

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

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1. Preamble

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

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

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

2. Procedure and communication with authorities

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

Prior to submission of a COVID-19 related trial, contact the FAMHP via email (Mali Stephanie Stephanie.Mali@fagg-afmps.be and Eglem Steve Steve.Eglem@fagg-afmps.be with in cc: ct.rd@fagg-afmps.be).

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

All other submissions to the FAMHP should be done exclusively electronically via CESP. Clearly mark all applications with 'COVID-19' in the subject field and indicate this in the cover letter as well.

For national COVID-19 related interventional trials: the accelerated CTR Pilot is strongly recommended. The pilot has the benefit that a single submission to the national contact point (FAMHP) is **sufficient** and that **a single review by the selected evaluating EC (without possible local ECs)** is foreseen. The submitted dossier can follow the requirements of the law of 7 May 2004 or the requirements of the CTR.

The requirements of the CTR are described in the CTR Pilot Project procedure for sponsors

https://www.fagg.be/sites/default/files/content/ctr_pilot_project_guidance_for_sponsors_v_8.0_19-12-2019.pdf (section 8).

If the dossier requirements of the law of 7 May 2004 are followed for a submission in the accelerated CTR Pilot, please provide the FAMHP also with the documents that are to be evaluated by the EC and additionally with the document in annex 1 (written statement) for each site.

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

At the validation of the dossier, it will be accepted that some administrative documents (e.g. written statement of the suitability of a site, assurance certificate) are lacking. The sponsor is requested to provide any lacking document together with the answers to the Request For Information (RFI).

It is to be reminded that Scientific Technical Advice (sta-wta@fagg-afmps.be) can be requested, where upon submission of the corresponding CTA for the pilot in the following two years, the fee does not have to be paid.

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

For non-ATMP Covid-19 trials in the CTR pilot the FAMHP commits to review in four working days after submission of a complete dossier (as indicated by the T0) to the first round of questions, as will do the evaluating EC.

If the sponsor wants to submit through the standard 2004 procedure, also for non-ATMP COVID-19 related trials, the FAMHP commits to review in four working days after submission of a complete dossier (as indicated by the T0) to the first round of questions.

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

As we do not know how long the current crisis may last, it is also asked to the sponsor to provide the listing/overview of measures taken, at regular basis, every 4 months to ct.rd@fagg-afmps.be and the EC (for standard 2004 dossiers) or to ctrpilot@fagg-afmps.be (for CTR Pilot dossiers).

3. Restrictions of visits to healthcare facilities

In those conditions where it is not advised to have the subjects going to the investigator site for a trial 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 a contact via phone. This may be required to identify adverse events and ensure continuous medical care and oversight. This is already foreseen in the European Guidance.

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

trial and (ii) on the Royal Decree of 14th Dec 2006 Art 105 or Art 107/1 (Compassionate use).

4. Shipment from the site to the patient

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

Direct shipment from sponsor to patient is not allowed in Belgium. What is allowed under these exceptional COVID-19 times under exceptional conditions:

In cases where, for the protection of the rights (confidentiality) and the safety of the participants, a continued supply of trial medication needs to be maintained at home, trial medication may also be shipped directly, under responsibility of the principal investigator, from the trial site to the trial participants via courier. It is allowed also to send the shipment from the distributor to the patient provided that all the conditions prescribed in the European and the national guidance (here below) are respected except that for Belgium the distributor (not the courier service) is not allowed to work with the details of the clinical trial's participant but just 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 trial participant names, address and contact details should never be provided to the sponsor and the distributor. The distributor can only have access to the trial participant's number in order to track the shipment and its preparation, storage at the distributor site. Only the courier service will be able to have the details (name, address) of the trial participants communicated by the PI staff. The only link between distributor and courier service must be the trial participant number. Said in another way : the distributor and the investigator have just to communicate on the participant n°, the size, the number of kits and the quality state (t° and status) reported by the investigator after reception by the trial participant. Only the courier service will have the details of the participant (just name and address, no health information) and they should not store the personal data of the trial participant for a longer period than is required for the purpose of dispatching the IMP.

