

Questions and answers
CTR information session on 23 September 2021

ASMF	Active Substance Master File
AoR	Acknowledgement of receipt
ASR	Annual Safety Report
ATMP	Advanced Therapy Medicinal Product
BAREC	Belgian Association of Research Ethics Committees
CA	Competent Authority
CESP	Common European Submission Platform
CMS	Concerned Member State
CRO	Clinical Research Organisation
CSR	Clinical Study Report
CTA	Clinical Trial Application (submission dossier for a clinical trial)
CTC	Clinical Trials Centre (in a hospital)
CTD	Clinical Trials Directive 2001/20/EC
CTFG	Clinical Trials Facilitation Group (working group of the Heads of Medicines Agencies)
CTR	Clinical Trials Regulation 536/2014
CV	Curriculum Vitae
DPO	Data Protection Officer
DSUR	Development Safety Update Report
EC	Ethics Committee
EEA	European Economic Area
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
Eudralink	The Eudralink system has been designed to enable files to be sent securely over the internet via a user-friendly web interface. Access to Eudralink is available to the EMA, Member State Agencies, Industrial Pharmaceutical Companies, Members of Working Parties/Committees and National Experts.
FAMHP	Federal Agency for Medicinal and Health Products
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
HA	Health Authority
ICF	Inform Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LEC	Leading Ethics Committee
LOC ID	Location ID
LSLV	Last Subject Last Visit
MDR	Medical Devices Regulation
MS	Member State

NCP	National Contact Point
OMS	Organisation Management Service
ORG ID	Organisation Identification Number
PI	Principal Investigator
RA	Regulatory Authority
RMS	Reporting Member State
RFI	Request for Information (questions to the sponsor during the validation phase or assessment phase of the evaluation process in CTIS)
SaMs	Safety assessment Member State
SM	Substantial Modification
SME	Small and Medium Enterprise
SUSAR	Suspected Unexpected Serious Adverse Reaction
VHP	Voluntary Harmonised Procedure

1. [Would the EU portal facilitate the work of the FAMHP in terms of workload? What are your expectations?](#)

For dossiers that will be submitted through the Clinical Trials Information System (CTIS) portal, most exchanges between all parties involved in the dossier will occur through CTIS. It will no longer be necessary to send e-mails or Eudralinks or to extract the dossiers from the submission e-mail of the Common European Submission Platform (CESP), nor to create records or archives locally.

We will certainly need to adapt to the new way of working but we really hope this will facilitate our work in the future and have a positive impact on the workload.

2. [If the last pilot dossier has to be submitted before 14 October 2021, what will happen to new dossiers between 14 October 2021 and 31 January 2022?](#)

New dossiers will have to be submitted following the Clinical Trials Directive (CTD) process (law of 7 May 2004).

3. [For a trial that has received initial approval under the CTR Pilot, do we have to submit a substantial amendment the Pilot as well, or can we use the Directive process even after the CTR implementation?](#)

No, the CTD process cannot be used. Trials that have been approved in the Clinical Trials Regulation (CTR) pilot process must continue in the CTR pilot process. CTR pilot substantial modifications will be accepted until the end of the three-year transition period. If a trial will still be ongoing after 31 January 2025, the application to transition the trial from CTD to the CTR will need to be submitted in CTIS at least 60 days before 31 January 2025.

4. [A glossary of the acronyms would be useful for non-experts or non-specialists. There are also patient representatives involved in the EC.](#)

We will take note of this remark and will incorporate it in our next communications/presentations.

5. [CTR pilot submissions of Substantial Modifications \(SMs\) can continue until 31 January 2025: can we keep submitting them as zip files through the Common European Submission Platform \(CESP\) or should we switch to CTIS? Will there still be no fee?](#)

Yes, the SMs can still be submitted via CESP. The dossier can also be switched from the CTD to the CTR before the next substantial modification is submitted through CTIS, but this is not mandatory.

Yes there will still be no fee.

If a trial will still be ongoing after 31 January 2025, the application to transition the trial from the CTD to the CTR will need to be submitted in CTIS at least 60 days before 31 January 2025.

