

**HELLENIC REPUBLIC - MINISTRY OF HEALTH**

**NATIONAL ORGANISATION FOR MEDICINES**

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# Special supplementary recommendations for Greece, regarding the EU Guidance on the management of Clinical Trial during the COVID-19 pandemic

**Version 2 Athens, 13 May 2020**

The European Authorities have issued new guidelines to mitigate the effects of the COVID-19 pandemic on the conduct of clinical trials.

You can access the updated guidelines (28/04/2020, Version 3):

* at the EMA (European Medicines Agency) website  [https://www.ema.europa.eu/en/human-regulatory/research- development/compliance/good-clinical-practice#guidance-on-clinical-trial-management- during-the-covid-19-pandemic-section](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice%23guidance-on-clinical-trial-management-during-the-covid-19-pandemic-section)
* at the European Commission’s website for Community legislation (Eudralex, Vol. 10)

<https://ec.europa.eu/health/documents/eudralex/vol-10_en>

Sponsors and Investigators should take due account of the fact that, although the above guidelines are the result of a harmonised approach on EU level, they are supplemented by additional guidelines on any matters which are still governed by national laws and regulations. It is acknowledged that the extraordinary circumstances created by the COVID-19 pandemic have forced the Sponsor/CRO to apply emergency measures to ensure non-disruption of the clinical trials, secure the safety of participants and ensure reliability of clinical research results. These additional matters relating to the conduct of clinical trials are specified in the following recommendations.

**It is noted that, due to the ever-changing circumstances prevailing due to the COVID-19 pandemic, the recommendations may be modified by new notification.**

**The changes from Version 1 relate primarily to source document review procedures, participant information and consent to the changes made to the distribution of IMPs and the Sponsor’s/CRO’s actions to inform EOF/EED.**

1. **Recommendations for changes in Monitoring practices**
2. Remote monitoring

The monitoring planning can be modified to ensure that clinical trials are monitored remotely. These changes are intended to promote centralised monitoring and telephone communications at the expense of on-site visits, where this is possible. The Sponsor/CRO is liable to assess the potential effects of changes to the monitoring planning and ensure that any reduction in visits to the centre will have no impact on the quality of the research or the safety of participants. Any justified departures from the effective monitoring plan must be thoroughly documented and modified by the Sponsor/CRO where necessary.

 b) Source Document Verification (SDV)

It is important to bear in mind that patient source documents may not be reviewed remotely, which means that SDV is not permitted in Greece. This means that, even if patient identification information is redacted at the trial site, these documents may under no circumstances be forwarded to the monitoring officer for remote verification. The Sponsor/CRO will have to plan and apply all remedial actions necessary to mitigate the effects of reduced monitoring, as soon as things get back to normal.

 c) Source Document Review specifically for COVID-19 clinical trials

 Special cases

Taking into account the critical nature of the current situation, remote SDV practices could be exceptionally permitted exclusively in relation to COVID-19 clinical testing, in any individual situations where this is considered imperative on a case-by-case basis, provided that all other monitoring alternatives have been excluded. Such exceptional application of SDV methods may expand to include pilot clinical trials for serious or life-threatening conditions with no satisfactory treatment option, in the final data cleaning steps before database lock, strictly during the public health crisis*.*

Such remote SDV methods can be exceptionally applied to COVID-19 clinical trials and to the clinical trials for serious or life-threatening conditions mentioned above, if the following requirements are met:

* The remote SDV methods have been carefully evaluated and they are described in a specific SOP document and in the Sponsor's/CRO monitoring plan. The remote SDV methods should be evaluated with due regard to protecting the rights of participants and avoiding to place any disproportionate burden on the research sites and should be consistent with the rules of necessity and proportionality.
* The remote SDV methods have been evaluated and authorised by the National Ethics Committee (“EED”).
* The remote SDV methods have been authorised in writing by the research centre where they are to be applied [in an understanding with the research centre’s the Data Protection Officer (DPO) ]. In particular, the implementation of these emergency measures by Sponsors/CRO, Investigators and Hospital Institutions must be conforming with the GDPR (Regulation 2016/679), in particular Article 5(1) (c) (data minimisation) and (f) (integrity and confidentiality).
* The remote SDV methods are described in the ICF, so that they are available to patients and patient consent is obtained.
* The remote SDV methods are described in a confidentiality agreement signed by the monitoring officer, which prohibits the copying and storage of the electronic footprints (screen shots, electronic correspondence archives etc.) generated from the remote SDV method applied.

Subject to the above requirements, the remote SDV method may involve disclosure of source documents by the research centre to the monitoring officer through video calls, or emails including copies of pseudo-anonymised files and also through remotely-controlled access of the monitoring officer to a certified electronic medical record of participants, which is already installed at the research centre.

We should further note that the above may also apply to the special categories of clinical trial described in point (1c), provided that they are submitted to EOF/EED as substantial amendments, with documentation equivalent to that required for COVID-19 trials, having due account to the requirements of Annex 1 to the updated Guidelines of the European Authorities (28.4.2020) on the protection of the rights of participants.

# ICF and obtaining patient consent for COVID-19 clinical trials

There are obvious objective reasons which currently render it difficult to obtain consent from COVID-19 patients while they are in a negative pressure room or in isolation. In line with what is mentioned in LA dated 30.3.2020 "Measures to combat the COVID-19 Coronavirus Pandemic and other Emergency Regulations” (GG A 75), in any situations where it is impossible to obtain the written consent of a patient or his/her relatives or legal representatives, the main researcher may obtain such consent by any other expedient means e.g. by email, sms or even orally, in which case he/she shall note this in the clinical trial records.