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

Any additional training from the participant, care giver, nurse or physician must be documented. Special attention should be paid to capturing adverse events and informing the PI of the subject's health and wellbeing in this off-site setting.

The GMDP and GCP requirements for transport and storage of investigational medicinal products remain in place.

Concluding:

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

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

Administratively:

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

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

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

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

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

A temporary halt (e.g. recruitment halt, halt of the trial on a site) of the trial shall be submitted by the sponsor to the FAMHP and the EC within 15 days of the decision. A temporary halt is not a substantial amendment but it is communicated via CESP to the FAMHP through the Substantial Amendment Notification Form (Annex II Section E.4.). Only a confirmation of receipt is sent, no official approval.

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

In order to restart the trial after temporary halt, a substantial amendment must therefore be submitted. The trial can only restart upon approval by the EC and if no motivated objections have been raised by the FAMHP within legal deadline.

If the temporary halt of recruitment is only due to the COVID-19 crisis, it will be acceptable to restart the recruitment when again possible after a notification only to the FAMHP and to the EC.

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

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

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

6. Remote Source Data Verification

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

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

7. Electronic way of working and accepting possible electronic signatures

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

Annex 1 – written statement on the suitability of the CT site

Statement of CEO/ person acting on behalf of CEO

Concerning

Name of Institution:

PI:

CTC name and internal number (if applicable):

Sponsor:

Title:

EUDRACT number:

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

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

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

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

Signature of PI: _____

Print Name:

Date: (dd/mm/yyyy)

Signature Institution: _____

Print Name:

Date: (dd/mm/yyyy)

Annex 2 Frequently asked questions with answers

Questions are in normal text and answers are in *Italic*.

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

- 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).
Should the FAMHP (and CT-College) not recommend sponsors to stop the submission of 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 might quickly change, for the moment, the FAMHP has decided (based on risk assessment) not to prohibit the submission of new non-COVID-19 related trials. 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, independent whether it is 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 are to 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 mostly be regarded as not urgent by the ethics committees or prohibited at the trial sites.
Please consult the website of the concerned ECs to verify the timelines for evaluation of this type of trials. Each EC will do every effort to maintain the official timelines as much as possible.*

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

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

B. Procedural

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

When you plan to submit a COVID-19 trial, take into account the following recommendations:

- *Prior to submission, contact the FAMHP via email (Mali Stephanie <Stephanie.Mali@fagg-afmps.be> and Eglem Steve Steve.Eglem@fagg-afmps.be with in cc: ct.rd@fagg-afmps.be).*
- *Be prepared to answer the question through which regulatory procedure you plan to submit: through the accelerated Voluntary Harmonisation Procedure (multi-country trials only), the standard 2004 procedure (4 working days for the FAMHP) or the accelerated CTR-Pilot – which is strongly recommended (4 working days for FAMHP and evaluating EC).*
- *Please send in 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.*
- *For the protocol title, in the protocol, the synopsis and especially in the EudraCT application form: please ensure that it starts with “COVID-19”.*
- *In any case: for the FAMHP: submit 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.*
- *For the standard 2004 procedure, submit - as usual - additionally to each of the ECs. We cannot guarantee that each EC will perform the standard 2004 procedure evaluation in 4 working days.*
- *When applying 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 only contact point for the sponsor.*

4 It is specified that 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 07MAY2004 or that of the 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 COVID-19 trials, this is correct. All COVID-19 CTAs will undergo an expedited review by 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 that 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 becomes larger than the FAMHP's enhanced capacity, the FAMHP might decide to apply criteria to prioritise the submitted CTAs.

- 5 In case the CTA is submitted via the accelerated CTR Pilot, the FAMHP commits to validate and review all COVID-19 related CTAs in 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 give an opinion within four working days?

In the case the dossier is submitted according to the standard 2004 procedure, every local EC needs to deliver its advice. The timelines handled by the different ECs may differ. It is recommended to consult the website of the concerned leading EC to verify the timelines for these types of evaluations.

- 6 When the CTR Pilot procedure is followed :
Will a new central EC be chosen for studies already underway (which were not initially approved through CTR Pilot) that submit an amendment following COVID-19, or will the original CEC (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.

