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

This update is related to remote source data verification (rSDV) options during the COVID-19 pandemic and the possibility of using the e-informed consent process.

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1. Preamble

Please note that this document should 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 Federal Agency for Medicines and Health Products (FAMHP), the Clinical Trial College and the Belgian Association of Research Ethics Committees (BAREC).

The information in this guidance should be applied from the moment of publication until a new version becomes available. 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 email addresses for information requests:

- ct.rd@fagg-afmps.be;
- ctrpilot@fagg-afmps.be (for information requests on pilot dossiers).

2. Procedure and communication with the authorities

2.1. General principles

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

In order to allow the FAMHP to prepare and to plan all incoming COVID-19 submissions, sponsors/applicants are requested to contact the FAMHP preferably two weeks before submission of the dossier:

- for pilot dossiers: ctrpilot@fagg-afmps.be;
- for all other procedures: ct.rd@fagg-afmps.be.

Please be reminded that Scientific Technical Advice can be requested via sta-wta@fagg-afmps.be. If the corresponding CTA for the pilot is submitted in the following two years, the fee does not have to be paid.

2.2. Submission of the COVID-19 trial

When considering submitting a multi-country trial related to COVID-19, please consider the accelerated Voluntary Harmonisation Procedure. All other submissions to the FAMHP should be done exclusively electronically via the Common European Submission Portal (CESP). Clearly mark all applications with 'COVID-19' in the subject field and indicate this in the cover letter as well.

For national interventional trials related to COVID-19: the submitted dossier can follow the requirements of the law of 7 May 2004 or the requirements of the CTR. However, the accelerated CTR pilot is strongly recommended. The pilot has the advantage that a single submission to the national contact point (FAMHP) is sufficient and that a single review by the selected evaluating EC (without any local ECs) is foreseen.
The requirements of the CTR are described in the CTR Pilot Project procedure for sponsors (section 8).

As of 15 February 2021, the FAMHP adapted a temporary procedure with time slots for CTR pilot applications, in order to limit the number of CTR pilot initial applications accepted per period of time (two per week). However, these time slots do not apply to COVID-19 initial applications and, as such, COVID-19 applications can be submitted

within the CTR pilot without having a reserved time slot. More information on clinical trial applications is available on the FAMHP website.

The Clinical Trial College (CT-College) can use adapted criteria to select the evaluating EC and send the dossier to an EC of the CTR Pilot that has applied to take part in this procedure and has committed to perform the review within the short delays that apply for COVID-19 applications (see 2.2). This may be the EC of the site.

When validating the dossier, it will be accepted that certain other administrative documents (e.g. written statement on the suitability of a site, assurance certificate) are missing. The sponsor is requested to provide any missing documents together with the answers to the Request For Information (RFI).

2.3. Modifications to ongoing non-COVID trials

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 master file of the trial's site, this summary report should be provided to the FAMHP and EC by the national end of trial date.

In order to avoid over-reporting, sponsors are asked to keep a list/overview of all mitigation measures taken due to the COVID-19 situation that are not permanent amendments/modifications of the protocol and not urgent safety measures. Sponsors should provide a description, explanation and justification of each measure taken.

The sponsor is also requested to provide the list/overview of measures taken and the concerned ECs (for standard 2004 dossiers) every four months to:

- for pilot dossiers: ctrpilot@fagg-afmps.be;
- for all other procedures: ct.rd@fagg-afmps.be.

2.4. Timelines

For non-ATMP (Advanced Therapy Medicinal Products)/non-GMO (Genetically Modified Organisms) COVID-19 trials, the FAMHP commits to review the complete dossier within four working days after submission (as indicated by the T0) to the first round of questions. For clinical trials involving advanced therapies (somatic-cell therapy medicinal products, tissue-engineered products or gene therapy medicinal products) or medicinal products containing genetically modified organisms (GMOs), a shorter deadline of ten working days applies. These timelines apply both for CTA applications according the standard 2004 procedure as for CTR pilot applications. The timelines also apply to the evaluating EC for CTR pilot applications.

2.5. Management of COVID-19 vaccination for subjects participating in ongoing non-COVID-19 clinical trials

Sponsors of ongoing clinical trials for indications other than treatment or prophylaxis of COVID-19 are required to evaluate the impact of the current government programme for the deployment of a COVID-19 vaccine on each trial for which they are responsible. The sponsor should conduct a specific risk assessment for concomitant use of a COVID-19 vaccine for each Investigational Medical Product (IMP) and with specific consideration for the trial population. Any changes to the protocol regarding the possibility for trial participants to receive the vaccine should be submitted as a substantial amendment to the FAMHP (for CTR pilot applications) and concerned ECs (for CTA applications according the standard 2004 procedure).

For new trials, sponsors are encouraged to address potential vaccination in advance in their protocol and include the appropriate flexibilities in order to avoid the need for substantial amendments at a later stage.

3. Restrictions on visits to healthcare facilities

In circumstances where it is not advisable for subjects to go to the trial site for a visit, or where they would not be allowed to do so (e.g. due to quarantine conditions), the visit may be replaced by home nursing (visit of a health care professional at home), or by contact via phone. This may be required to identify adverse events and ensure continuous medical care and supervision. This is already provided for in the European Guidance.

