Essais cliniques

Covid 19 - Ongoing clinical trials

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The epidemic context allowed during this summer for the normal resumption of clinical with due regard for the protection of research participants and caregivers.
However, the temporary measures for the conduct of clinical trials proposed from March 2020 by the ANSM in conjunction with the Ministry of Health can be considered, depending on the health situation and the specific needs for the various research sites (depending on the epidemic incidence and the burden on healthcare institutions).

If it is necessary to reactivate in the same way transitional measures already authorised during the 1st wave and then suspended, information from the ANSM and the Ethic Committee is requested (substantial modification for information). Notification of an urgent safety measure followed by a substantial modification for authorisation is not required.

For Ethic Committees, this recommendation also applies to Cat. 2 and Cat. 3 researches.

Previous recommendations are available following these links :

- recommendations for lockdown period (20/05/2020) (59 ko)
- post lockdown recommendations (10/08/2020) (139 ko)

The French national recommendations are in line with the European guidelines established collectively and published by the European Commission .

ANSM would in particular like to bring to the attention of sponsors certain elements relating to the management of clinical trials in the current situation:

1. **Diagnosis and treatment of SARS-Cov2 patients in clinical trial**
2. **Traceability of adaptations and information of the competent authorities**
3. **Resumption of clinical trials /Cancellation of temporary measures /reactivation of transitional measures** (11/17/2020)
4. **Follow-up visits**
5. **Direct to patient delivery for investigational products**
6. **Distant monitoring**
7. **Submission of COVID-19 clinical trials**
8. **Safety reporting for COVID-19 trials**

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

Diagnosis and treatment of SARS-Cov2 patients in clinical trials

The ANSM reminds that the management of COVID-19 patients in France must be carried out in accordance with the recommendations of the Haut Conseil de Santé Publique (High Council of Public Health), available at Haut Conseil de Santé Publique - "Le point sur le Coronavirus " and

according to the recommendations of the Scientific Council COVID-19 available on the website of the Ministry of Health .

Sponsors are responsible for ensuring that research subjects receive a standard of care that is consistent with these national recommendations, whether they are patients included in a trial specific to the management of CoV-2 SARS infection and its consequences or subjects included in another trials.

In accordance with the general provisions necessary to face the Covid-19 epidemic taken by ministerial order of the French Health Minister, it is sponsor's responsibility to ensure that the diagnostic test(s) used for the detection of SARS-CoV-2 in the clinical trial are registered on the list published by the Ministry of Solidarity and Health .

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Traceability of adaptations and information of the competent authorities

The sponsor, in coordination with the investigators, has to evaluate and justify the implementation of any transitory measure 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.

If exceptional measures are needed, 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).

National recommendation are available on ANSM website for medicinal products and medical devices .

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 then not required.

=> **Substantial Modification and notification:** e-mail submission at 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 at vig-essaiscliniques@ansm.sante.fr

Caution: it is mandatory to name the e-mail as follows COVID-19_MUS EudraCT_substance code or trial code.

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

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Resumption of clinical trials / Cancellation of temporary measures / reactivation of transitional measures

How to resume interrupted clinical trials due to the COVID-19 context?

The resumption of clinical trials that were interrupted in the context of the COVID-19 health crisis. 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 temporary measures put in place due to the epidemic context.

=> If the resumption of inclusions is performed with a modified protocol, an authorization by ANSM and/or EC's opinion is required (SM-A).

Caution : When a trial is resumed, the addition of a non-inclusion criteria for patients with SARS-Cov2 infection does not require the submission of a substantial amendment if the rest of the protocol remains identical to the version authorised prior to March 2020. The mention of this addition in the letter of resumption of the trial sent for information to the ANSM is sufficient.

How can the temporary 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 temporary 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 temporary measures are put in place.

=> If the sponsor plans to maintain some of the measures on a permanent basis: a consolidated version of the amended protocol must be submitted for authorisation to ANSM and/or opinion to EC (SM-A).

How to reactivate transitional measures in necessary according to epidemiological developments?

11/17/2020

As mentioned in the introduction to this update of the recommendations, the reactivation of a previously authorised exact same measure requires information from the ANSM and the Ethic Committee. A new USM followed by an SM is not necessary for the measures that had required it.

For the transmission of information to the Ethic Committee in charge of the trial, the notifications are made in the usual way, i.e. via the SIRIPH, trial by trial, or by a specific e-mail for each study in the case of trials prior to the SI.

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Follow up visits

In case of impossibility to ensure on site follow up visits, 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 Good Clinical Practice (GCP) (§ 5.20 of 24 NOV 2006 decision). 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, new follow-up criteria and/or implementation of teleconsultation for all trial patients is considered as a substantial amendment to be submitted for authorisation (SM-A).

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Direct to patient delivery for investigational products

Direct to patient delivery for investigational products could still be considered in necessary, 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.

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 far as possible the additional workload for the research site and pharmacy, and 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.

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Distant monitoring

Sponsors are invited to take into consideration the European guidance that presents general considerations for possible solutions. Sending copies of medical records, even pseudonymised, is not authorized. Subsequent developments will be established through a specific consultation process.

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

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Submission of COVID-19 clinical trials

ANSM and Ministry of Health have proposed accelerated procedures for the initial assessment of COVID-19 related clinical trial applications. 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 at 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.

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Safety reporting for COVID-19 trials

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 without safety urgent measures: COVID-19_FN_ EudraCT_substance code or trial code.
- For annual safety report submission: COVID-19_ASR_EUDRACT Number*_DCI or substance name (or trial code)_ASR version
- 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_20200815_IMP_ 2015-000000-12_FR-2018-000000_(1)_CT_C

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For any question related to clinical trials, you can 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