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

So :

This gives the sponsor the opportunity to submit its COVID-19 trial via a single submission to the national contact point (which forwards the file to FAMHP assessors and College for the single evaluating EC), with the file structure according to the law of 7 May 2004 (submission package according to Directive 2001/20/EC), with the only additional addition being a written statement from each participating site. Has this been interpreted correctly?

Yes, but please be aware to include in this single submission all the documents that are to be evaluated by the EC.

- 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: Normally the CT-College selects an evaluating EC independent of the sites where the trial is conducted. The criteria to do so are described in the Royal Decree of 9 October 2017. The CT-College selects among a list of 15 ECs (that are recognized or aim to be recognized according to the law of 7 May 2017). For the evaluation of COVID-19 trials about 10 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.

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

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

- 10 In our question whether IMP can be shipped from site to patient and whether this can be performed by CRO or whether sponsor can recommend courier services, we received the reply that this is possible “provided there is a documented agreement of the PI and the final shipment is signed for approval by the site, and the rules of patient privacy remain respected”. What is exactly meant by “documented agreement of the PI”, is this a signed contract, a signed addendum to the contract, or does it just need to be documented, unsigned by both parties?

This means an approval (signed, or when not possible the confirmation 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. In any way, there must be a proof of the fact 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.

- 11 Would the Belgian authorities allow labelling at site? (Sponsor would want an unblinded pharmacist to blind the medication on site) We were wondering if we could have the possibility for having that approved based on the grounds of importance of this drug?

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

- 12 Sponsor wants to add a new trial site for an approved Covid-19 trial in BE. As is stated in article 11 of the law of 7th May 2004: § 14, a new trial site can only added after a 3-month period – between approval and substantial amendment - has lapsed.

Given the urgency of adding trial sites to COVID-19 trials, we would like to ask the Ethics Committees to accept substantial amendments to add new sites sooner than three months after the initial single opinion of the EC.

Ethics committees will accept that the sponsor adds 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

- 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 needs to be provided in the language of the participants (FR and/or NL).

- 14 Would it be acceptable to NOT use the BAREC ICF template, on specific sponsor's request, in order to limit the turn-around-time in ICF approval process by the sponsor. It would drastically speed up the process if we could use Sponsor ICF template instead of the BAREC ICF template.

We cannot oblige the sponsor to use the ICF-template for COVID-19 related trials but the reasoning that it "would drastically speed up the process" needs some nuance. If the template will be followed, the evaluating EC will not have comments on the fixed paragraphs of the template. This will speed up the evaluation process.

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

In case of urgency the law of 7th May 2004 (Art 9) and the law of 22 august 2002 (Wet patiëntenrechten, Art 8, §5) is to be followed.

If the sponsor would like to use the law of 22 august 2002 (Wet patiëntenrechten, Art 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.

- 16 Do you have specific guidance for ICF signatures of those patients in isolation (mainly those in ICU)? As no visits are allowed, the legal representative is not easily reachable.

As described in the guideline ICH 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 (Art 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.

- 17 Please add an explanation of the (re)consent procedure.

Example: for a COVID-19 patient participating in a non-covid-19 trial, due to quarantine conditions that apply in the hospital, a written re-consent is not feasible. In this case an impartial witness present 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 into a COVID-19 trial. If the approved protocol includes an emergency consent procedure, the patient may be included, but as soon as he/she regains consciousness, he/she 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 he/she has used.

18 There are also additional concerns about the ICF:

ICF amendments may be sent to patients (electronic/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 2 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?

The procedure for this is described in the [EU guidance](#), but in order to specifically answer the question, the best option is to first contact the patients by telephone, give the necessary explanation and deliver the ICF amendment to the patient preferably by e-mail and not by post, given the discussions about the risk of infection and transmission on paper (further information can be found on the Sciensano website [https://epidemiology.wiv-isp.be/ID/Documents/Covid19/COVID-19 InterimGuidelines Treatment ENG.pdf](https://epidemiology.wiv-isp.be/ID/Documents/Covid19/COVID-19%20InterimGuidelines%20Treatment%20ENG.pdf)). This process should be clearly and completely noted 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 already included trial participants. 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 e-mail, mail or courier before re-consent is obtained. Any consent obtained 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."