If a patient is in a state of unconsciousness, the procedure to obtain consent is laid down in Article 9 (Informed Consent) and Article 12 (Clinical Trials in Emergency Situations) of Ministerial Decision Γ5α/59676 (GG 4131/22.12.2016).

In respect of any patients who maintain consciousness and are considered capable of granting written consent, the following options are available:

* The patient may grant his/her consent orally, in the presence of a legally capable individual who is not howsoever involved in the clinical trial. Such person will be acting as a witness (Article 2(j) of Directive 2001/20/EC) and will sign the ICF. The main researcher is liable to write down how the witness was selected.
* The witness and the person that obtained consent shall each sign the ICF separately. The ICF document signed by the researcher is then temporarily stored in the researcher's archive, whereas the copy signed by the patient remains in the negative pressure/isolation room. Alternatively, a photo is taken of the ICF page bearing the patient’s signature inside a transparent separation membrane and the photo is stored in the researcher's archive. A properly signed ICF document is delivered to the participant as soon as this becomes possible thereafter.

# Recommendations for changes in the distribution of investigational medicinal products (IMPs)

Direct delivery of investigational medicines by the Sponsor to trial participants (“Direct from sponsor to trial participant”) is not permitted in Greece and may only be permitted following an amendment to the relevant national laws.

 a) Direct IMP delivery from the centre

Taking into account that access to many research centres is currently difficult and many trial participants are isolated at home, IMPs and non-IMPs, which could be normally delivered, can be delivered by the research centres to participants by care of the principal investigator. This ensures efficient protection of patient data by the Sponsor and effective handling of investigational medicines before they are distributed to patients (e.g. documented delivery of investigational medicines in good status and recording of IMP temperature throughout the transport, IVRS procedures, kit-patient matching procedures, completion of medicine accounting records etc.).

It is noted that this direct delivery process may only be applied if the IMP concerned can be taken at home. The identification and address information of participants must not be disclosed to third parties outside the centre, save for any documents essentially accompanying the IMPs which are being delivered directly by the centre to participants. Documentation of the delivery shall only be maintained by the centre, for tracking purposes. If any copies of the delivery documents are required by the Sponsor/CRO, e.g. for the purpose of identifying any departures from the applicable protocol or for quality assessment purposes, any patient identification/address information must be permanently redacted before the copies exit the centre.

To execute a direct IMP delivery, the centre may use a courier service either on demand or on the basis of a standing agreement with the Sponsor. Chapter 9 of the updated Guidelines of the EU Authorities (28/04/2020) provides information on the terms of the agreements to be signed between the Sponsor and third parties for home IMP deliveries. In any case, delivery costs shall not be charged to the participants.

The principal investigator may assign part of its responsibilities (e.g. IMP delivery to patients at their homes) to specialised members of its staff, by its own (investigator’s) responsibility (ICH GCP Articles 4.2.5 and 4.2.6). For information concerning clinical trials conducted at patient homes rather than at research centres and for information concerning the investigator's ability to assign responsibilities to third parties during the clinical trial procedure, please refer to the GCP Q&A link (Questions 10 and 11) at the EMA website:

[https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp) [practice/qa-good-clinical-practice-gcp](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp)

 b) Participant information and consent to IMP distribution changes

Trial participants must be informed of and then consent to and become familiar with all changes made to the IMP distribution process.

Participant information and consent in relation to these changes may be provided/obtained orally and remotely (by telephone or video-call). The above actions may be documented by means of confirmation emails or alternative methods (e.g. voice messages) and may be recorded by the investigator in the patient’s record.

This process must be recorded in the ICF in the form of an ICF Addendum with provisional effect, by way of documentation of the participant’s oral consent. Such Addendum may consist either in the confirmation email or in a consent confirmation letter signed by the participant upon delivery of the IMP by the courier service.

In light of the urgency of the situation, the above can be implemented instantly, however the changes introduced to clinical trial procedures must be recorded in the consent form by means of a permanent ICF Addendum or an updated/new version of the existing ICF (depending on the nature of the changes applied) and must be submitted with EOF/EED for authorisation as a material amendment. The authorised ICF Addendum or new version of the existing ICF must be signed by the participant the next time he/she visits the research site after things get back to normal or the next time he/she is delivered a medicine by courier service (attention must be paid in this situation to ensure that the participant is delivered the final form which bears the signature of the principal investigator).

It is noted that , for as long as the pandemic continues, IMPs can be delivered to close relatives or care takers of the participants, provided that this is documented in the clinical trial records. The consent form, however, must be signed by the participant.

# Sponsor/CRO actions to notify EOF/EED

As it is described in Chapter 6 of the updated EU Guidelines (28/04/2020), it is up to the Sponsor to assess the effects the changes introduced to a clinical trial may have on the safety of the participants, on the risk/benefit balance and on the scientific value of the trial and to take such emergency safety measures, introduce such material amendments or carry out such notifications as may be necessary in relation to the departures that were made from the protocol.

As regards the submission of documents to the EOF registration department, we refer once again to [communication dated 23/03/20, as same was updated on 07/04/2020](https://www.eof.gr/web/guest/home?p_p_id=62_INSTANCE_0eNL&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-2&p_p_col_count=11&_62_INSTANCE_0eNL_struts_action=/journal_articles/view&_62_INSTANCE_0eNL_groupId=12225&_62_INSTANCE_0eNL_articleId=4844572&_62_INSTANCE_0eNL_version=1.0), on the implementation of a digital protocol, and encourage you to refer to EOF's website for updated communications on the operation of the protocol.