6. [CTR pilot submission of notification: why did we not receive an acknowledgement of receipt \(AoR\) after notifications? Without an AoR, we have no way to know if the FAMHP and the EC have actually received the notification.](#)

For the moment, we do not have the capacity to send an acknowledgement of receipt, neither for an initial CTR pilot dossier nor for an SM. This will be resolved for CTR dossiers. CTIS will register the date of each submission.

7. [Do you have any experience with unauthorized auxiliary medicinal products?](#)

A simplified dossier can be submitted in case of authorized auxiliary medicinal products, and it is recommended to use authorized auxiliary medicinal products. In case of non-authorized auxiliary medicinal products, a full dossier (similar to the Investigational Medicinal Product Dossier-IMPD) must be provided and is assessed by the quality assessors of the FAMHP.

8. [The assessment of submissions in the CTR pilot is still very slow \(for understandable reasons\), however will it stay this slow or will you be able to commit to the intended timelines \(15 or 28 days\) soon again? Can we start the trial/implementation of the substantial changes if we don't hear anything from you within the required timeframe?](#)

With the end of the summer holidays period, we now have a higher capacity to assess submission. We will also have some reinforcement of the team by the end of 2021. We therefore anticipate that timelines for the assessment of submissions will improve.

According to the principle of silent approval, the change can be implemented after the legal period has passed (as described in article 13 of the law of 7 May 2004) provided that no objections have been raised by the FAMHP during this period and the approval from the ethics committee has been obtained. We do everything possible to respect the timelines but given the current situation, we indeed have some delays in providing our feedback and the approval from the ethics committee. We thank you for your understanding.

9. Do the points of attention that were presented for clinical and non-clinical trials apply only to Belgium or to all EU countries? Have all those points of attention emerged after the CTR pilot?

The points of attention presented were issues observed during the assessment of the pilots and for which we feel that it was useful to bring them to the attention of the participants, to contribute to a fluent processing of clinical trial applications. Our assessment is based on existing EU legislation and guidelines, so those points are in principle not only valid for Belgium but they are based on experience in the Belgian pilot. It can also be noted that guidance on clinical trial application is still under further development at EU level.

10. As we are an international CRO with international clients, where will we be able to obtain the information whether the medicine substance has already been reviewed by the agency before?

The manufacturer of the active substance should be aware of this, as they have to provide a letter of access to allow our agency to access the Active Substance Master File (ASMF). The sponsor of the trial can therefore ask the manufacturer if the ASMF has already been submitted and assessed by the FAMHP.

11. Are the recommendations/requirements for the CTA dossier specific to Belgium or are they all based on the EU Regulation? Reference was often made to the EU guidance, so can we assume there are no Belgian-specific requirements?

Yes, requirements and recommendations are based on the legislation (CTR) and on the EU guidance. Some of the recommendations are given to help you prepare and complete clear documentation for a clear and quick comprehension of the different aspects of the product and of the trial by the FAMHP assessors. If everything is as clear as possible from the submission of the dossier, this can avoid that one or several RFI's will be provided to the applicant.

12. Will the use of the templates that are being developed or adapted by the WGs be mandatory or strongly recommended?

The templates are strongly recommended, except for the written statement of the site (suitability of the site) which is a mandatory template.

13. Are the recent updated versions of the templates (investigator CV, etc.) immediately applicable or is there a transition period to allow smooth implementation of those new templates?

Response of College: the date of application of the new versions of the investigator CV and the written statement template is 1 October 2021. The reference date is the date of signature.

14. Where can we find the templates/information documents (slide 6 DGGS)?

[The documents](#) are available on the website of the Clinical Trials College, under the tab "Publications".

15. Some sponsors used the ICF template for vaccine trials in healthy adult volunteers but still received over 30 questions linked to the wording of the template (not linked to the sponsor additions/wording). We used the template as mentioned to avoid questions but it seems this is not working. How can the Committee support us with this problem?

Response of College: the ICF template for interventional clinical trials with IMP on adult patients is currently under revision. The College hopes this will also improve the Vaccine ICF template.

16. We are a local ethics committee and we are wondering if our ethics committee will still receive a financial compensation for a study that is ongoing in our hospital.