D. Temp halts and Urgent Safety Measures

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

When the institution or site decides to temporarily stop recruitment of new patients in interventional studies, should we list all ongoing drug studies and make a temporary stop notification?

Then you must submit a recruitment stop notification to the FAMHP and the EC.

- 20 Should a temporary halt of recruitment be notified within 15 days only if this decision is taken on a global level, on a country level (so recruitment halt for all Belgian sites) or on a site level?

Independent of the level, if there is a temporary halt, notify it within 15 days of the decision.

Important: In order to restart the trial after a temporary treatment halt, a substantial amendment must therefore be submitted. The trial can only restart upon approval by the EC and if no motivated objections have been raised by the FAMHP within legal deadline.

If the temporary halt is only a halt in recruitment due to the COVID-19 crisis, it will be acceptable to restart the recruitment when again possible after a notification only to the FAMHP and to the EC.

- 21 Is there a different requirement for notification to the FAMHP in case:
- a. it is **only** a temporary halt of recruitment (and patient treatments are continued), or
 - b. it is a complete temporary halt of the trial (including recruitment and treatment halt)

In the first case, since there is likely no impact on the safety of the participating patients, should the FAMHP be notified?

Yes and the EC too.

In the second case, there is likely impact on patient safety due to the stop of patient treatment, it is understood that the FAMHP (and the EC) must be notified within 15 days of the decision.

Yes and the EC too.

- 22 Is it required to submit a substantial amendment following each USM?

Yes

- 23 Can a substantial amendment following an USM, contain other changes than the USM changes?

Yes

- 24 Normally 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 we could either submit an additional SA during the review of a previously submitted SA or add extra changes to an already submitted SA?

You can indeed submit a substantial amendment that is related to the COVID-19 pandemic while a previous one is still under evaluation. However, generally, 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 of course e.g. 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 e.g. an IMPD amendment, this IMPD amendment can already be submitted while the evaluation of the legal representative amendment is still ongoing. We are also in favour that you would group as much as possible the amendments that are linked.

- 25 In the national guidance is mentioned : “Urgent safety measures taken in the context of coronavirus, this may be taken without prior notification to FAMHP and the EC. The sponsor must inform as soon as possible the FAMHP and the EC of the measures taken and the plan for further action. This should be reported to the FAMHP via CESP or ct.rd@fagg-afmps.be (or ctrPilot@fagg-afmps.be for Pilot Projects) and a substantial amendment must be submitted afterwards.”

A protocol deviation (control of visits,...) should be considered as an USM if the change has to be directly implemented for the patient’s safety and if it is considered as a substantial amendment (cf. definition of substantial amendment, national and European coronavirus guidelines).

Could you please advise if you would consider these measures as substantial urgent safety measures that should be notified as soon as possible to the FAMHP and EC?

Yes, these measures are to be considered as substantial urgent safety measures that should be notified as soon as possible to the FAMHP and EC.

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

Is there a specific starting date or do we start counting 4 months from the first deviation reported?

Please start counting from the first deviation reported, then add 4 months.

- 27 In general, we found it sometimes difficult to be certain of what is expected for the reporting and classification (USM vs Substantial amendment vs non-critical Protocol Deviations). It would be really great and helpful if this could have the 3 sorts of reporting (e.g. USM, substantial amendments and all the rest in a 4-monthly report) and clear definitions on what should be considered USM, vs critical PD vs non-critical PD.

This concerns especially the non-critical protocol deviations which are taken in the 4-monthly listing. The sponsor and investigator need to analyse and document each decision whether it is a substantial amendment or not.

Overall:

- Anything that changes for the patient, i.e. that was 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.

