AIFA notice

(update of the AIFA notices published on 12 March and 7 April 2020)

Clinical trials' management in Italy during the COVID-19 (*coronavirus disease 19*) emergency (Version 3 of 17 September 2020)

Following the number of requests received by the Clinical Trial Office/Pre-Authorization Area and by the GCP Inspections Office from the various stakeholders, the Italian Medicines Agency provides indications regarding the management of clinical trials and substantial amendments in Italy after the exceptional restrictive measures introduced by the Italian Government in order to fight the COVID-19 pandemic, and following the maintenance of the emergency and urgent provisions aimed at containing the spread of the virus referred to in the Decree Law 30 July 2020, no 83.

Clinical trials must be conducted according to common sense principles, with the highest protection of trial participants and maintaining adequate supervision by the Principal Investigators (PIs).

To this end, please consult the *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic* published on the European Commission website, EudraLex Volume 10 *Clinical trials* (https://ec.europa.eu/health/documents/eudralex/vol-10_en).

Submission of clinical trials and substantial amendments

Without prejudice to the circular on simplified procedures for studies and programs of compassionate therapeutic use for the emergency from COVID-19 (https://www.aifa.gov.it/documents/20142/1123276/CIRCOLARE_ART-40_studi_programmi_COVI-19_22.05.2020.pdf/ca6d36a9-caa6-9ad4-31fc-4e44acae480d), and following what already set down in the previous notices, AIFA clarifies that, also in the period of validity of the emergency provisions due to COVID-19, the submission of authorization requests for clinical trials and substantial amendments must be done through the OsSC, according to current rules. Anyway, considering that many pharmaceutical companies, no-profit Sponsors and CROs still applies smart-working in order to continue their activities related to clinical trials, AIFA will validate/evaluate requests submitted via OsSC even if relevant paper documentation and CD-rom have not yet arrived (however, they will have to be sent as soon as possible).

It is recommended to apply the stamp duty on the cover letter (excluding cases of exemption from this tax pursuant to Article 17 of Legislative Decree 460/1997 and of Article 82, paragraph 5, of Legislative Decree no. Lgs. 117/2017) according to provisions set down in the AIFA notice "Applications filed electronically to the Italian Medicines Agency: stamp duty method of payment" published on the AIFA website on 26 March 2020 (https://www.aifa.gov.it/web/guest/-/istanze-presentate-all-agenzia-italiana-del-farmaco-per-via-telematica-modalita-di-assolvimento-dell-imposta-di-bollo).

In case the submission via OsSC is not possible due to system's malfunctions or technical obstacles, it will be necessary to adopt the temporary paper transmission way. Transmission by e-mail of clinical trials and substantial amendments' requests for authorisation will not be accepted. However, any responses to integration requests in the validation phase or to grounds for non-acceptance in the evaluaton phase can be sent by e-mail, except in the case of original documentation initially missing. Such documentation

will be evaluated without waiting for the paper documents and the final provision will be issued, being understood that paper documentation must be sent as soon as possible.

Submission of clinical trials and substantial amendments of studies for the treatment of COVID-19

As far as submission of clinical trials for the treatment of COVID-19 in general, it is necessary to comply with provisions set down by the circular of 22 May 2020 published on the AIFA website (https://www.aifa.gov.it/web/guest/-/nuova-circolare-sulle-procedure-semplificate-per-gli-studi-e-gli-usi-compassionevoli-per-l-emergenza-da-covid-19), as required by art. 40 of the Law Decree 8 April 2020, no. 23 containing "Urgent provisions on clinical trials of drugs for the epidemiological emergency from COVID", converted by Law no. 40/2020.

According to the afore-mentioned Law Decree, clinical trial protocols of Phase I, II, III and IV, of observational studies on drugs, and of compassionate therapeutic use programs are preliminarily evaluated by the AIFA Technical Scientific Committee (CTS) and subsequently approved, after evaluation by the AIFA Competent Authority (Clinical Trial Office) and by the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome, acting as single national Ethics Committee for the evaluation of clinical trials of medicinal products for human use, of observational studies on drugs, and of compassionate therapeutic use programs for patients affected by COVID-19 which expresses the national opinion, also on the basis of the evaluation of the AIFA's CTS.