Response of College: The local ethics committee will not receive any compensation when the studies are submitted through an administrative pathway involving the College.

17. A question for the ICF working group. When will there be an ICF template available in Belgium with a reasonable amount of pages to read for the patient? The length of the ICF today is too long and discourages patients to read the document. In other countries, the ICF can't exceed a couple of pages in order to get approved.

Response of College: The ICF template for interventional clinical trials with IMP on adult patients is currently under revision. The College hopes this will improve the length of the template.

18. The participants documents are being evaluated in the language of the chosen EC, but what if the EC is French-speaking, and the participants will be Dutch-speaking (and no French ICF is provided)? Does this mean we always have to provide the ICF in multiple languages?

See question 19.

19. In how many languages should the participant's documents be provided in the dossier. It is not known beforehand which EC will evaluate the dossier. Should Dutch, French, German and English be included in Belgium?

We refer you to the [CTR pilot guidance for sponsors](#).

ICFs and other participants documents have to be provided at least in the official national language(s) of the region(s) where the trial is conducted.

20. Related to the ICF language: in case a trial is conducted in Flanders only, will this trial be assessed by an EC in Flanders by default? A French version of the ICF is not normally submitted in such case, so would it be impossible for an EC in Wallonia to assess the ICF?

Response of College: We refer you to [the CTR pilot guidance for sponsors](#).

ICFs and other participants documents have to be provided at least in the official national language(s) of the region(s) where the trial is conducted. So indeed, the trial would not be evaluated by a French-speaking EC.

21. Could you consider consulting the hospitals (CTC) for practical CTR-MDR? Issues that arise: GDPR, DPO advice by the selected EC, managing conflicts of interest etc. These are practical issues that are no longer covered anymore by the CTR or at least it is not clear to centres.

Response of College: The College proposes to give this responsibility to the Ethics Committees recognized under the law of 2017. The Ethics Committees could then ask the advice from the clinical trials centres of the institutions they represent.

22. Will the new CV template be also recognised by Transclerate?

Response of College: No. The CV investigator has to be compliant with the CV investigator template. The CV investigator has to clearly describe the specific clinical trial/study experience relevant for the Clinical Trial Application (CTA) with EudraCT number.

23. Which documents in Word were needed for CTR pilot and are still needed for CTR?

Response of College: College asked the question to European Medicines Agency (EMA).

24. Should the CV for investigator be adapted for each study with a detailed background related to study? That sounds very difficult as we already have issues to obtain current updated CV.

Response of College: The Belgian ECs need to have a clear view on what is the expertise of the investigator in order to evaluate whether the investigator is suited to perform the clinical trial. The CVs are sometimes very long and it is unclear what is the relevant information for the specific trial. With the Belgian addendum to the CV investigator, the investigator is requested to reflect on what makes them a suitable investigator for the submitted particular trial. The EU template for CV investigator requests to limit the given information to the preceding ten years. It is possible that an investigator provides its full "standard" CV and an addendum

with the requested information, i.e. experience relevant for the submitted CTA (preceding ten years) and if applicable any relevant technical experience.

25. If as a private site, we are not allowed to use the federal 'ombudsman' or the EC 'ombudsman', which one should we refer to in the ICF when we have no other available?

Response of College: This question is currently under discussion.

26. What will be the role of the EC in ASR/SUSAR assessment?

Response of College: Within the framework of the CTR pilot project, the ASR/SUSAR have to be addressed directly to the evaluating Ethics Committee and to FAMHP. If the evaluating Ethics Committee has a concern, they may send their concern to the FAMHP. The FAMHP will then take the appropriate action. After the CTR goes live, for the CTAs submitted via CTIS, all safety aspects will be communicated through CTIS by the sponsor. The Annual Safety Report will be assessed by the SaMs (Safety assessment Member State). With the CTIS organization model for Belgium: ECs are not involved in the assessment neither of ASRs nor of SUSARs.

27. Is it foreseen to prepare a template regarding the information to be provided on the financing of the CT? Or what information is expected by the FAMHP and EC?

Response of College: A draft contract between the site and the sponsor should be provided. Pharma.be developed a template for this purpose.