28 In “Section 2: Procedure and communication” of the national guidance is mentioned:
“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.” and “As we do not know how long the current crisis may last and as the virus may be seasonal, it is also asked to the sponsor to provide the listing/overview of measures taken, at regular basis, every 4 months to CT.RD@fagg-afmps.be.”

a) Could we maybe simplify the process to have a listing/overview filed at site and sent to FAMHP and EC every 4 months until the end of the crisis and remove the need to provide it by the end of trial?

It is important to provide a listing every 4 months, as well as the overall summary at the end of trial.

b) Is the 4-month listing to be sent at the same frequency to FAMHP and EC?

Yes

c) Have both minor and major issues to be reported in the listing?

It is important that Substantial amendments are filed and everything what is not according to CT-1 a substantial amendment and what is not a temporary halt, will be on the 4 months listing and at the overall summary at the end of the trial.

d) We understand it is one listing per trial. Is it correct?

One listing per sponsor, then per trial, each of the measures taken, in chronological order.

29 In “Section 5: Temporary halt and urgent safety measures” of the national guidance is mentioned:

“A protocol deviation (control of visits,...) should be considered as an USM if the change has to be directly implemented for the patient’s safety and if it is considered as a substantial amendment (cf. definition of substantial amendment, national and European coronavirus guidelines). ... A substantial amendment shall only be submitted for critical protocol deviations (those which are really impacting safety), not for minor deviations.”

“control of visits,...” can we get more information about this? Would a phone visit vs an onsite visit or a visit that is delayed outside of the required protocol window be considered substantial?

No, but must be well explained and documented on site and must be part of the non-SA listing (every 4 month). Nevertheless, if the ICF needs to be adapted, this should be considered as a substantial amendment.

E. Risk assessment

30 The EU guidance (section 5) mentions:

“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.”

The national guidance (section 2) mentions:

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

What about international drug studies in which the sponsor did not carry out a risk assessment? Should the national coordinating centre in each country take over this task as 'sponsor of that country'? Can this be determined separately for each country? We received this information for a particular study: "Thus, as national coordinating centres, the decision to continue or suspend study procedures in your country is yours."

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 centers 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.’

31 Who should decide to place the recruitment "on hold", the hospital/investigator or the sponsor?

In the European Guidance (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf) the following is mentioned:

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

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

This means only follow-up. What about IMP administration and the related windows/time points? If this cannot be maintained, what are the measures? withdrawal? Other?

The national guidance specifies already 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.

- 33 Could you clarify what is meant by "home nursing" under point 3 of the national guidance: follow-up by home visit through the home nurse?

This means that if a visit at the hospital (e.g. for treatment or follow-up) is not possible, a health care professional can do this visit at the participant's home.

34 In the “section 4. Shipment from the site to the patient” is mentioned:

“This is only possible provided that the product is suitable for transport, storage at home and administration at home use.”

What does this mean, suitable for transport?

This means that it has to be possible to keep the IMP at the 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 as well. The temperature should be logged for documentation purposes. Likewise, while oral tablets might be suitable for home use, intravenous infusion may not be without the help of a registered and trained nurse.

35 In the “section 4. Shipment from the site to the patient” is mentioned:

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

a) It is an additional burden for the patient to be responsible for reception, handling and storage of medication. This is overshooting of documenting shipment and IMP handling.

b) How will participants be trained? How is this training organized/documented?

Instead of the patient, a family member or care giver 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. Where 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 his or her judgment. Protocol stopping criteria may apply in this case.

Participants may be trained by (video) calls, providing written instructions, etc.

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.

36 In the “section 4. Shipment from the site to the patient” is mentioned:

“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.”

Implementation only after EC approval?

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 4 working days after submission of a complete dossier to first round of questions.

- 37 In agreement with the EU “Guidance on the management of clinical trials during the COVID-19 pandemic”, all on-site monitoring activities have been cancelled at our phase I unit. In addition, we fully agree and comply with the prohibition that sharing medical dossiers or charts of patients is not allowed for reasons of privacy imposed by the national law and GDPR. Nevertheless, we would like to be able to allow a database lock for some of our recently completed trials in healthy volunteers for which only a limited amount of source data still needs to be verified by the sponsor without the need for access to medical records. The source data we would like to share electronically are clinical trial data only which have all been captured in a pseudonymised way and only include a randomization code / allocation number without any reference to the participant’s identity. Therefore, we feel that, by sharing these pseudonymised trial data we do not violate the trial participant’s rights in any way and would therefore like to provide these data electronically to the monitors of the involved trials.