Special cases may arise, for example when a Belgian patient is enrolled in a trial in another member state. As a result of the COVID-19 situation, the foreign site closes down. The Belgian patient returns to Belgium. The same trial is not started in Belgium. The patient wants to continue the experimental treatment as he benefits from it. The principal investigator (PI) and the sponsor are asked to find a solution in the best interest of the participating patient. In this case there are two possibilities:

- a new trial is launched in Belgium (initial CTA dossier to be submitted to both EC and FAMHP) which is not recommended in current circumstances;
- or the sponsor relies on the patient to drop out of the clinical trial on the basis of the Royal Decree of 14 December 2006, articles 105 and 107/1 (compassionate use).

4. Shipment from the site to the patient

The European Guidance states that: "Direct IMP delivery from sponsor to trial participant is accepted in a few member states in this emergency situation. The sponsor should consult the national competent authority (NCA) guidance on the possibility of direct shipment from sponsor to trial participant, as it is likely that such measures can only be implemented for a limited period and under specified conditions (e.g. agreement with sites, special couriers with procedures to allow direct delivery only 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.)."

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, in order to protect the rights (confidentiality) and safety of the participants, a continued supply of trial medication must be kept at home.
the trial medication may also be shipped directly from the trial site to the trial participants via courier, under responsibility of the principal investigator.

It is allowed to send the shipment from the distributor to the patient provided that all the conditions prescribed in the European and the national guidance (below) are met, except that for Belgium the distributor (not the courier service) is not allowed to work with the data of the clinical trial's participant but only with the trial number of each participant. This is only possible provided that the product is suitable for transport, storage at home and administration at home use.

The participant's name, address and contact details may never be disclosed to the sponsor and distributor. The distributor will only have access to the participant's trial number in order to track the shipment, its preparation and storage at the distributor site. Only the courier service has access to the full details (name, address) of the trial

participants communicated by the PI staff. The only link between the distributor and courier service should be the participant's trial number. In other words, the distributor and the investigator only need to communicate on the participant's number, as well as the size, number and the quality state of the kits (temperature and status) reported by the investigator upon receipt by the trial participant. Only the courier service has access to the participant's data (only name and address, no health information), this personal data should not be stored for a longer period than is required for the purpose of dispatching the IMP.

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

Any additional training of the participant, care giver, nurse or physician should be documented. Special attention should be paid to recording 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.

Summary of home administration:
- under PI's responsibility;
- shipment without sponsor involvement (personal data protection);
- under correct shipping conditions;
- with correct and traceable documentation;
- patient is trained for storage, administration at home or administration is conducted by a trained (i.e. trained in terms of the protocol) caregiver, nurse or physician.

It is important to emphasize that documentation is of utmost importance. 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 (name and address) of the patient. The responsibilities of each party in this process have to be documented.
It should also be clear that the shipment cannot take place at the patient's expense.

What needs to be done 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 for the participant, caregiver, 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 to 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.
Administration of trial medication by site staff, general practitioner, nursing staff are indeed possible outside the site (e.g. at home, alternative location). This change should be requested by the study site. A substantial amendment should be submitted to the FAMHP and the EC. All changes in shipment should be paid for by the sponsor if they are necessary to ensure the continuity of the study.

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

A temporary halt (e.g. recruitment halt, halt of the trial at a site) of the trial shall be submitted by the sponsor to the FAMHP and the EC within fifteen 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 well be sent, not an official approval.

If the reason for stopping the recruitment for several ongoing clinical trials is the same for each one of the clinical trials, it is necessary and sufficient for the sponsor to only send one temporary halt notification listing all clinical trials concerned.

In order to restart the trial after temporary halt, a substantial amendment must 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 this is again possible after notification to the FAMHP and the EC.

Urgent safety measures taken in the context of the coronavirus may be taken without prior notification to FAMHP and the EC. However, the sponsor must inform the FAMHP and the EC as soon as possible of the measures taken and the plan for further action. Sponsors can report to the FAMHP via CESP or ct.rd@fagg-afmps.be (for pilot projects: ctrpilot@fagg-afmps.be). A substantial amendment must be submitted afterwards.

A protocol deviation (control of visits, etc.) should be considered as an urgent safety measure (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 should only be submitted for critical protocol deviations (those which are really impacting safety), not for minor deviations.

An individual DIL (dear investigator letter, per study/compound) has to be reported to the FAMHP and EC if it is part of an USM and/or a substantial amendment. Once again only DILs 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 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 verification of source data (e.g. providing sponsor with copies of medical records/charts of the participant or remote access to electronic medical records) which would require the site staff to redact all medical records, would likely be too burdensome for the sites at this time, nor would it allow sufficient verification by observers.

However, remote source data verification (SDV) could be approved during the current healthcare crisis for trials involving COVID-19 treatment or prevention, or for trials in the final stages of data cleaning before database lockdown, or in pivotal trials investigating

serious or life-threatening conditions with no satisfactory treatment option and under the following conditions:

- on site monitoring is not allowed by the institution or is not feasible.