28. The College informs "the site" at three different occasions during the CTR pilot assessment. What is meant by "the site" is this the PI or is this the local EC that is informed?

Response of College: By sites, the College means the general direction/CEO of hospitals where the clinical trial will be carried out.

29. In an international environment as a global CRO, where Belgium is just one of the countries, it is unfortunate that we left the door open for local evaluation as this may delay the submission of part II in Belgium and will put back the timelines as compared to other EU MS. Have you taken the impact into consideration?

Response of College: The role of the local ECs is not within the competence of the College.

Response of the FAMHP: this will be discussed internally and with the Belgian Association of Research Ethics Committees (BAREC).

30. Not informing the centres directly of the decision will lead to delays in the contract management. Sponsors and authorities should be aware of that. We are waiting for the approval to have the contracts signed. It can be an issue for the timelines of the study set up.

Response of College: It is up to the sponsor/investigator to provide the sites with the decision and the final approved documents.

31. Do you evaluate the need of requiring DPOs as mandatory members of ECs?

Response of College: This will be discussed with the College Board.

32. Could you please provide some information on data protection and need for redaction?

This statement will be displayed upon a user's first login into CTIS and it will be necessary to declare that the user will comply with it. Module 12 of the [CTIS modular training program](#) focuses on data protection in CTIS.

33. Is there any possibility to request an extension of the RFI based on the questions (e.g. if the question would request the sponsor to run some additional experiments)?

No. As stated in the regulation, the maximum timeline given to the sponsor to answer the RFI is twelve days.

34. Due to the very tight timeline, patients have not been directly associated in this pilot phase (but through their umbrella associations). Many practical improvements are still desirable to facilitate their evaluation of the IC Formulators. How will this issue be addressed during the rollout phase starting in February 2022?

Response of College: Patient umbrella associations were involved in the preparation of the ICF template.

35. The GDPR evaluation is an important issue because the centres will eventually be condemned. Tasks and responsibilities must be clearly defined.

Response of College: This will be discussed with the College Board (see response to question 31).

36. What would happen if not all questions are addressed during the single round of questions (e.g. if question was not clear for the sponsor and response doesn't fully meet the expectations)?

See questions 37.

37. When the EU CTR will be implemented, if questions are raised during RFI (either from the HA or the EC) that are not clear enough, can we ask for clarification by contacting the HA directly (either RMS for Part I questions or CMS for part II questions), i.e. outside of CTIS (for example by e-mail exchange)? Or do we need to submit clarification questions within CTIS?

The questions provided to the sponsor should be as clear and as complete as possible. The same applies to the answers to the RFI that will be provided by the sponsor within CTIS. However, if clarification is needed, this will have to be done outside CTIS. If Belgium is the Reporting Member State (RMS), an e-mail will have to be sent to the National Contact Point's (NCP) e-mail address: CTR@fagg-afmps.be.

38. What is the process for the selection of the RMS, at the time of CTR submission?

According to the CTR Regulation, at the time of the submission of the initial clinical trial dossier the sponsor must propose a RMS among the member states concerned. There can be discussions between all member states concerned and within CTIS to decide which one will actually be the Reporting Member State. However, if no other member state concerned volunteers the proposed RMS will become the RMS at the end of the RMS selection step (by day six after submission of the initial dossier).

39. Can ECs ask questions on the protocol (part I)?

Yes, the EC will participate in the assessment of part I of the dossier. Only the quality part will not be accessible to the EC.

40. Regarding the local EC procedures and documents – will there be a general guidance, discussion, ... to avoid this in order not to delay the site activation in Belgium, and to remain a competitive "interesting" country for clinical trials and sponsors?

Response of College: The role of the local ECs is not the competence of the College.

41. Will the procedure with time slots remain after CTR implementation?

No, time slots were only applicable for CTR pilot dossiers. All submitted dossiers in CTR with Belgium as concerned member state will be processed.

42. Concerning the request to harmonize local procedures and eliminate them as much as possible: is there a forum involving sites, where this can be addressed?

Response of College: as far as College is informed there is currently no forum. Representatives of the academic Clinical Trials Centres (CTCs) meet each other on a regular basis.

43. Are there any requirements for clinical benefits and cost-effects of a new drug?

Response of College: The College is not aware of this.