The submission of authorization's requests for COVID 19 trials of Phase I, I/II and I/III follows the usual submission process, to which the preliminary assessment of the CTS for the part concerning the protocol is added.

The substantial amendments to the authorized COVID 19 studies follow the normal authorization process by AIFA - Clinical Trial Office, which informs the CTS at the end of the evaluation or consults it in case of significant changes to the protocol.

Art. 40 of the Law Decree 8 April 2020, no 23 specified, with respect to art. 17 of the Law Decree of 17 March 2020, no 18 (from the same Art. 40, repealed), some aspects for studies related to COVID-19, in particular:

- the preliminary assessment of the trials by the CTS is also envisaged for Phase I clinical trials;
- the CTS and the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome evaluate studies only on medicines;
- the need for an ad hoc insurance for no profit studies is abolished.

Even for COVID-19 clinical trials and the related substantial amendments, under current legislation, submission must take place via OsSC, in accordance with the provisions set down in the previous paragraph. If it is not possible to submit via OsSC, due to blocks or technical constraints of the system, it is allowed to send documentation in paper format to AIFA and in electronic format to the ordinary email of the National Ethics Committee of INMI Lazzaro Spallanzani - IRCCS (comitatoetico@inmi.it).

The submission via PEC is no longer considered acceptable.

In addition, preliminary study proposals are no longer taken into consideration, but only applications for authorization of clinical trials and observational studies protocols submitted in complete form.

Pursuant to art. 40 of the Law Decree 8 April 2020, no 23, the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome, having to issue the single national opinion, must be identified in the OsSC as the coordinating Ethics Committee and, therefore, the coordinating center must be the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome. This does not necessarily leads to the involvement of the PI of the center (instead of the Name and Surname of the PI, only "Not applicable" can be selected).

An accelerated timing is foreseen for the assessment of COVID-19 studies.

Please remember that the wording "COVID-19" must be reported in the title of such clinical studies for their easier identification, and it is also recommended to insert the wording "COVID-19" in the subject of the relative requests for assistance to the HelpDesk.

For the supporting documentation to the request for authorization of clinical trials inherent to the treatment of COVID-19 in general, reference is made to the document list provided for the ordinary submissions via OsSC (in case of submission through the temporary paper modality, in addition to the afore-mentioned documentation, it is necessary to submit also the authorization request form or Appendix 5 and the xml file).

Please note that, pursuant to paragraph 6, art. 40 of the Law Decree 8 April 2020, no 23, no profit clinical trials on COVID-19 do not require a specific insurance policy.

The sites that, in addition to the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome, are intended to be involved in the study, will have to be included as satellites in section G.2 of the *Clinical Trial Application* (CTA or Appendix 5). The relevant Ethics Committees are not called to express themselves and do not have to issue an opinion. The single opinion of the National Ethics Committee is notified to them through the OsSC (if submitted via OsSC) or by local investigators (if not submitted via OsSC) and is accepted by the relevant Ethics Committees by filling in Appendix 8.

The release of Appendix 8, not being formally provided for by art. 40 of the Law Decree 8 April 2020, no 23, can be carried out by the Ethics Committee collegially or by the Technical-Scientific Secretariat as an acknowledgment, in accordance with internal procedures. The release of Appendix 8 is not binding for the purposes of activating the site.

For COVID-19 studies in the OsSC, any substantial amendments to be evaluated must be submitted to AIFA, to the single national Ethics Committee for its opinion and to the other Ethics Committees that will accept the opinion as indicated above.

In particular, as regards the possible addition of sites to clinical trials already approved or the change of the PI, the competence of the National Single Ethics Committee remains valid (by inserting it as an additional recipient in the OsSC) and the subsequent acknowledgment by the Ethics Committee of the new site that is intended to be involved or impacted by the PI change.

