

Addendum to the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic

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Version: v1

1. Preamble

Please note that this document is to be read in conjunction with the [latest version of the European guidance](#) and that the national guidance provides some more detailed clarifications and additional topics of interest. This text was written by the FAMHP, the Clinical Trial College and the Belgian Association of Research Ethics Committees (BAREC).

The information in this guidance can be applied from the moment of publication until there is a new version. The situation is evolving rapidly and further updates to this guidance are therefore expected.

Questions related to this guideline can be addressed to the FAMHP: Please use the existing mail addresses for requests for information ct.rd@fagg-afmps.be and ctrpilot@fagg-afmps.be (the latter for Pilot dossiers)

2. Procedure and communication with authorities

Priority is given to any (new) clinical trial applications for the treatment or prevention of COVID-19 infection, and/or substantial amendment applications and notifications to existing clinical trials necessary as a result of COVID-19.

Please contact the FAMHP (ct.rd@fagg-afmps.be) prior to submitting a COVID-19 related trial.

When considering submitting a multi-country COVID-19 related trial, please consider the accelerated Voluntary Harmonisation Procedure.

For the FAMHP: Please submit exclusively electronically via CESP, clearly mark all applications with 'COVID-19' in the subject field and indicate this in the cover letter as well.

For national COVID-19 related trials: the accelerated CTR Pilot is strongly recommended. The pilot has the benefit that a single submission to the national contact point is **sufficient** and that **a single review by the selected evaluating EC (without possible local ECs)** is foreseen. The structure of the submitted dossier can follow the requirements of the law of 7 May 2004 or the structure of the CTR. If the structure of the dossier of the law of 7 May 2004 is followed, please provide additionally the document in annex (written statement) for each site.

The FAMHP commits to validate and review in four working days, as will do the evaluating EC.

The CT-College may use adapted criteria to select the evaluating EC and send the dossier to an EC of the CTR Pilot **who has applied to take part in this procedure and committed** to perform the review in four working days after submission. This may be the EC of the site.

At the validation of the dossier, it will be accepted that a written statement of the suitability of the site is lacking. The sponsor is requested to provide any lacking written statement together with the answers to the Request For Information (RFI)-letter. It is to be reminded that Scientific Technical Advice (sta-wta@fagg-afmps.be) can be requested, where upon submission of the corresponding CTA for the pilot in the following two years, the fee does not have to be paid.

All measures taken for the ongoing trials due to the COVID-19 pandemic need to be documented by the sponsor together with a justification and benefit/risk evaluation. A summary report of all measures should be available in the site master file of the trial and provided to the FAMHP and EC by the national end of trial.

In order to avoid over-reporting it is asked to the sponsors to keep a listing/overview of all mitigation measures taken due to the COVID-19 situation that are not permanent amendment/modification of the protocol and not urgent safety measures, with description, explanation and justification of each taken measure.

As we do not know how long the current crisis may last and as the virus may be seasonal, it is also asked to the sponsor to provide the listing/overview of measures taken, at regular basis, every 4 months to CT.RD@fagg-afmps.be.

3. Restrictions of visits to healthcare facilities

In those conditions where it is not advised to have the subjects going to the investigator site, or where they would not be allowed to do so (e.g. due to quarantine conditions), home nursing/contact via phone may be required to identify adverse events and ensure continuous medical care and oversight. This is already foreseen in the European Guidance.

There might be particular cases: as e.g. a Belgian patient is enrolled in a trial in another member state. Owing to the COVID-19 situation the foreign site closes. The Belgian patient returns to Belgium. The same trial is not launched in Belgium. The patient wants to continue the experimental treatment, as he benefits from it. The principal investigator and the sponsor are invited to obtain a solution in the best interest of the participating patient. In this case there are two possibilities: either a new trial is launched in Belgium (initial CTA dossier to be submitted to both EC and FAMHP) which is in current circumstances not recommended, or one relies on (i) the patient drops out of the clinical trial and (ii) on the Royal Decree of 14th Dec 2006 Art 105 or Art 107/1 (Compassionate use).

4. Shipment from the site to the patient

The European Guidance states: "Direct from sponsor to trial participant IMP delivery is accepted in a few member states under this emergency situation. The sponsor should check the NCA guidance regarding the possibility of direct sponsor to trial participant shipment, as it is likely that such measures can only be implemented under specified conditions (e.g. agreement with sites, dedicated couriers with procedures to only allow delivery directly to a trial participant or his/her care giver, solid shipment and receipt procedures, informed consent provisions if necessary for the sponsor's third party to handle personal information etc.), and for a limited period."

Direct shipment from sponsor to patient is not allowed in Belgium. What is allowed under these exceptional COVID-19 times under exceptional conditions:
In cases where, for the protection of the rights (confidentiality) and the safety of the participants, a continued supply of trial medication needs to be maintained at home, trial medication may also be shipped directly, under responsibility of the principal

investigator, from the trial site to the trial participants via courier. This is only possible provided that the product is suitable for transport, storage at home and administration at home use.

In case of home administration by the participant, a care giver, nurse or physician, training on administration at home (i.e. trained in terms of the protocol) must be provided to the participant, care giver, nurse or physician.

Any additional training from the participant, care giver, nurse or physician must be documented. Special attention should be paid to capturing adverse events and informing the PI of the subject's health and wellbeing in this off-site setting. The GMDP and GCP requirements for transport and storage of investigational medicinal products remain in place.