44. The negotiating sponsor site is not included as you mentioned. Is it possible that different sites receive a different amount of money?

Response of College: Yes.

45. Is there quality control of translation of the IC?

Response of College: It is the responsibility of the sponsor to have an ICF translation procedure.

46. Can the role of the local EC be defined better, similar to the suitability of site assessment?

Response of College: Local ECs do not fall within the competence of the College; a new template for the written statement is available since July 2021.

47. Patient representative also need training. Is this something on the agenda before the rollout?

Patients will consult the public website of CTIS. For anyone making use of the public website, the EMA is developing a training module called 'Introduction to CTIS for Public Users'. This module will likely be available by the end of December.

48. It was mentioned that Belgium now has more experience which places us in a competitive position. However, CTR will be a collaboration between different countries, will this cause delays due to lack of experience in other countries?

We believe that there will be no delay since there are tacit validations of the dossiers and tacit approvals in CTIS.

49. Not being informed as a site about the decision (only submission) will interfere with follow up of the studies by the CTC and with the start of studies.

Response of College: it is up to the sponsor/investigator to provide the sites with the decision and the final approved documents.

50. Could you please indicate when the new ICF template will be available?

Response of College: The ICF template is currently under revision. Discussions with the BAREC are ongoing.

51. It is expected that templates currently used for part II under the pilot procedure will be used for EU CTR submission? Is it expected that other documents will also be requested?

Response of College: The CTR pilot project aims to prepare the various stakeholders for the CTR. The templates used in the CTR pilot project will be the same when the CTR will enter into force.

52. Concerning the translation of the protocol synopsis (e.g. in French), do you expect under EU CTR that a Belgium specific French translation should be used for Belgium or is it possible to use the same protocol synopsis translated for France.

The protocol will be the same document for all concerned member states (part I is common for all countries). Therefore it is assumed that the protocol synopsis will also be common for all countries. And only one French translation will be needed.

53. Will the EC be chosen based on the region where the study will be conducted?

Response of College: The evaluating Ethics Committees are chosen in rotation according to the criteria of the royal decree of 9 October 2017. Additionally, the language of the EC is also taken into account for the assignation of the evaluating Ethics Committee.

54. The new EU regulation will be applicable as of January 2022 but won't be mandatory during the first year. The company for which I am working won't start using the CTIS platform in 2022. How should we submit dossiers to the agency as of 31 January 2022 if we are not using the new platform?

During the first year after implementation of CTR, the Directive process can still be chosen instead of the CTR process. Submission must therefore be done via CESP, as is the case now.

55. Will the accelerated review process for COVID-19 trials continue as the pilot project comes to an end?

Yes, but with adapted timelines.

Please consult the [news](#) published on the FAMHP website on 19 November 2021 about the updated timelines for applications for COVID-19 clinical trials.

Before the implementation of CTR, submission will have to be done following the Directive process.

56. Will the pilot phase remain via CESP as of February 2022, even after CTR come into force? Yes, submission of the CTR pilot substantial modification should still to be made via CESP.

57. Apart from the examples provided in the EMA questions and answers document and depicted in the EU CTR, do you foresee any other country specific Part II SMs under EU CTR?

Response of College: the list of examples in the [EU CTR questions and answers document](#) is not exhaustive. Other SMs may be possible.

58. GCP requires the PI to communicate/submit to EC, this will no longer be possible. What is the FAHMP's point of view ?

That is correct, the new procedure is no longer in line with the [ICH GCP guideline](#). This will be discussed internally by the FAMHP GCP inspectors.

59. If we have a multi country Ph1 trial. Is it allowed in the CTR to submit a CTA first for the BE (as RMS) to profit of the short timelines and start the trial and subsequently by a SM add the second MSC?

Yes, this is allowed.

60. Sponsors have three years to start applying the new EU regulation and use the CTIS portal. If the sponsor decides not to apply it as of 31 January 2022, how should they submit dossiers (initials, end of trial ...) for the studies outside of the CTR pilot?

Initial trials can still be submitted following the CTD process until 31 January 2023. If the sponsor decides to submit according to CTD and for all trials already approved following the CTD process, the current CTD rules will continue to apply until 31 January 2025 at the latest. From 1 February 2025 all trials will have to be processed according to the CTR rules.