For extra-OsSC COVID-19 studies, the substantial amendments to be assessed must be submitted in paper format to AIFA and in electronic format to the ordinary e-mail of the National Single Ethics Committee of the INMI Lazzaro Spallanzani - IRCCS (comitatoetico@inmi.it).

For multinational studies, we invite you to consider the possibility of a VHP submission and to contact the EMA for any *Scientific Advice* procedure, both in an accelerated mode, in accordance with the provisions of the *Guidance on the Management of Clinical Trials during the COVID- 19 (Coronavirus) pandemic*.

Expression of the Ethics Committees opinions on clinical trials/substantial amendments

Without prejudice to current legislation and to internal procedures of each Ethics Committee, their meetings may also be held in web-conference or through other types of computerised means, with the appropriate frequency to manage the urgencies linked to the current emergency.

Methods of communicating essential measures that modify the execution or management of clinical trials to comply with the measures in place due to COVID-19

In consideration of the changed epidemiological situation, exclusively in the event that, to limit the risk of coronavirus contagion and/or to comply with the measures in place due to COVID-19, there are exceptional urgent and essential reasons requiring the implementation of measures that modify the execution or management of clinical trials (including temporary changes to the protocol), an urgent safety measure must be notified in the manner prescribed by current legislation.

In the event that the Sponsor temporarily halts enrollment and/or treatment in a clinical trial, to comply with the measures in place due to COVID-19, it will be necessary to notify an urgent safety measure.

In the event that the trial is restarted without changes compared to the initial authorization, it will still be possible to select Yes in the "D.2.2.3 Other" field and fill in the "D.2.2.3.1 If other, specify" field, so that the amendment appears as notified. In the event that the trial is restarted with substantial changes to the documentation, that are intended to be kept even after the restart of the study, it will be necessary to submit the relevant substantial amendment for the restart of the study, for evaluation.

If the measures to be adopted do not require immediate implementation, or if there are no reasons for urgency, it will be necessary to submit the substantial amendment for evaluation, without prejudice to the competence of the Ethics Committees in verifying the operational and procedural aspects in the assessment, e.g. of any home administration of the study drug, blood sampling and visits at home or at another site, dedicated staff and procedures to be adopted in case of emergency.

For more details on the ways of communicating to the competent Authority and the Ethics Committees the actions taken/to be taken to protect subjects in clinical trials, please refer to point 6 of the *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic*.

Finally, it should be noted that the current epidemiological framework, also considering the adoption of less rigid and not generalized restrictive measures, does not allow to consider justified the implementation of emergency measures by itself, having to adequately justify time after time the conditions that make the immediate implementation of the measures urgent and essential.

Possibility of managing clinical trial activities outside the trial site

Investigators and Sponsors are invited to consider the opportunity to limit visits to those strictly necessary, cancelling unnecessary ones and also providing, where possible, for the extension of the duration of the trial.

In this regard, Sponsors/CROs are invited, taking into account the indications of the DPCM relating to urgent measures regarding the containment and management of the pandemic emergency from COVID-19 and the specific regional ordinances, to draw up a risk assessment plan and to implement an action plan proportionate to the risk, in the pre-eminent protection of the trials subjects, in view of the urgent need to minimize contacts between patients and clinical trial staff and in order not to overload the health facilities. Sponsors are also invited to inform the trial sites and to agree with them in good time all the alternative measures, linked to the contingent situation, adopted for the management of the trials subjects.

Provided that they are compatible with the feasibility at the participant's home, carrying out procedures directly at the patient's home, carried out by the staff of the trial site or by third parties, may be considered. These home health care activities may include both clinical procedures that cannot otherwise be performed (e.g.: collection of adverse events, vital signs, etc.), and the administration of non-self-administered therapies (e.g. infusions).

