COVID 19 - Ongoing clinical trials - FAQ

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The COVID-19 pandemic led to the establishment in March 2020 of national guidelines for the conduct of clinical trials. The ANSM, in coordination with the French Ministry of Health, proposes practical solutions for implementing the necessary adaptations for ongoing clinical trials in the current situation.
The French national recommendations are in line with the European guidelines established collectively and published by the European Commission

Updates have been proposed according to the evolution of the epidemic context. In particular, the resumption of inclusions may be considered in interrupted clinical trials, while respecting measures to protect research participants and caregivers. However, transitional measures may still be necessary, considering that the health crisis has not been resolved and that the need for adaptation may vary according to the research sites. The criteria for the end of a health crisis are not yet precisely defined. In the meantime, the sponsor, in coordination with the investigators , has to evaluate and justify the continuation of any transitory measures for each trial concerned, taking into account the safety of human subjects and the integrity of the trial data, with priority given to the safety of human subjects. This assessment should be made available upon request to the authorities.

In a context of exceptional measures, it remains essential to ensure that good practices are respected. The importance of optimal traceability of possible protocol deviations induced by the epidemic context and of the adaptations put in place should be particularly emphasized. The documents exchanged between the sponsor and the authorities (ANSM and EC) should also be kept in the master file of the clinical trial and at each research site.

Modifications related to the COVID-19 pandemic that have a significant impact on the protection and safety of persons such as those described in the ANSM recommendations (in particular stopping or suspending experimental treatments, delivery of treatments in the patient's home, amendments to the monitoring arrangements) may have been put in place as urgent safety measures (USM) notified for information to ANSM and the concerned EC. The USM must be followed by the submission of substantial amendment for authorisation (SA-M) to ANSM and/or concerned EC within 15 days of the implementation of these measures (article R. 1123-62 du code de la santé publique).

- Amendments dealing of transitory modifications during the epidemic period should preferably be submitted as an addendum to the Protocol, accompanied by the SM application form.

- Modifications that are likely to become permanent will be incorporated into an amended version of the protocol, together with the other documents of the SM application file, and the complete dossier will be evaluated accordingly.

- If the modifications implemented as part of an USM do not need to be maintained, the trial can then be conducted according to the last authorised version of the protocol, before

implementation of transitory measures related to the epidemic context, the sponsor may notify the revocation by simple notification (SM-I).

1. **Suspension/resumption**
2. **Follow-up visits**
3. **Delivery of investigational products**
4. **Monitoring**
5. **Infection during trial**
6. **Safety reporting**

SM-A: Substantial modification for authorisation (MSA modification substantielle pour autorisation)
SM-I: Substantial modification for information ie notification (MSI: modification substantielle pour information)
USM: Urgent Safety Measure
EC: Ethics Committee

1 / Suspension/resumption

Can a trial be suspended due to the COVID-19 pandemic?

A decision to suspend inclusions may be still justified by the context of the study and/or the unavailability of teams (sponsor or investigators).

The continuation or not of ongoing treatments must be specified and justified. A decision to discontinue ongoing treatments must be evaluated according to the clinical context of each patient and associated risks.

- **In case of suspension of inclusions:** inform the EC and the ANSM (SM-I)
- **In case of discontinuation of experimental treatments:** inform the ANSM and the CPP with an USM followed in a second step by a SM-A

How to organize the resumption of inclusions in a trial suspended due to the COVID-19 pandemic?

The resumption of clinical trials must always be assessed in light of the medical need of research participants and the potential risks inherent in the COVID-19 epidemic. In all cases, the sponsor must take full responsibility for ensuring that it has full and complete capacity to monitor and follow up these trials in conjunction with the investigators and hospital teams.

- This evaluation must be carried out taking into account the possible specificities of the research sites, both in terms of the local epidemic context and the availability of personnel.
- A notification to EC and ANSM (SM-I) allows resumption of inclusions in trials suspended due to the COVID-19 pandemic. The sponsor has to certify that it will resume the inclusions under the conditions prior to the transitional measures put in place due to the epidemic context.

How can the transitional measures put in place due to the COVID-19 context be revoked?

In case of a return to the pre-existing conditions under which the research was conducted (ie according to the latest version of the protocol authorised before the transitional measures related to the epidemic context):

- notification to EC and ANSM (SM-I). The sponsor has to certify that the trial is continuing in accordance with the version of the protocol authorised before the transitional measures are put in place.

A resumption of inclusions with an amended protocol is subject to authorization (SM-A).

2/ Follow-up visits

Can adaptations for patient follow-up visits be maintained?

