The future of clinical trials across Europe

Progress is being made to restart clinical trials that were paused or delayed due to the pandemic. Most of the issues that caused delays to trials were due to patient enrolment issues and availability of test sites, due to having to prioritise the pandemic. However, for those trials that were able to continue, we saw how technology was revolutionary in allowing them to progress. The use of digital technology, such as wearables, virtual inspections and apps meant that players involved from sponsors and clinicians to regulators were forced to embrace technology[2]. But will this become the norm? Regulators across Europe have announced that they hope to return to *normal* from mid to late 2021 and also the Clinical Trial Regulation issued in 2014 is about to be enforced, despite the fact that it does not take into account the possibility of the brand new technology tools in the context of clinical trials, in particular during pandemics

Thus, it shows that there will still be a journey ahead for pharmaceutical companies and other businesses involved in the process to get technology firmly embedded into the clinical trials process.

[2] 2020https://www.iconplc.com/insights/blog/2020/08/05/post-pandemic-clinical-tr/ .

Contacts

Olivier Lantrès
Partner, Co-Head of Life Sciences & Healthcare, Regulatory, France
+33 (0)1 70 37 81 00
olivier.lantres@fieldfisher.com

Alexandra Lauré
Associate, Life Sciences, Regulatory France
+33 (0)1 70 37 81 49
alexandra.laure@fieldfisher.com

Héctor Jausàs
Partner, Life Sciences, Regulatory Spain
+34 (0)934 150 088
hector.jausas@fieldfisher.com

Cord Wilhoeft
Partner, Life Sciences, Regulatory Germany
+49 (0)89 620 306 245
cord.willhoeft@fieldfisher.com

Pierpaolo Maio
Partner, Life Sciences, Privacy Italy
+39 (0)51 997 11
pierpaolo.maio@fieldfisher.com

Cliodhna McDonough-Stevens
Director, Life Sciences, Regulatory United Kingdom/ Ireland
+44 (0)207 861 4330
cliodhna.mcdonough@fieldfisher.com

Claudio Mereu
Partner, Life Sciences Belgium
+32 27 427 060
claudio.mereu@fieldfisher.com

Tim Van Canneyt
Partner, Life Sciences, Privacy Belgium
+32 27 427 036
tim.vancanneyt@fieldfisher.com

Marcel Willems
Partner, Life Sciences, Restructuring and Insolvency, Netherlands
+31 20 225 2215
marcel.willems@fieldfisher.com

Stefanie Greifeneder
Partner, Life Sciences, Commercial IP Germany
+49 (0)89 620 306 221
stefanie.greifeneder@fieldfisher.com

Janita Good
Partner, Co-Head of Life Sciences, Corporate, United Kingdom
+(0)207 861 4615
janita.good@fieldfisher.com

JP McDowell
Managing Partner, Public & Regulatory Ireland
+353 (0)1 828 0630
jp.mcdowell@fieldfisher.com

fieldfisher