Reiterating that these measures must be understood as extraordinary and limited to the narrow period of coronavirus emergency, derogating from FAQ 11 of the EMA document "*Q&A: Good clinical practice (GCP)" - GCP Matters* (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp) it is possible for the Sponsor/CRO to directly stipulate contracts with these specialized agencies/third-party companies. All other indications of the afore-mentioned FAQ remain applicable, as well as the compliance with the rules on the personal data protection, such as for example:

- the need that the PI maintains the supervision
- that efficient communication ways are established between the personnel in charge and the PI
- that the personnel in charge is properly trained and the related duties and responsibilities are indicated in the contract and/or delegation log
- that the protection of the confidentiality of sensitive personal data is guaranteed
- that the relationships between these third parties and the trial sites are governed pursuant to art. 28 of the General Data Protection Regulation 2016/679, through a contract or other legal act for the designation of data controller.

It is necessary for the Sponsor to verify that the insurance taken out for the clinical trial also covers the changes implemented for the coronavirus emergency.

It should be noted that, if the trial sites (data controllers) entrust part of the activities aimed at guaranteeing therapeutic continuity to third parties (also through collaboration with the Sponsors), the relationships between these third parties and the trial sites must be governed by pursuant to art. 28 of the General Data Protection Regulation 2016/679, through a contract or other legal act for the designation of the person responsible for the personal data processing.

Investigational medicinal product (IMP) management

Where possible, if the subject comes to the trial site for a visit, it may be useful to provide a quantity of drug that covers a longer time interval than that normally estimated and that the expiry date goes beyond the expected treatment period, in order to avoid erroneous assumptions of expired drug by the subject.

In the event of difficulty by the participant to go to the clinical site and to limit travel, the possibility is also envisaged that the drug is delivered to a family member or other person (for example a caregiver), who must have been delegated by the participant himself, as established by the law in such cases.

The evaluation of the period for which the supply of a greater quantity of drug is foreseen is carried out by the investigating doctor who must keep a constant check on the correct intake by the subject, in accordance with the clinical protocol. In fact, the supply of additional trial drug corresponds, in this case, to all intents and purposes to a prescription by the investigator with all the ethical, clinical and legal responsibilities connected to it.

In accordance with current legislation (article 7 of the Ministerial Decree of 21 December 2007), the medicines required for the trial must be sent by the Sponsor/CRO to the Pharmacy of the health facility, site of the trial, which will arrange for their appropriate registration, storage and delivery to the investigator. Therefore, considering the serious COVID-19 emergency, even if the priority route remains the delivery to the hospital Pharmacy, direct deliveries from the hospital Pharmacy to the subjects enrolled in the trial can be agreed upon on the recommendation of the Director of the hospital Pharmacy and the principal investigator (PI), also for through dedicated couriers. The supervision of the process by the hospital Pharmacy and constant information from the Pharmacy itself and the PI of the delivery in the manner required for the correct conduct of the trial and the risk plan of the Sponsor mentioned in the introduction, which must take into account the type of IMP, methods of administration, storage and transport, remain necessary.

Where the Sponsor/CRO has already identified or has an authorized warehouse, where the drug is stored, given the highly restrictive provisions adopted at national level for the COVID-19 emergency aimed at reducing travel and additional steps as much as possible, source of further risk, it could be considered, only for the period limited to the afore-mentioned emergency, the direct delivery by the deposit to the trial participant. For this, specific procedures must be identified for maintaining all the guarantees of control and traceability of the delivery, including transport conditions and agreements in this regard with the trial sites. In this context, it is necessary to consider solutions such as the use of a dedicated courier, which operates according to procedures for the direct delivery of investigational drugs to the participating subjects and which also implements all measures aimed at guaranteeing the confidentiality of subject information, such as the instructions referred to in art. 29 of the GDPR, which the data controller is required to provide to anyone acting under his authority, or, where appropriate, the designation of data controller pursuant to art. 28 of the GDPR.

The GCPs (§§ 5.14.4, 8.2.15 and 8.3.8) require the Sponsor/CRO to keep the IMP delivery documentation, but these points obviously refer only to the shipment from the Sponsor/CRO to the hospital Pharmacies of the investigational sites. As this is an extraordinary procedure, this does not apply to direct delivery to the subjects' home and therefore the relative documentation must be kept directly at the investigational site to ensure the confidentiality of the data.