Concluding:

- a) Under PI's responsibility
- b) Shipment without sponsor involvement (personal data protection)
- c) Under correct shipping conditions
- d) With correct & traceable documentation
- e) Patient is trained for storage, administration at home or administration is conducted by a trained (i.e. trained in terms of the protocol) care giver, nurse or physician

To emphasize: documentation is paramount. A courier under contract of the sponsor may be implied for the shipment upon condition that documentation is present before shipment, that the PI is informed, that the patient's personal data are protected and that the sponsor under no circumstances can obtain the personal data (like name and address) of the patient. The responsibilities of each party in this have to be documented. It must be clear that this shipment cannot happen on the expenses of the patient.

Administratively:

- The shipping arrangements can be considered as a **non-substantial** amendment to be included with the next substantial amendment.
- If any training is provided to the participant, care giver, nurse or physician that is not mentioned in the protocol, a **substantial** amendment is required.
- If it concerns temporary changes to the informed consent, these changes are preferably described in an **addendum to the ICF** which is temporarily valid. Non-substantial and substantial amendments on the ICF have to be submitted to the EC as soon as possible.

Apart from the investigational treatment (IMP and any other medication and material specifically used for the trial), this rule can also be applied – under the same conditions mentioned above - for patient diaries, pregnancy tests.

Administrations of study medication by site staff / general practitioner / nursing staff are indeed possible outside the site (for example at home, alternative location). This should be requested by the study site. A substantial amendment should be submitted to the FAMHP and the EC in accordance with questions 10 and 11 of the Q&A: Good clinical practice (GCP): <https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp>

"All of these changes in shipment should be budgeted for by the sponsor if they are necessary to ensure the continuity of the studies."

5. Temporary halts and urgent safety measures (USM) need to be notified

A temporary halt (e.g. recruitment halt, halt of the trial on a site) of the trial shall be submitted to the FAMHP and the EC within 15 days of the decision. A temporary halt is

not a substantial amendment but it is communicated via CESP to the FAMHP through the Substantial Amendment Notification Form (Annex II Section E.4.). Only a confirmation of receipt is sent, no official approval.

If the rationale to discontinue the recruitment into the ongoing clinical trials is the same for all clinical trials, it is needed and sufficient that the applicant sends only one temporary halt notification that lists all the concerned clinical trials.

In order to restart the trial after temporary halt, a substantial amendment must therefore be submitted. The trial can only restart upon approval by the EC and if no motivated objections have been raised by the FAMHP within legal deadline. If the temporary halt of recruitment is only due to the COVID-19 crisis, it will be acceptable to restart the recruitment when again possible after a notification only to the FAMHP and to the EC.

Urgent safety measures taken in the context of coronavirus may be taken without prior notification to FAMHP and the EC. However, the sponsor must inform as soon as possible the FAMHP and the EC of the measures taken and the plan for further action. This should be reported to the FAMHP via CESP or ct.rd@fagg-afmps.be (or CTRPilot@fagg-afmps.be for Pilot Projects). A substantial amendment must be submitted afterwards.

A protocol deviation (control of visits,...) should be considered as an USM if the change has to be directly implemented for the patient's safety and if it is considered as a substantial amendment (cf. definition of substantial amendment, national and European coronavirus guidelines). The protocol deviations need to be included in the ICH E3 clinical study report. A substantial amendment shall only be submitted for critical protocol deviations (those which are really impacting safety), not for minor deviations.

An individual DIL (dear investigator letters, per study/compound) has to be reported to FAMHP and EC if it is part of an USM and/or a substantial amendment. Once again only DIL related to measures that are really impacting safety of the participants have to be submitted as part of USM or of a substantial amendment. If it is not, the DIL is considered as non-substantial. The sponsor does not have to notify non-substantial amendments to the national competent authority or the Ethics Committee. However, non-substantial amendments should be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment.

6. Remote Source Data Verification

Several investigators have cancelled on-site monitoring at their study site. Remote source data verification (e.g. providing sponsor with copies of medical records or remote access to electronic medical records) is currently not allowed in Belgium as it violates trial participants' rights. In addition, requiring the site staff to redact all medical charts would most likely put too much burden on the sites at this time, nor does it allow sufficient verification by monitors. Therefore this process is not recommended. Special attention to on-site monitoring will be required once allowed again.

Please note that with source we mean the medical dossier, the charts of the participant.

7. Electronic way of working and accepting possible electronic signatures

- For the informed consent form (ICF) or to obtain (re-)consent, please follow the European guidance.

- For other documents (cover letter, application form, protocol): A scan or photograph of the signed paper will be accepted.
- To send in a word or a PDF file which is unsigned and mentioning that a signed version will follow later is currently accepted.
- If qualified electronic signatures are available (with qualified certificates on this list <https://webgate.ec.europa.eu/tl-browser/#/>) this will be accepted. However – in these circumstances, points 1 to 3 will be accepted as well. It should be clear that under these circumstances qualified electronic signatures are not mandatory.

Annex – written statement

Statement of CEO/ person acting on behalf of CEO

Concerning

Name of Institution:

PI:

CTC name and internal number (if applicable):

Sponsor:

Title:

EUDRACT number:

I hereby confirm that the clinical trial (see details above) may be carried out at our Institution taking into account internal procedures of the institution and the confirmation of the following elements:

- **This site has all the facilities and equipment to conduct the clinical trial and expects to be able to include the planned number of subjects.**
- **Availability and expertise of staff**
- **Declaration of the Principal Investigator (PI):**

As PI I declare I have read the protocol and all related documentation as part of the application dossier, I have no ethical or scientific objections and I, together with my study staff, can perform the study in accordance with the protocol. All necessary precautions are taken at the study site to protect the safety of the study subjects.

I confirm study subjects will be correctly informed about the standard of care (and what will be charged to the patient and their health insurance) and what interventions/examinations are extra for the trial (always paid by the clinical trial budget).

Signature of PI: _____

Print Name:

Date: (dd/mm/yyyy)

Signature Institution: _____

Print Name:

Date: (dd/mm/yyyy)