The collection of information by teleconsultation is still possible on an exceptional basis, with a focus on safety data and primary objective endpoints.
Any data that cannot be assessed remotely will be noted as missing.
The failure to complete a protocol visit will not be considered as a reason for study discontinuation and, beyond the necessary documentation, will not be considered as a major deviation that must be notified to the ANSM according to GCP § 5.20.
Deviations shall nevertheless be reported and evaluated in the final study report (see ICH guideline E3).

- Document any protocol deviations for subsequent analyses.
- Adaptation of follow-up visits and the use of teleconsultation are options to be considered on a case-by-case basis, depending on the clinical situation and the local epidemic context
- Modification of the schedule of protocol visits and/or follow-up criteria for all trial. patients is considered a substantial amendment to be submitted for authorisation (SM-A).

Is the delivery of investigational products for longer durations still allowed?

Yes in compliance with safety instructions, patient information and traceability.

If visits during which the investigational medicinal products or devices should have been delivered to patients are skipped, arrangements must be made to assess the tolerability of the treatment and to adjust the treatment if necessary, for example by teleconsultation.

➦ Notification to ANSM (SM-I) including additional measures on follow-up.

Caution : narcotic products are excluded from this measure.

Is the delivery of investigational products to the patient's home still allowed?

Yes in compliance with all safety instructions, patient information, traceability and the sponsor's instructions, established if necessary in conjunction with the manufacturer, in agreement with the research site.

The adequacy of the arrangements put in place as a result of the pandemic should be assessed by the sponsor on a case-by-case basis. Their continuation must be justified and the reasons must be made available to the authorities.

- USM then SM-A specifying the conditions for delivery, monitoring and information of participants.
- The delivery of the products necessary for the research to the patient remains the responsibility of the investigator and, if available at the research site, of the site's pharmacy.
- The sponsor provides the research site with logistical support for the transport of the products necessary for the research to the patient. If requested by the research site/pharmacy, the sponsor provides the packaging and labels. In all cases, the promoter finances the transport.
- Industrial sponsors will simplify as much as possible their procedures for transporting the products needed for the research. The solutions chosen, including financial support, must limit as much as possible any additional workload for the research site and pharmacy; it must take into account the situation of each research site.

For more details on the requirements to be met and the possible circuits, see the complementary document drawn up by ANSM / DGS / CNRIPH / CNIL (in French)

These recommendations do not apply to the implementation of home delivery of non-self-administered investigational drugs. If exceptionally such modalities should be considered, it is requested to submit a SM-A to the ANSM to ensure that all safety conditions are met for parenteral administration in the patient's home.

4/ Monitoring

What are the recommended procedures for monitoring clinical trials?

Sponsors are invited to take into consideration the European guidance.
The modalities of their application in France are currently being discussed with the various stakeholders, in particular the CNIL, and will be specified in a forthcoming update.
Sending copies of medical records, even pseudonymised, is not authorized.

The sponsor is encouraged to contact the investigators in order to adapt to the constraints of each trial site.

5/ Infection during the trial

What should be done if a patient included in a trial and under treatment becomes infected with SARS-CoV-2?

The continuation or suspension of investigational products should be evaluated by the investigator in liaison with the sponsor based on the clinical context.

Testing strategy for clinical trials patients have to be in line with national recommendations.

- Documentation on file
- COVID-19 infection should not be declared as a new event except in the case of specific measures taken by the sponsor.

However, if this event corresponds to the definition of SUSAR, that is suspicion of an unexpected serious adverse effect, or of a serious adverse event that may be linked to the act of implementing the medical device, it should be declared to the ANSM according to the current requirements.

6/ Safety reporting

Should the investigator report serious adverse events to the sponsor?

Yes
The investigator must immediately report serious adverse events to the sponsor according to the current regulation except those mentioned in the protocol or in the brochure for the investigator as not requiring immediate notification.

If the sponsor is unable to assess the events declared, may he postpone his declaration to SUSARs?

No
The sponsor is requested to continue to declare the SUSARs as well as all the immediate vigilance notifications in accordance with the French regulation in force.

- For the notifications rules, please refer to the current explanatory note available on ANSM website *Déclaration - Evènements et effets indésirables graves, faits nouveaux avec ou sans mesures urgentes de sécurité, rapport annuel de sécurité - ANSM : Agence nationale de sécurité du médicament et des produits de santé* Add the term “COVID-19" a the beginning of notifications naming for trials related to the management of the pandemic COVID-19 (see examples below)

Can confirmed cases of COVID 19 be considered "expected" if viral infections are described in the Reference Safety Information (RSI) of the investigational medicinal products?