Appropriate remote communication mechanisms with interested parties must be guaranteed in order to allow the exchange of all information that will no longer be provided in person. Depending on the case, where deemed necessary, the phone and/or video call may be used in order to facilitate the information of the subject or provide detailed instructions. It is recommended to keep a documented trace of communications, of any kind, which occurred in this emergency situation.

This, without prejudice to the conditions set out in FAQ 10 of the EMA document *"Q&A: Good clinical practice (GCP)"* – GCP Matters (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp), where possible.

If the CRA of the study cannot carry out the control of the final accounting of the drug for the purpose of reconciliation, this action, if it cannot be done later, can be carried out by a pharmacist of the hospital Pharmacy or by the study coordinator/data manager, designated subjects to the processing of personal data, pursuant to art. 2-quaterdecies of the Italian Personal Data Protection Code, Legislative Decree 30 June 2003, no 196, and properly instructed. The IMP can be returned to the Sponsor/CRO directly from the hospital Pharmacy.

Always for limiting travel and contacts as much as possible, it is considered acceptable, for those drugs close to the expiration date, to adopt the solution of keeping the drug at the hospital Pharmacy, in specially designated and segregated areas, until the emergency is resolved, putting in place the appropriate precautions, provided for by a specific procedure, aimed at avoiding the erroneous use of expired or deteriorated drug.

Clinical tests

With regard to the conduct of clinical and/or medical tests (e.g. CAT, MRI, X-ray) essential for the participants' safety, being aware of the need they must be performed in laboratories near to the patient's home, public facilities should preferably be chosen; if private, they must be recognized as suitable for conducting clinical trials pursuant to the Ministerial Decree of 19 March 1998 or be self-certified private laboratories pursuant to AIFA Determination 809/2015. The use of private facilities not having such recognition of suitability or not self-certified, must be carefully evaluated and implemented only if it represents the unique possibility to protect the subjects safety; the subsequent use of the data produced by these facilities, if connected with the trial endpoints, should be explained and discussed in the study report.

It should be noted, as mentioned above, that, even in this case, the data controller (investigational site or Sponsor/CRO) is required to regulate relations with the afore-mentioned facilities pursuant to art. 28 of the GDPR, if they act in the name and on behalf of the data controller, or if they must be considered as independent data controllers, pursuant to art. 24 of the afore-mentioned Regulation.

Possibility of exceptional expenses reimbursement

Given that from the application of the emergency measures for COVID-19 there must be no additional cost for public finances or for individuals, taking into account this exceptional situation, if, in order to implement urgent measures for the protection of participants involved in a clinical trial, expenses may be borne initially by the participants, similarly to what is already allowed in extraordinary cases (e.g. trials on rare diseases), and the Sponsor/CRO is allowed to reimburse such expenses to the participants. In order to avoid direct contacts between subjects and Sponsor/CRO, the favourite way would be the shipment of the receipts or the delivery by the subject (when possible) to the trial site, which will invoice this amount to the Sponsor/CRO and reimburse expenses, through its administration. The costs incurred must be adequately documented and the receipts issued by external facilities must clearly indicate the protocol code or the EudraCT number of the study.

Whether the costs for the services provided for by the protocols are burdensome and unsustainable by the subjects who should anticipate them (and for this reason can generate conduct, as a result of which, failure to adhere to all the trial procedures can jeopardize both the safety of patients that the quality of the data collected), Sponsors are suggested to identify among the public or private structures (but

recognized as suitable for conducting clinical studies pursuant to the Ministerial Decree of 19 March 1998) those suitable for being included in a series of sites at which patients can carry out the examinations without having to anticipate the costs, subject to the agreement of the site/Sponsor.

These sites must be in an adequate number to ensure compliance with the measures that reduce the subjects travelling to the minimum and strictly necessary and thus ensure compliance with the investigational protocols.

Is some Sponsors cannot apply this method, a further alternative could be represented by providing, for booking and payment in solvency the necessary services foreseen by the investigational protocols, through a third party and therefore without direct reimbursement by the Sponsor to the patient.