- An agreement has been setup describing rSDV which is approved by all parties (institution, principal investigator and the sponsor or the CRO assigned).
- The rSDV can be organized by the investigator's site and is therefore technically feasible without compromising the confidentiality of the Electronic Medical Records data.

Evidence of the above conditions must be added to the submission file.

In case of ongoing trials, the introduction of remote source data verification should be submitted via a substantial amendment.

7. Electronic submission of dossiers and electronic signatures

- For the informed consent form (ICF) or to obtain (re-)consent, please follow the European guidance.
  More detailed information on the e-consent process can be found in the e-ICF guidance on the website of the CT-College.
- For other documents (cover letter, application form, protocol): a scan or photograph of the signed paper will be accepted.
- It is currently accepted to submit a word or a PDF file which is unsigned and mentioning that a signed version will follow later.
- Qualified electronic signatures will be accepted if using a trusted service provider, but are not mandatory.

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Annex 1: Frequently asked questions

Answers to the frequently asked questions are written in *Italics.*
The answers given below are valid at the time of publication, but views might change due to altered circumstances.

Where mentioned that the Ethics committee is to be notified, this means:

- for COVID-19 trials evaluated in the Pilot Project the sponsor needs to submit the notification to the FAMHP (which will transfer it to the College for transfer to the evaluating EC). A notification that is submitted to the FAMHP as a substantial modification, will also be transferred to the site's CEO (and EC).
- for COVID-19 trials evaluated in the standard 2004 procedure, the sponsor needs to submit the notification to the FAMHP and to all ECs involved in the approval procedure, central and local ECs.

A. Priorities

Question 1
All hospitals have reduced their non-urgent activities in order to be prepared for COVID patient care. Nevertheless, Ethics Committees continue to receive submissions of new non-COVID-19-related CTAs (via the standard 2004 procedure or via the CTR pilot project).

Why is the FAMHP (and CT-College) not recommending sponsors to stop submitting new non-COVID-19 trials and as such support all ECs to be prepared to evaluate COVID-19 trials with priority?

For non-COVID-19-related CTAs submitted to the FAMHP:
although the situation may change rapidly the FAMHP has currently decided not to prohibit the submission of new non-COVID-19-related trials, based on a risk assessment. If the CEO of a hospital has recently signed a written statement (for a CTR Pilot Project trial), we all assume this is an important trial, regardless of whether it is related to COVID-19 or not. If a less urgent trial has been accepted by a hospital before the outbreak of the Corona pandemic, changed priorities for the evaluation should be discussed with the sponsor and/or investigator.

For non-COVID-19-related CTAs submitted to the ECs:
submissions of non-COVID-19-related or purely observational trials will usually be regarded as non-urgent by the Ethics Committees or prohibited at the trial sites. Please consult the website of the relevant ECs to verify the timelines for the evaluation of these types of trials. Each EC will make every effort to maintain the official timelines as much as possible.

Question 2
The COVID-19-related trials are mainly carried out in university hospitals. Does the national guidance also apply to other hospitals?

The national guidance is applicable to all clinical trial sites in Belgium.

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B. Procedures

Question 3
I want to submit a COVID-19 trial. When should I contact the EC and the FAMHP?

If you are planning to submit a COVID-19 trial, please take into account the following recommendations:

- *Contact the FAMHP via email as soon as possible before submission and if possible no later than two weeks before submission:*
  - *ct.rd@fagg-afmps.be* for standard 2004 procedure;
  - *ctrpilot@fagg-afmps.be* for CTR pilot procedure.
- *Select the correct regulatory procedure you will use to submit the application:*
  - *the accelerated Voluntary Harmonisation Procedure (multi-*country trials only);
  - *the standard 2004 procedure (four working days for the FAMHP for non ATMP/non GMO medicinal products);*
  - *the accelerated CTR-Pilot – which is strongly recommended (four working days for FAMHP and evaluating EC for non ATMP/non GMO medicinal products).*
- *Please submit trial applications that are complete (except for some administrative documentation). Incomplete dossiers are a burden for both the FAMHP, College as Ethics committees and this does not speed up the evaluation process. Incomplete dossiers might be considered invalid.*
- *Please ensure the protocol title, the synopsis and the EudraCT application form start with "COVID-19".*
- *Always submit the application to the FAMHP through CESP. Clearly mark all applications with "COVID-19" in the subject or comment field and indicate this in the cover letter as well. If you encounter difficulties in the submission of the dossier via CESP, please contact FAMHP via email.*
- *If submitting via the standard 2004 procedure, please submit to each of the ECs. We cannot guarantee that each EC will perform the standard 2004 procedure evaluation in four or ten working days.*
- *When applying via the highly recommended CTR Pilot, the clinical trial application has to be submitted only to the FAMHP. In that case, it is not allowed to submit in parallel to the EC. In the CTR pilot procedure the National Contact Point (ctrpilot@fagg-afmps.be) is the sole contact point for the sponsor.*

Question 4
The FAMHP will process COVID-19-related CTAs submitted via the CTR Pilot procedure within four working days (regardless of whether this is according to the structure of 7 May 2004 or that of CTR 536/2014).
Is this also the case for files submitted under the current regulations (Directive 2001/20/EC) – the standard 2004 procedure?