Can the FAMHP agree with our interpretation and therefore agree that remote source data verification as described in the paragraph above does not violate the participant’s rights and can therefore be allowed given the current exceptional circumstances?

The way the question is worded shows that it is data base review and not Source Data Verification (SDV). Therefore, we agree with your interpretation.

- 38 Could the possibility of remote monitoring be considered by the Belgian authorities? This will be needed if the situation is lasting, e.g. for critical situation (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. What is not allowed is Source Data Verification (SDV), verification directly in the “e-Health Records, Patients files, Medical files” as definition of the main “source documents” of a CT. It is important that remote monitoring does not involve extra burden and workload for the site.

- 39 Direct shipment from sponsor to patient in clinical trials is prohibited. The guidance indicates that "A courier under contract of the sponsor may be implied for the shipment upon condition that documentation is present before shipment, that the PI is informed, that the patient’s personal data are protected and that the sponsor under no circumstances can obtain the personal data (like name and address) of the patient".

Our client would like to expand its activities to the shipping of clinical products, like 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 our client be regarded as a courier in the sense of the guidance? If our 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)?

Your client is indeed a courier. A tri-party agreement is needed to clarify responsibilities. Under no way the sponsor may obtain patient personal data, and this is part of the agreement.

A documented agreement of the principal investigator / sub investigator is mandatory to approve this way of actions taken to provide the patient with IMP. This contract is filed at the Investigator Site File.

40 Section 4: Shipment from the site to the patient

“The shipping arrangements can be considered as a non-substantial amendment to be included with the next substantial amendment.”

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.”

a) When only shipping arrangements are modified, this can be considered a non-substantial amendment. Could it be rather a mitigation measure that has to be included in the 4-month listing?

Yes, provided there is no additional training to patient.

b) In case of training on home administration not already foreseen in the protocol has to be given to the patient/caregiver, nurse, then it is a substantial amendment?

Yes

c) What is the definition of training? Are instructions for oral medication or self-administration already in place before the decision of direct shipment of the medicine is not training?

If the patient is indeed already self-administrating, then 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.

d) If the training at home necessitates an amendment to the protocol, then a substantial amendment is to be submitted to FAMHP/EC. When occurs the deployment of the training? Could it be before submission of amendment?

This should be risk-based, if urgent, then immediately, so based on a risk analysis. For FAMHP: If they are part of the USM, they can be done before submission, but submission has to be done as soon as possible.

See below for changes to the ICF, but if measures are urgent they can be considered as USM.

e) We understand that the addendum to the ICF is only needed in case of training on home administration not already foreseen in the protocol, with the patient before the decision of direct shipment of the medicines.

Then the addendum has to be submitted for approval to the EC. Could the measure be deployed before the approval by the ECs?

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 (4 working days from submission of a complete dossier to first round of questions.

f) For the other cases (no addendum of the ICF), could it be documented that the DTP (direct to patient) has been discussed with the patient and agreement has been received orally ?

Orally is not accepted. It must be documented and it is preferred that there is also email conversation for this process.

g) Could it be a mitigation measure that has to be included in the 4-month listing?
For FAMHP: yes, has to be included on the listings and same as for question a above, see answer: "Provided there is no additional training".

h) "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. "

If our understanding for the shipment of medicines here above is correct, we understand that it applies for the patient diaries and pregnancy tests. Is it correct.

This is correct: 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 his/her patient. Given that there is less control by the investigator on these tests, careful consideration should be put on this decision. It should be properly documented in the Investigator site file (ISF) where the tests were performed in deviation of the normal practice of the trial.

41 Section about DIL

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

be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment.”

For DILs which are not a Substantial Amendment, since we will be reporting the actually taken measurements in the 4-monthly reports, the submission as a non-substantial amendment seems redundant. Could the need of this reporting be re-considered to avoid over-reporting (so only in the 4-month listing)?