Pending the restoration of the investigational sites for all the trial procedures, we invite you to put in place the measures aimed at maintaining traceability of the tests carried out at these sites.

Closing of sites

If a site is "closed" to the public for COVID-19 containment measures, it should be carefully assessed if the clinical trial staff is able to ensure the continuity of the trial itself. In case the trial staff is unable to follow the patients enrolled in the trial, the study should be temporarily halted or, where possible, enrolled patients should be transferred to the closest active trial site. Obviously, information exchange between the PIs of the two sites must be assured, as well as the transmission of clinical documentation and other trial material (e.g. IMPs) between sites. In such cases, the complete transfer of the trial to another site involves the transfer of responsibility to the other PI of the new site. In the case, instead, of a temporary transfer not of all the trial but of single procedures (for example visits) related to the study, the initial PI remains responsible for the trial.

Contracts between Sponsor/CRO and health facilities involved must be updated according to new agreements.

A site not authorized to participate in the specific clinical trial is not considered as suitable as back-up, since it is not active, it does not know the trial and could not ensure a proper clinical management of the patient.

Clinical trial monitoring

By analogy with what previously stated, Sponsors are invited to draw up a risk assessment plan or to update the existing monitoring plan, in order to implement an action plan taking into account the need to reduce unnecessary contacts in this period of COVID-19 epidemiological emergency and to obtain a balanced and appropriate compromise between the supervision by the Sponsor and the associated risks. First of all, it should be assessed whether on-site monitoring visits can be replaced, or temporarily reduced in frequency, or postponed, by the introduction and/or an enhanced centralised monitoring and central data review.

To maintain a control on the progress of the trial and on the conditions of the subjects, it is preferably suggested to intensify the exchange of information by strengthening the activities carried out from the outside (off site-monitoring), which usually complement the activity of on-site monitoring, such as

phone calls with the site, video conferences, e-mails and other online communication tools with the investigator and the clinical staff.

However, when suitable guarantees to protect the fundamental rights and freedoms of the interested parties exist, in consideration of the urgency or the urgent need for supervision by the Sponsor/CRO, temporary and alternative monitoring methods can be implemented according to methods established by the data controller and consistent with the security measures adopted by the data controller himself, that take into account the highest level of risk associated with this methodology.

If, in accordance with the Sponsor's risk assessment, the SDV (Source Data Verification) cannot be postponed and, where appropriately justified by the intent to protect the rights and wellbeing of the trial participants (GCP-ICH § 5.18.1 (a)), other remote monitoring methods (for example, temporary access to the data contained in the electronic medical records of the healthcare facility relevant for the purposes of the trial), can be considered; anyway, they must be clearly described in a procedure that must be agreed with all the subjects involved (e.g. the CRO) and having heard their respective Data Protection Officers (DPO), in accordance with the provisions of art. 37 and following of EU Regulation 2016/679.

In case access to electronic medical records is unfeasible, the transmission of source documents in pseudonymised form or the sharing of such pseudonymised documents in protected and validated virtual spaces, with particular regard to the protection of the subjects information security, represent a temporary situation practicable on an exceptional basis. However, these solutions are to be considered subject to the availability of the site, for which the transformation into pdf of numerous documents and their pseudo-anonymization could represent a burden of work, subject to an agreement with the investigator and after hearing the opinion of the DPO of the Institution which must be provided with all the information on the characteristics of the system to allow an assessment. The Sponsor has the task of identifying the appropriate systems for functionality, security, validation, etc., to share documents and information, based on risk assessments that justify their use in compliance with the subjects rights and the conditions indicated above.

For details on the use of pseudonymised source documents, for the purpose of the SDV, please refer to Annex 1, relating to the "Protection of trial participants' rights during remote source data verification" of the *Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic* published on the European Commission's website, EudraLex Volume 10 *Clinical trials* (https://ec.europa.eu/health/documents/eudralex/vol-10_en).

Results of adjusted monitoring/review measures must be documented in monitoring reports and this modality must be described in the final Clinical Study Report.