For non-ATMP/non-GMO COVID-19 trials, this is correct. All COVID-19 CTAs will undergo an accelerated review by the FAMHP (four working days after submission of a complete dossier, as indicated by the T0, to the first round of questions). The four working days do not take into account these questions, requests for information (RFIs in the CTR Pilot Project procedure) or grounds for non-acceptance (GNA's in the standard 2004 procedure), are being sent out.

These timelines will also depend on the number of COVID-19 trials and the FAMHP's capacity. If the volume of COVID-19 trials exceeds the FAMHP's enhanced capacity, the FAMHP may decide to apply criteria to prioritise the submitted CTAs.

Question 5
If the CTA is submitted via the accelerated CTR Pilot, the FAMHP commits to validate and review all COVID-19-related CTAs within four working days, as will do the evaluating EC.

What are the timelines in case a multi-centric COVID-19-related CTA (or non-IMP study) is submitted under the current regulations (standard 2004 procedure)? Will each local EC as well as the central EC have to issue an opinion within four working days?

If the dossier is submitted under the standard 2004 procedure, every local must provide an opinion. The timelines applied by the different ECs may differ. It is recommended to consult the website of the relevant lead EC to verify the timelines for these types of evaluations.

Question 6
When the CTR Pilot procedure is followed: will a new central EC be chosen for studies already in progress (which were not initially approved through CTR Pilot) submitting an amendment following COVID-19, or will the original EC (which was not chosen under CTR Pilot procedure) simply be the EC of the sponsor's site?

For ongoing trials, the EC remains the same.

Question 7
What are the requirement to submit a COVID-19 CTA trial via the CTR pilot procedure?

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 a written statement on the suitability of the site for each site.

If you choose to submit a COVID-19 CTA dossier following the CTR pilot procedure, please use the dossier structure according to the CTR pilot guidance for sponsors (V9.1, section 8) as available on the FAMHP website.

Question 8
The national guidance mentions: "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."

Does this mean that a participating centre would be allowed to give advice?

In the CTR Pilot project: the CT-College usually selects an evaluating EC independent of the sites where the trial is conducted. The criteria are described in the Royal Decree of 9 October 2017. The CT-College selects from a list of fifteen ECs (that are recognized or aim to be recognized according to the law of 7 May 2017). For the evaluation of COVID-19 trials around ten Ecs (from this list) have committed to perform the review in four working days after submission. In some particular cases (e.g. due to lack of capacity), the CT-College may assign the evaluation of the CTA to the EC of a site where the trial is conducted.

Question 9
Is the FAMHP still actively working/available to review new trials?

Yes, but COVID-19 trials have a much higher priority (see also Q1).

Question 10
What are the requirements for the IMP to be shipped from a site to the patient by CRO and can a sponsor recommend courier services?

There should be a documented agreement of the PI, the final shipment should be signed for approval by the site, and the rules of patient privacy should be respected.

This means an approval (signed, or if not possible confirmed by email) from the PI (or treating sub-investigator, SI) that he/she agrees that 'this amount XXX of IMP XXX' can be shipped to the patient as alternative way of providing the IMP to the patient. There should always be proof that the PI/site has oversight and that the treating physician takes the decision on the IMP shipment, and off course that the privacy of the patient is not violated.

Question 11
Do the Belgian authorities allow on-site labelling if the sponsor wants an unblinded pharmacist to blind the medication on-site?

Yes, provided it is for COVID-19 medication and there is a clear blinding plan.

Question 12
A sponsor wants to add a new trial site for an approved COVID-19 trial in Belgium. As is stated in article 11 of the law of 7 May 2004 a new trial site can only added after a three-month period has lapsed between approval and substantial amendment.
Given the urgency of adding trial sites to COVID-19 trials, would the Ethics Committees accept substantial amendments to add new sites sooner than three months after the initial single opinion of the EC.

Ethics committees will accept sponsors to add new sites to a COVID-19 trial via a substantial amendment/modification, even if the time period of three months – between approval and substantial amendment - was not lapsed.

C. ICF and ICF procedure

Question 13
Would it be acceptable to only submit an English ICF in the initial package, and the translations in Dutch and French a few days later?

The ICF document should be provided in the language of the participants (French and/or Dutch).

Question 14
Would it be acceptable to not use the BAREC ICF template, upon specific request of the sponsor, to reduce the turnaround time in the ICF approval process by the sponsor?

We cannot oblige the sponsor to use the ICF template for COVID-19-related trials but if the template is used, the evaluating EC will not have comments on the fixed paragraphs of the template. This will speed up the evaluation process.

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Question 15
Is a consent of the participant necessary in case of urgency?

In case of urgency the law of 7 May 2004 (Article 9) and the law of 22 august 2002 (Wet patiëntenrechten, Article 8, §5) must be followed.
If the sponsor would like to use the law of 22 august 2002 (Wet patiëntenrechten, Article 8, §5) this needs to be described in the protocol. In addition, an ICF must be available when the patient is recovered, to ask his/her consent.
The investigator is expected to record why it was not possible to obtain consent from the participant prior to enrolment.

Question 16
What are the guidelines for ICF signatures of patients in isolation (mainly in ICU)?