61. If the sponsor is submitting a notification as non-substantial but the authority classifies it as SM, will it be rejected?

This could be processed as a corrective measure: a member state could request for the submission of a substantial modification instead of the submission of the non-substantial modification (more precisely, a change relevant to the supervision of the trial following article 81.9).

However, this remains the responsibility of the sponsor to determine how the modification should be submitted within CTIS. We refer you to the [CTR questions and answers in EudraLex volume 10](#) for examples of modifications and how to submit them.

62. It appears that CTIS allows the submission of separate non-substantial modifications, while this is not in line with the questions and answers or regulation.

When CTR will come into force, there will be three types of modifications:

- a substantial modification (article 2.2.13);
- a change that is relevant to the supervision of the trial (article 81.9) which are called non-substantial modifications within CTIS (see module 19 of the EMA CTIS training modules, [Step-by-step guide 4](#), page 12);
- a change outside the scope of substantial modifications and irrelevant to the supervision of the trial.

Only substantial modifications (article 2.2.13) will be assessed following the substantial modifications evaluation process as described in the regulation text.

However, changes relevant for the supervision of the trials have also to be submitted within CTIS (81.9NSM in "Annex III. Classification of changes to ongoing clinical trials" in the [CTR Q&A](#) in Eudralex volume 10).

Changes outside the scope of substantial modifications and irrelevant to the supervision of the trial (see annex III of the CTR questions and answers) should not be submitted stand-alone

within CTIS and should be kept by the sponsor to be submitted together with the next substantial modification.

63. Should the initial dossier (part I and II) be submitted to all member states at the same time? The final decision won't be provided at the same time: is this because not all member states apply the same timelines or because initial submission should not be done to all MS at the same time?

Only one dossier will be submitted within CTIS for all member states concerned where the sponsor wishes to organise the trial. If part I and part II are submitted together, the difference in approval dates could come from RFI on part II in some countries if there is no question on part I and part I, the conclusion will already be provided on day 45. Or it could also come from a difference in the decision date in the last step of the evaluation process, when each member state has 5 days to provide its final national decision within CTIS. Another option could be that additional country/countries are added to the concerned member states after initial approval, by the means of an article 14 procedure. In this case, the approval date will also be different in the additional member state(s) compared to the original ones.

64. Will there be a centralized/streamlined approach to avoid overloading the hospital sites with instructions and FU communication related to the registration of their Organization Identification Number (ORG ID) and their Location ID (LOC ID), which is mandatory for the clinical trial application for interventional trials?

The FAMHP is planning to contact the hospitals in order to inform them about the registration process in the Organisation Management Service (OMS, an EMA service).

65. How will hospitals be informed of the need to register their OMS ID number in time?

Registration is mandatory via the OMS. Once done, the organisation (sponsor, hospital, etc.) has a unique ID for the organisation itself linked to another unique ID for the location. The IDs are available via the OMS at any time, so hospitals should not be overloaded by instructions once the registration is done.

Registration of the hospitals in OMS should be done as soon as possible.

[All information related to the registration in OMS](#) in order to be recognised as an organisation in CTIS can be found on the EMA website.

In addition, the FAMHP is planning to contact the hospitals in order to inform them about the registration process in OMS.

66. Will FAGG use a specific logic to allocate certain registered ECs to certain clinical trials (for example depending on therapeutic area or location) or will the choice be made based only on ECs availability?

Response of College: the evaluating Ethics Committee is chosen in rotation according to the criteria of the royal decree of 9 October 2017. Additionally, the language of the EC is also taken into account for the assignation of the evaluating Ethics Committee.

67. Do we need to transition trials for which all patients are followed up in the long term?

Yes, all studies that fall within the scope of the CTD and the CTR (in fact same scope: interventional trials) must be transitioned before 31 January 2025 if not finalised at that moment.

If a trial will still be ongoing after 31 January 2025, the application to transition the trial from the CTD to the CTR will need to be submitted in CTIS at least 60 days before 31 January 2025.