Please note that alternative methods must be implemented in full guarantee that access occurs only to the documentation of the trial subjects, limited to the period of involvement in the trial itself.

These alternative solutions are to be considered exceptional derogations and limited to the period in which the emergency conditions persist; subsequently it will be necessary for the Sponsor/CRO to assess the impact of these different forms of monitoring and to foresee, as soon as the situation is normalised, robust follow-up measures, including an increased number of on-site visits, to eventually fill gaps due to the reduced frequency of on-site monitoring.

Among the follow-up measures, please take into consideration the need to submit to on-site monitoring the data that has been subject to remote monitoring, especially those contained in pseudonymised

documents, which cannot be considered as source documents to all effects and considering that remote monitoring is expected to only have focused on the most critical information.

Alternative procedures to obtain the Informed Consent

Given the current emergency situation, the inclusion and enrollment of new participants in clinical trials should be avoided as much as possible, except for those cases whose participation in the study is of fundamental necessity, such as in the absence of a valid therapeutic alternative, or of course, in cases of enrollment in studies where COVID-19 drugs are tested. In case it is necessary to obtain an informed consent (initiation of new studies or amendment to the informed consent for ongoing studies or for the implementation of emergency measures referred to in this notice or simply to avoid exchanges of paper material, which can be a possible source of contagion), where not possible in the usual way, alternative procedures for obtaining it must be considered. The implementation of such alternative procedures (phone calls, followed by e-mail confirmation or validated electronic systems) does not exempt from obtaining written consent as soon as possible, on the first occasion in which the participant goes to the site.

The opportunity to acquire consent from the participants must always be privileged over other solutions, even in cases of subjects who are in physical isolation, for which cameras or photographs of the documentation can be taken through transparent isolation barriers.

In the event that it is not possible to obtain an informed consent signed in writing by the patient pursuant to art. 3, paragraph 1, letter d) of Legislative Decree 211/2003, a temporary oral consent is accepted. In such cases, the presence of an impartial witness who certifies that the consent has successfully been given, by dating and signing the informed consent document at the site, is required. The investigator is responsible for certifying how the impartial witness was selected.

In any case, rules on the personal data processing remain unchanged, with particular reference to the acquisition of the consent to the personal data processing itself carried out in the context of the clinical trial. According to the accountability principle, the data controllers are required to identify suitable measures and prove the successful acquisition of a valid consent to the personal data processing, for example through the voice recording of the consent given by phone or the e-mail keeping.

Compliance with the personal data protection rules

Without prejudice to the preliminary indications provided above also in relation to some fulfilments related to the personal data protection regulation, it is understood that it is up to each individual data controller to identify, if necessary, the technical and organizational measures necessary to ensure that these alternative methods for the clinical trials management comply with the personal data protection regulation set out in EU Regulation 2016/679, with the Personal Data Protection Code, with the deontological Rules for processing data for statistical or scientific research purposes published pursuant to art. 20, paragraph 4, of Legislative Decree 10 August 2018, no. 101 - 19 December 2018, attachment A5 to the Code, and to the Prescriptions relating to the personal data processing carried out for scientific research purposes, attachment no. 5 to the Measure containing the provisions relating to the processing of particular categories of data, pursuant to art. 21, paragraph 1 of Legislative Decree 10 August 2018, no. 101, dated 5 June 2019. In applying the COVID-19 emergency measures, in fact, the principles applicable to the personal data processing enshrined in EU Regulation 2016/679 must be respected, with particular reference to the principles of minimization, integrity and confidentiality of data (art. 5,

paragraph 1, letters c) and f)), according to the solutions deemed, from time to time, more appropriate and suitable for the specific case. To this end, please note that each data controller can take advantage of the advice and support of the data protection officer, designated pursuant to art. 37 of the GDPR.

General considerations

The measures contained in this notice are of an exceptional nature and represent a derogation from the applicable rules and practices, therefore a CRO cannot proceed to apply these exceptional measures without informing the Sponsor, who, in accordance with the GCP, remains the final person responsible for the trial.