As described in the ICH guideline 4.8.9. and in the EU guidance: "If written consent by the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given orally by the trial participant (Article 2(j) of Directive 2001/20/EC) in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent document and the investigator is expected to record how the impartial witness was selected." This witness may also be a health care professional that is working in the quarantine area.

Question 17
What is the (re)consent procedure?

For example: if a COVID-19 patient participating in a non-COVID-19 trial, due to quarantine conditions that apply in the hospital, is not able to give a written re-consent, an impartial witness may record the oral consent of the subject. Once the COVID-19 patient is not contagious anymore, a written re-consent should be obtained.

Another example: a COVID-19 patient is not conscious but eligible for a COVID-19 trial. If the approved protocol includes an emergency consent procedure, the patient may be included, but as soon as they regain consciousness, they should sign an ICF to confirm his/her continuation in the trial.

The process to obtain consent should be described in the protocol and/or ICF (or temporary valid protocol/ICF addendum to be submitted via a substantial amendment) and approved by the EC. The investigator should document clearly which procedure of (re)consent they have used.

Question 18
ICF amendments may be sent to patients (electronically/by post), subject to clarification of the changes to the ICF.
Can patients send the signed ICF back and then have it signed by the physician (i.e. possibility on two different dates between patient and physician)?
Or should any amendments be communicated to the patient by telephone and not be signed by both parties until the next on-site visit?

This procedure is described in the EU guidance. The best option is to contact the patients by telephone first, give the necessary explanation and deliver the ICF amendment to the patient preferably by email and not by post, given the discussions about the risk of infection and transmission on paper.

This process should be clearly and completely recorded in the relevant patient study file, medical chart and/or electronic patient record EPD. Afterwards, once the patient can go to the hospital again for his next visit, the patient and the investigator have to sign the ICF together.

For other ongoing trials, there may be a need to re-consent trial participants that were already included. However, avoid the need for trial participants to visit investigator sites for the sole purpose of obtaining re-consent. If re-consents are necessary for the implementation of new urgent changes in trial conduct (mainly expected for reasons related to COVID-19), alternative ways of obtaining such re-consents should be considered during the pandemic e.g. contacting the trial participants via phone or video-calls and obtaining oral consents supplemented with email confirmation.

Approved updated ICFs should be provided to trial participants by email, mail or courier before re-consent is obtained. Any consent obtained in this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites.
In addition, as stated in the EU guidance: "Any validated and secure electronic system already used in the trial in the particular member state for obtaining informed consent can be used as per usual practice and if in compliance with national legislation."
More information can also be found in the e-informed consent guidance.

D. Temp halts and Urgent Safety Measures

Question 19
When the institution or site decides to temporarily stop recruitment of new patients in interventional studies, should all ongoing drug studies be listed and should a temporary stop notification be made?

The national guidance mentions: "If the rational to discontinue the recruitment into the ongoing clinical trials is the same for all clinical trials, it is needed and sufficient that the sponsor sends only one temporary halt notification that lists all the concerned clinical trials."

Only a recruitment stop notification should be submitted to the FAMHP and the EC.

Question 20
Should a temporary halt of recruitment be notified within fifteen days if this decision is taken on a global level, on a country level (recruitment halt for all Belgian sites) or on a site level?

Independent of the level, if there is a temporary halt, it should be notified within fifteen days of the decision.

Important: in order to restart the trial after a temporary treatment halt, a substantial amendment must 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 is only a halt in recruitment due to the COVID-19 crisis, it will be acceptable to restart the recruitment when it is possible again after notification to the FAMHP and to the EC.

Question 21

Should the FAMHP be notified in case of a temporary halt of recruitment (and patient treatments are continued) and in case of a complete temporary halt of the trial (including recruitment and treatment halt).

Yes, in both cases the FAMHP and the EC should be notified.

Question 22
In case of a complete temporary halt of the trial should the FAMHP (and the EC) must be notified within fifteen days of the decision?

Yes, both the FAMHP and the EC should be notified within fifteen days of the decision.

Question 23
Is it required to submit a substantial amendment following each USM?

Yes.

Question 24
Can a substantial amendment following an USM, contain other changes than the USM changes?

Yes.

Question 25
Usually it is not possible to submit a new substantial amendment (SA) if a SA is currently under review by the EC and/or FAMHP. Would there be some flexibility during the pandemic period, so that an additional SA can be submitted during the review of a previously submitted SA or to add extra changes to an already submitted SA?

A substantial amendment that is related to the COVID-19 pandemic can be submitted while a previous SA is still under evaluation. However, if the two amendments would be linked e.g. protocol and IB amendment, we advise you to submit them together, or for example to await the feedback of an IB amendment before submitting a protocol amendment (unless very urgent in the current pandemic situation) since the review of the IB can have an influence on the protocol as well, e.g. risk mitigation measures. In that case, you could already take into account possible protocol remarks (coming from the IB assessment) when you submit the protocol amendment.

But if the first amendment is a legal representative amendment, and the second one for example an IMPD amendment, this IMPD amendment can already be submitted while the evaluation of the legal representative amendment is still ongoing. Sponsors should group amendments that are linked as much as possible.