68. Trials under CTD that have submitted an end of trial notification before 31 January 2025, but have not yet submitted the CSR, should they be transitioned to CTR or not?

No, the trial should not be transitioned to CTR. Eudra-CT will still be available for submission of clinical study reports after complete implementation of the CTR (after 31 January 2025).

69. When a dossier becomes public, which version of the IB becomes public? Is this the current IB at that time, or/and any of the previous versions of the IB from previous years?

All versions will be available for the public.

70. Is there a template for a transition cover letter?

Not for the whole cover letter, but the Clinical Trials Facilitation Group (CTFG) has developed a template for the statement to be included in the cover letter. It can be found in the annex of the [Best Practice Guide for sponsors of transition multinational clinical trials](#) (page 4).

71. In case of phase I studies with Belgium as only EEA country: will the assessment remain 15 days or will the regulation timelines be followed?

As foreseen in the law of 7 May 2017, short timelines will remain for phase I mono-national trials. The timeline will be 20 days, validation included.

72. When should the Clinical Study Report be published?

See questions 73.

73. Could you please tell us more about the transparency? Which document will be made public?

We refer you to the following documents available on the EMA website:

- [Appendix on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited."](#)
- [Revision of section 6 of the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" setting out features to support making information public.](#)

74. CTR pilot submissions of SMs can continue until 31 January 2025: Can we keep submitting them as zip files through CESP or should we switch to CTIS? Will there still be no fee? Is it recommended to keep these studies in the CTR pilot or is it better to transition them to CTR rules (submissions through CTIS to multiple member states) between January 2022 and January 2025?

Yes, the rules for submissions of CTR pilot substantial modifications will remain the same (through CESP). There will still be no fee. It is up to the sponsor to decide if the trial will be transitioned or not. However, all trials should be transitioned by 31 January 2025 at the latest.

75. Can you please explain what will happen for VHP+ submissions. What will happen when VHP will be decommissioned? Will the independent EC take over the substantial amendment until the CTR switch? Or do we need to submit to LEC and non-LECs at once?

We refer you to question 11.9 of the [CTR Q&A](#) in Eudralex volume 10: "In order to benefit from the advantages of harmonisation a sponsor should transition VHP trials as soon as possible after the entry into application of the Regulation, and at the latest before any new submission concerning a trial. So if possible trials should be transitioned as soon as possible after implementation of CTR and substantial modifications submitted afterwards within CTIS. If this is not possible to wait for the implementation of CTR because the substantial modification is urgent, it can be submitted following the CTR pilot (non-VHP plus) usual process and it will be proceeded by the independent EC".

76. Could you please clarify if there are any specific Belgian requirements on transparency and documents to be made publicly available? Which documents need to be edited for Belgium? Belgium follows the rules as stated in the CTR and guidance documents on transparency.

77. Will the FAMHP have enough capacity to complete assessments under CTR in the required timeframes? Tacit approval will apply, so if no RFI is received in time, can we consider the application approved?

FAMHP will play its full role in the evaluation of CTA applications under the CTR. The tacit approval indeed applies on the entire evaluation process, from validation to final decision on the application, for the competent authorities, for the ECs and for the sponsors.

78. If a document is approved in RMS for one member state is it approved in other member states as well?

Yes, as stated in the regulation text one could disagree with the RMS final conclusion on part I (under conditions described in the CTR text) or part II conclusion could be negative in a member state. Therefore, the final decision would be refusal in that member state.

79. We submitted a study in Belgium this year (not a pilot study). Should we submit the cover Letter, CTIS application form and harmonised or consolidated protocol to CTIS by 31 January 2022? What else should be completed on our side?

If you would like to transition the trial as soon as CTR will come into force, you can submit the trial within CTIS. We refer you to question 11 (arrangements for the transitional period) in the [CTR Q&A](#) from Eudralex to see what should be submitted within CTIS to transition the trial from CTD to CTR.

80. Does the end of the transition period refer to LSLV or CSR due date?

To our understanding, the end of the transition period refers to the end of the trial which should be defined in the protocol (most of the time Last Subject Last Visit/LSLV). Eudra-CT will still be available several years after CTR will enter into force, to allow submission of CSR for directive dossiers still ongoing during the transition period. Eudra-CT will even still be available after the end of the transition period to allow submission of CSR for those directive dossiers which will end during the last year of the transition period.