No
The expected serious undesirable effects mentioned in the RSI should correspond to a specific preferential term (PT) of the MedDRA classification in force.

Is it possible to submit annual safety reports (ASR/DSUR) without a handwritten signature?

Yes

It is possible to send annual safety reports (also named DSUR for drugs) with a scanned signature or a simple mention in the email specifying the name of the person who validated the document.

May the deadline for submitting annual safety report (ASR) be extended?

Yes

A maximum period of 2 additional months may be granted after informing the ANSM by email on its usual mail boxes. Note that the sponsor already has 2 months to submit the report after the end of the period covered by the ASR .

May the meetings of the safety committees be postponed due to the lack of monitoring and / or the non-availability of members?

Yes

If it is impossible to set up the planned meetings of the safety committee, the sponsor may consider postponing after assessing the consequences for the safety of participants. As appropriate, the sponsor may also take measures, for example the suspension of inclusions pending the next meeting.

Documentation

- Postponement decision : communication to the members of the supervisory committee and to the investigators as well as to the ANSM and the CPP (substantial amendment for information)
- Other measures: documentation and transmission to the ANSM and the CPP according to their nature as previously detailed : i.e. substantial amendment for information in case of suspension of inclusions and substantial amendment for authorization if urgent safety measures are taken.

Submission to ANSM for adaptation in ongoing trials when related to COVID-19

National recommendation are available on ANSM website

Sponsors are encouraged to present modifications put in place specifically and temporarily for the pandemic period as an addendum.
A modified version of the protocol is not required.

➦ Substantial Modification and notification

- e-mail submission to : ams-essaiscliniques@ansm.sante.fr

Caution: it is **mandatory to name the e-mail** as follows :

- "**MSA-COVID-19** / Type d'essai / N° Phase d'essai / N° EudraCT / Domaine thérapeutique"
  or
- "**MSI-COVID-19** / Type d'essai / N° Phase d'essai / N° EudraCT / Domaine thérapeutique "

➡ Urgent Safety Mesure

- e-mail submission to : vig-essaiscliniques@ansm.sante.fr

Caution: it is **mandatory to name the e-mail** as follows **: COVID-19_MUS** EudraCT_code substance

➡ For Medical Device trials

- : e-mail : EC.DM-COS@ansm.sante.fr

Modalities for the evaluation of clinical trials related to the management of the pandemic COVID-19

Accelerated procedures for the initial assessment of applications for authorisation have been put in place by ANSM, DGS and all ECs.
In order to ensure the proper follow-up of these dossiers, contact should be made in order to prioritize the clinical trial, guide the evaluation and determine whether additional information is needed.

Submission of an initial clinical trial application

➡ ANSM

- e-mail submission to : aec-essaiscliniques@ansm.sante.fr
  according to national recommendation

Caution : it is **mandatory to name the e-mail** as follows **: " AEC-COVID-19 /** Type d'essai **/** N° Phase d'essai **/** N° EudraCT **/** Domaine thérapeutique**"**

- For Medical Device trials: use the following email address : **EC.DM-COS@ansm.sante.fr**

➡ Simultaneous contact with ccs-pole-recherche@sante.gouv.fr to organize ethics committee's evaluation

As requested by the WHO, sponsor must ensure that the WHO official acronym for the coronavirus disease (COVID-19) is entered in the title field of the trial registration data set.

A contact with Ministery of Health (DGOS) is possible for information on the selected research sites: DGOS-PF4@sante.gouv.fr .

Similarly for vigilance statements (individual cases, news events and annual safety report) relating to these clinical trials, add the mention "COVID-19" at the beginning of the naming of the usual emails and attached file(s).

> For example for a new event with safety urgent measures: COVID-19_MUS EudraCT_code substance.

Concerning the notification of individual cases included SUSARs, the mention “COVID-19” should be added at the beginning of the naming of emails and attached CIOMS (or ICSR).

> For example: COVID-19_20200515_IMP_ 2015-004523-12_FR-2018-000152_(1)_CT_C

It should be noted that the developers of medicines or vaccines are invited to contact EMA as soon as possible with information about their proposed development by emailing 2019-ncov@ema.europa.eu .
EMA provides a full fee waiver and a fast-track procedure for scientific advice .

For any question related to clinical trials, you may contact :

ANSM submission: questions.clinicaltrials@ansm.sante.fr please mention "COVID-19" in the subject of your message

Ethics Committee submission: ccs-pole-recherche@sante.gouv.fr