Question 26
What measures are considered as substantial urgent safety measures (USM) that should be notified as soon as possible to the FAMHP and EC?

A protocol deviation (control of visits, …) should be considered as a 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). These measures are to be considered as substantial urgent safety measures and should be notified as soon as possible to the FAMHP and EC.

The national guidance mentions: "Urgent safety measures taken in the context of coronavirus, may be taken without prior notification to FAMHP and the EC. The sponsor must inform the FAMHP and the EC as soon as possible 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) and a substantial amendment must be submitted afterwards."

Question 27
How often should the sponsor provide the listing/overview of measures taken?

The sponsor should provide the listing/overview of measures taken every four months to CT.RD@fagg-afmps.be. Please start counting from the first reported deviation reported, then add four months.

Question 28
What is expected for the reporting and classification (USM vs Substantial amendment vs non-critical Protocol Deviations)?

This concerns especially the non-critical protocol deviations which are taken in the four-monthly listing. The sponsor and investigator need to analyse and document each decision whether it is a substantial amendment or not.

- *Any changes for the patient, i.e. not provided for in the protocol and has already been explained to the participants, as well as the way in which this is communicated to the patient, must be reported to the EC immediately;*
- *new patient documents must be approved in a SA;*
- *if an abnormality poses a risk to the patient/other patients and/or the course of the study, this must also be reported immediately.*

Question 29
The national guidance mentions: "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." What are the specifications for this listing?

Sponsors should provide a listing every four months, as well as the overall summary at the end of trial.
The four-month listing should be sent at the same frequency to FAMHP and EC.

It is important that substantial amendments are filed and everything that is not according to CT-1 a substantial amendment and what is not a temporary halt, will be on the four-monthly listing and in the overall summary at the end of the trial.

There should be one listing per sponsor, per trial, including each of the measures taken, in chronological order.

Question 30
Which amendments regarding control visits are considered as urgent safety measures?

If an on-site visit is not possible and is delayed outside of the required protocol window it is not considered as an urgent safety measure, but must be well explained and documented on-site and must be part of the non-SA listing (every four month). Nevertheless, if the ICF needs to be adapted, this should be considered as a substantial amendment.

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E. Risk assessment

Question 31
What happens if the sponsor of an international drug study did not carry out a risk assessment? Should the national coordinating centre in each country take over this task as "sponsor of that country"? Could this be determined separately for each country?

The sponsor is responsible to perform risk assessment as described in ICH GCP 5.0 (specifically risk identification, risk evaluation and risk control). The national coordinating centres may play a crucial role in providing the necessary information and input on the best course of action. Even if the sponsor does not temporarily suspend the trial, the investigator is ultimately responsible for the safety and wellbeing of the trial participants in his/her study site and as such may decide to suspend some study procedures in order to guarantee the trial participant's safety. These actions need to be properly justified and documented.
The EU guidance also mentions: "changes to ongoing trials: … The changes above may also be initiated by the investigator sites contacting the sponsor."

Question 32
Who decides to place the recruitment "on hold", the hospital/investigator or the sponsor?

The European Guidance mentioned the following.

- *In section 2 (Initiating new trials):*

"The feasibility of starting a new clinical trial or including new trial participants in an ongoing trial should be critically assessed by sponsors. Additional risks to participants should be addressed in the risk benefit section of the protocol along with risk mitigation measures (see also "risk assessment" below)."

- *In section 5 (Risk management section):*

"All decisions to adjust clinical trial conduct should be based on a risk assessment by the sponsor (ICH GCP section 5.0). It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual participant and implements measures which prioritise subject safety and data validity. In case these two conflict, subject safety always prevails. These risk assessments should be based on relevant parties' input and should be documented on an ongoing basis. It is important that sponsors in their risk assessment consider prioritisation of critical tasks in the clinical trial and how these are best maintained.
The sponsor should reassess risks as the situation develops. This reassessment should also be documented."

- *In section 7 (Agreement with and communication to sites and participants):*

"In addition, trial participants should be informed by the investigator, in time, about changes in the conduct of the clinical trial relevant to participants (e.g. cancellation of visits, change in laboratory testing, delivery of IMP)."
So recruitment can be put on hold based on a thorough and documented risk analysis and in consultation with the research site.
There's no ban from the FAMHP on recruiting any more patients. However, the investigator may decide after a risk analysis that it is not in the interest of the patient to be included in an ongoing trial. The sponsor may also decide to (temporarily) discontinue recruitment for safety or data integrity reasons.

In all cases, whether it is the sponsor that decides to temporarily stop the recruitment or whether the hospital decides no further recruitment in ongoing clinical trials is allowed, the FAMHP and the EC should be notified of this decision (recruitment halt notification).”

F. Restrictions of visits to healthcare facilities

Question 33
If the subjects are advised against going to the investigator site, what are the possibilities for IMP administration and what happens if the determined timelines cannot be implemented?

The national guidance specifies the conditions under which home treatment of IMP can be considered. If IMP treatment intervals cannot be maintained according to protocol, the action will depend on the medicinal product and the protocol. It is up to the investigator and sponsor to determine the best course of action, taking into account that the subject’s safety is the primary concern.