If it is not a temporary halt, nor an USM nor an SA, then it must be in the 4-month listing.

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

Would you be able to advise, if in such cases it would be necessary to register a local investigator, who is able to perform remote visits for these patients and if so, then what would be the process for approval of these investigators?

The exceptional procedure described above with art 107/1 is to avoid that a trial has to be setup (approved by FAMHP and EC). Of course, it is preferable that a CTA is setup in Belgium – however this might require more resources, and would imply a site visit which is not permitted in most hospitals during the pandemic.

- 43 Is it allowed that the sponsor sets up an agreement with a courier service, and when needed, the site personnel can request an IMP shipment (t° controlled) from the site to the patient’s home, using this service?

This is allowed under exceptional conditions:

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

- 44 Would the following approach for changing to subcutaneous self-injection be allowed, given the current circumstances (COVID-19 pandemic) be allowed:

- a) For patients without experience in subcutaneous self-injections, would it be allowed to train the patients remotely on self-injection (e.g. via live video chat with study nurse/ study doctor, via telephone call with study nurse/study doctor, via instruction video..)?

In this case it is advised to let the participant confirm the training by email so as to have some documentation of training.

b) 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 health care professional to have the subcutaneous injection done?

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 on the condition that IMP information and dosing instruction on paper for example are also provided so they can provide these to their General Practitioner (GP).

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

"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.

d) Currently, prefilled syringes with IMP are used in this trial. The global study team is evaluating whether they can change from prefilled syringes to auto-injectors to ease patient use.

In case we can change to auto-injectors, would the change to auto-injectors be allowed given the current circumstances, or would this definitely require prior EC/FAMHP approval?

This involves a change to the IMPD so an approval of the FAMHP and EC will be required in this case.

To keep in mind that 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.

45 Since in Belgium we have a closed system for the delivery of EPO to patients, and EPO is only delivered to hospital pharmacies, I would have liked more information about whether EPO can also be sent to patients?

This is OK provided it goes via the hospital pharmacy and traceability is according the rules.

G. GDPR

46 In Art. 134 of the Belgian law of 30 July 2018 (protection of personal data) a deviation from GDPR is described. Is this a permissible deviation from GDPR, in these coronation times?

Exceptions on GDPR aspects have to be discussed with the Data protection officer (DPO) of the study site.

H. Contract management templates

- 47 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

- 48 One of the physicians within our hospital would like to initiate a study to reduce the transmission of COVID-19 to health care staff through blood group analysis.
The protocol includes the administration of probiotics by the health care staff to increase their levels of circulating natural antibodies. The goal is to obtain a sufficient level of protective antibodies (if this level is already present without probiotics, they will not be given).
The study does not aim to evaluate probiotics at all, but is used to make sure that staff are sufficiently protected. The study does focus on blood groups. Should we consider this as a clinical trial?

This is a clinical trial : submission to FAMHP and EC is required.

- 49 Many non IMP academic studies will start in the next days/weeks : we are afraid that the COVID patients will have to read and sign many ICF at the same time. Not sure that the consent given by those very ill patients will really be « éclairé » !
These studies are mainly prospective interventional : blood tests, treatment (non IMP) specific dosages, EU validated devices etc but can also be prospective non-interventional.
We will follow art 32 of the Belgian Law 7 /5/04 but practically how could we proceed ?
Could we imagine to set up a single ICF for this type of non-IMP studies where the patient arriving at the hospital accept to take part to studies approved by the Ethics committee ?

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

50 Can you please confirm that it is indeed not necessary to use qualified electronic signatures and that other ways of electronic signatures collection can be accepted? The language of section of the national guidance is unclear in this respect.

For your information: the sole acceptance of qualified signatures has some limitations according to our previous experience, namely IT issues, security layer issues and increased complexity for the collection of the e-signature. This may result in additional burdens to get documents signed during the Covid crisis (and in general).

If there are already qualified electronic signatures on documents – we accept them (provided the certificate is on the list)

But if there are no qualified electronic signatures on them – please follow second and or third bullet of section 7:

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

So indeed, qualified electronic signatures are not required.