Question 34
What does “home nursing” mean under point three of the national guidance?

This means that if a visit at the hospital (e.g. for treatment or follow-up) is not possible, a healthcare professional visit the participant’s home.

Question 35
When are products suitable for transport to the patient?

The IMP should be kept under proper storage conditions during transport and at the participant’s home. For example, if the IMP is to be stored at 2-8°C until administration, the transport will have to be in refrigerated conditions. The temperature should be logged for documentation purposes. While oral tablets might be suitable for home use, intravenous infusion may not be suitable without the help of a registered and trained nurse.

Question 36
Can another person be responsible for reception, handling and storage of medication besides the patient himself?

A *family member or caregiver may handle the receipt of the IMP. Documentation of shipments is essential in tracing the IMP in terms of dosage taken and avoiding IMP loss. If the burden of receiving IMP at home is too large in the opinion of the investigator, the trial participant may be instructed to go to the site. If this is not possible and the participant cannot receive the IMP at home, the investigator may decide to (temporarily) terminate the trial treatment according to their judgment. Protocol stopping criteria may apply in this case.*

Question 37
How will participants be trained? How is this training organized/documented?

Participants may be trained by (video) calls, providing written instructions. Acknowledgement of training can be done via email or other documentation. All instructions provided to a participant should be submitted as a substantial amendment to the EC.

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Question 38
Can amendments only be implemented after EC approval?

Section 4 "Shipment from the site to the patient" mentions:
"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."

Any written information provided to the participants should be approved by the EC. All COVID-19-related substantial amendments, submitted in the CTR Pilot project will be reviewed within four working days after submission of a complete dossier to first round of questions.

Question 39
Is it allowed to share clinical trial data which has been captured in a pseudonymised way without any reference to the participant's identity if a limited amount of data still needs to be verified by the sponsor without the need for access to medical records?

This is a data base review and not Source Data Verification (SDV). Therefore, it does not violate the participant's rights and can therefore be allowed given the current exceptional circumstances.

Question 40
Would remote monitoring be considered by the Belgian authorities in critical situations (e.g. in early phases)?

Remote monitoring is not forbidden, i.e. contact with the site, discussion on the e-CRF, on the Site Master File and Training of staff, ensuring the site pays attention to the input in the e-CRF, coaching them on the quality of the data reported in the CRF.

Update: according to version 3 of this guidance: Source Data Verification (SDV), i.e. verification directly in the "e-Health Records, Patients files, Medical files" as definition of the main "source documents" of a CT, is only allowed under certain conditions as specified in section 6 of this guidance.

Question 41
A client would like to expand its activities to the shipping of clinical products (investigational medicinal products and medical devices), from a clinical investigator site to the residential address of a patient registered as a clinical trial participant. This service would be offered to clinical trial sponsors, contract research organisations and other types of organisations involved in the performance of clinical trials.

Would this client be regarded as a courier in the sense of the guidance? If the client is regarded as a courier, is it sufficient to conclude a contract with the sponsor or must the principal investigator also be involved in the contract (a tri-party agreement)?

The client is indeed a courier. A tri–party agreement is needed to clarify responsibilities. Under no circumstances may the sponsor obtain patient personal data, and this should be part of the agreement.
A documented agreement of the principal investigator/sub-investigator is mandatory to approve this course of action to provide IMP to the patient. The agreement is part of the Investigator Site File.

Question 42
If the shipping arrangements are modified, should this be considered as a non-substantial amendment or is it a mitigation measure that has to be included in the four-month listing?

If the shipping arrangements are modified and there is no additional training for the patient, the amendment can be considered as non-substantial and should be included in the four-month listing.
If training is necessary for the patient, caregiver or nurse and this was not yet foreseen in the protocol it should be considered as a substantial amendment.

Question 43
If instructions for oral administration or self-administration are already in place and the patient is already self-administering the medicine, should the sponsor still provide training?

If the patient is already self-administrating the medicine, no additional training on self-administration would be required. There should however be handling and storage instructions for the IMP provided to the patient. These instructions do not constitute a substantial amendment when the patient is already self-administrating the IMP.

Question 44
If the training at home requires an amendment to the protocol, a substantial amendment has to be submitted to FAMHP/EC. When can the training be given? Could it be done before the submission of amendment and before approval by the ECs?

This should be based on the risk analysis. If urgent, the training should be given immediately. For FAMHP: if the amendment is a USM, the training can be done before submission, but submission has to be done as soon as possible.

ECs would like to receive the addendum before implementation. The evaluation process for a COVID-19-related substantial amendment will also follow the accelerated procedure: four working days from submission of a complete dossier to first round of questions.

Question 45
If the addendum of the ICF does not have to be amended, could the implementation of the training be documented that the DTP (direct to patient) has been discussed with the patient and agreement has been received orally?

An oral agreement will not be accepted. It must be documented and it is preferred that there is also an email conversation for this process.

Question 46
Is the implementation of training a mitigation measure that has to be included in the four-month listing?

Yes, it has to be included on the listings.

Question 47
Can the rules for the shipment of medicines as described in this document also be applied for patient diaries and pregnancy tests?

Yes, *template diaries and pregnancy tests could be sent to the patient, who in turn may provide the investigator with a picture of the result in those cases where it is considered necessary and appropriate by the investigator for their patient. Given that the investigator has less control on these tests, this decision should be carefully considered. It should be properly documented in the Investigator site file (ISF) where the tests have been performed in deviation of the normal practice of the trial.*

Question 48
For DILs which are not a substantial amendment, the submission as a non-substantial amendment seems redundant, since it will be reported in the four-monthly reports. Could the need for this reporting be re-considered to avoid over-reporting?

If it is not a temporary halt, nor an USM nor an SA is needed, then it must be in the four-month listing.

Question 49
If a Belgian patient is enrolled in a trial in another member state and the foreign site closes due to COVID-19. The Belgian patient returns to Belgium but the same trial is not launched in Belgium. The patient wants to continue the experimental treatment, as he benefits from it. Would it be necessary to register a local investigator, who is able to perform remote visits for these patients and if so, what would be the process for approval of these investigators?

The exceptional procedure described above is to avoid that a trial has to be set up (approved by FAMHP and EC). Of course, it is preferable that a CTA is set up in Belgium, however this might require more resources, and would imply a site visit which is not permitted in most hospitals during the pandemic.

Question 50
Is it allowed that the sponsor sets up an agreement with a courier service, and when needed, the site personnel requests an IMP shipment (temperature controlled) using this service from the site to the patient's home?

This is allowed under exceptional conditions:
- *under PI's responsibility;*
- *shipment without sponsor involvement (personal data protection);*
- *under correct shipping conditions;*
- *with correct and traceable documentation;*
- *patient is trained for storage, administration at home or administration is conducted by a trained (i.e. trained in terms of the protocol) caregiver, nurse or physician.*

Question 51
Would it be allowed to train patients remotely on self-injection for subcutaneous injections during this pandemic (e.g. via live videochat with study nurse/study doctor, via telephone call with study nurse/study doctor, via instruction video)?

Yes, but it is advised to let the participant confirm the training by email to have a documentation of the training.

Question 52
For patients who don't feel comfortable to self-inject, would it be allowed to ship the IMP to the patient's home and to ask them to visit their own healthcare professional to do the subcutaneous injection?

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 these exceptional circumstances we would accept this if the IMP information and dosing instructions are provided on paper for the General Practitioner (GP).

Question 53
Does the change to subcutaneous self-injection require an update to the ICF, or would the patient's oral consent be sufficient?

Any written information provided to the participants should be approved by the EC.

Question 54
Would it be allowed to change prefilled syringes with IMP to auto-injectors for easier use at home, or would this require prior EC/FAMHP approval?

This involves a change to the IMPD so an approval of the FAMHP and EC will be required. Changes to the IMP can have an important impact on the trial outcome/generated data, so the sponsor should first make a change assessment and the possible impact on the trial.

Question 55
Can EPO be sent to patients since in Belgium there is a closed system for the delivery of EPO to patients and EPO is only delivered to hospital pharmacies?

This is allowed, provided it goes via the hospital pharmacy and traceability is according to the rules.

G. GDPR

Question 56
Article 134 of the Belgian law of 30 July 2018 (protection of personal data) describes a deviation from GDPR. Is this a permissible deviation from GDPR during the COVID-19 pandemic?

Exceptions on GDPR aspects should be discussed with the Data protection officer (DPO) of the research site.

H. Contract management templates

Question 57

Contract management for commercial IMP studies : it should be helpful if the authorities require (make it mandatory) the use of the Pharma.be template for all the COVID studies. The timelines of contract management will be significantly decreased.

The FAMHP can only encourage the use of templates in this, not mandate them.

I. Experiments

Question 58
A physician would like to initiate a study to reduce the transmission of COVID-19 to healthcare staff through blood group analysis.

The protocol includes the administration of probiotics by the healthcare staff to increase their levels of circulating natural antibodies. The goal is to obtain a sufficient level of protective antibodies.

The study does not aim to evaluate probiotics, but is used to make sure that staff are sufficiently protected. The study does focus on blood groups. Should this be considered as a clinical trial?

Yes, this should be considered as a clinical trial: submission to FAMHP and EC is required.

Question 59
Can a hospital create a general ICF for non-IMP academic studies where the patient arriving at the hospital accepts to take part in studies approved by the Ethics committee without providing details on the nature of the study?

An EC needs to approve the ICF procedure. However, it is not legal to give a single ICF template to patients just with the information that they are participating in an experiment (or trial) that has been approved by the EC, without knowing the experimental nature of the specific trial that they will eventually participate in.

J. Signatures

Question 60
Is it necessary to use qualified electronic signatures or will other ways of electronic signatures collection be accepted?

Qualified electronic signatures are not required.
If there are already qualified electronic signatures on documents, we accept them (provided the certificate is listed).
But if there are no qualified electronic signatures on the documents, please follow the second and/or third bullet point of section 7:

- *for other documents (cover letter, application form, protocol): a scan or photograph of the signed paper will be accepted;*
- *it is currently accepted to send in a word or PDF file which is unsigned and mentioning that a signed version will follow later.*