81. I assume RFIs, approvals, etc. from the RA/EC will be visible in CTIS - will sponsors and CROs get e-mail notifications or do we need to check CTIS daily ourselves?

No, an e-mail notification will be sent by the system. Everything will be visible in CTIS. New events will be communicated via notices and alerts which will be available in the notices and alerts tab once logged into the system.

82. If I am not mistaken, GMO trials are part of CTR and if the evaluation of the trial itself is harmonised, this is not the case for the GMO evaluation which is sometimes submitted to the same CA and sometimes submitted to the Ministry of Environment. When it is the same CA which evaluates the trial and GMO, does it mean we will need to submit both in parallel via two channels?

Yes, the evaluation of the biosafety part of the dossier is not included within CTIS.

83. What about the safety reporting (SUSARs, ASRs/DSURs, etc.) during the transition period? Does it also depend on the choice of the trial submitted (CTD or CTR)? Does this mean that trials submitted in CTR during transition period no longer need to submit SUSARs and DSURs?

We refer you to the [CTR Q&A](#) document in Eudralex volume 10, questions 7.49 and 7.50: "In case one clinical trial is ongoing in alignment with the Clinical Trials Regulation (EU) 536/2014 while others are under the Directive 2001/20/EC, an ASR should be submitted to the database specified in the regulation. Sponsors are allowed to name all MSs concerned for all ongoing CTs in EU/EEA within Directive as well as Clinical Trials Regulation. Sponsors are still obliged as of CT-3 to submit ASRs to Ethics Committees according to national legislations in MSs with ongoing clinical trials within Directive 2001/20/EC and inform investigators of any new safety data or change in benefit-risk evaluation.

SUSARs need to be reported to the EV database. Double reporting is to be avoided, unless the NCA has had a national requirement for direct reporting of SUSARs. In addition, despite reporting to NCAs via EV, the reporting obligations as of CT-3 still need to be respected, especially reporting to Ethics Committees according to national legislations in MSs for all IMPs/CTs within Directive 2001/20/EC as well as reporting to investigators (CT-3 Article 109)".

84. The hospital has been registered in OMS with five different IDs. How can this be avoided?

OMS is performing actions on Data Quality Management. Those actions can be proactively, meaning that tasks in OMS are being reviewed as well as by monitoring the database. Those actions can also be reactively, based on issues reported to the service desk on data quality. A user may also submit a change request to add or update an organisation or a location.

85. If I understood correctly, the master trainer must provide access to the training portal. Who will do that for Belgium? When and how?

On the member state level of Belgium, there is a master trainer at the FAMHP to train the future FAMHP users and there is a master trainer within the College to train the future ethics committee users. In order to be able to train those future users, these master trainers are participating in the member state master trainer program. It is up to the master trainer to

decide what the appropriate moment is to deliver access to the future users. Sponsor organisations also had the possibility to express interest in nominating a master trainer for the sponsor master trainer program. The sponsor master trainer nominees that were chosen by EMA to participate in the sponsor master trainer program, are able to access the training environment from mid-end November 2021. They will be able to provide access to the future users of their sponsor organisation when they deem the moment is right.

86. Registration of organisation was specified for industry users. What about academic users?
Each organisation needs to be registered in OMS prior to going live.

87. Sponsors/investigators are not among the recognised persons for academic research in your slide? Study nurse but not the responsible person?

Every person of an organisation can take up certain responsibilities in CTIS, based on the roles given to that person. The aim of the user persona workshops organised by EMA was to identify the most frequent user profiles within sponsor organisations. In order to do so, feedback from different sponsor organisations was collected. EMA has split up the user personas between those more likely to be present within sponsors and CROs (CTIS Submission Manager, Regulatory Project Manager, In-Country Specialist), SMEs & academia (Study Coordinator, Clinical Trial Submission Specialist, Safety Specialist) and academia specifically (Study Nurse). More information on the identified sponsor user personas is available on [the EMA website](#).

88. Academic centres are requesting to test CTIS as soon as possible in order to be able to prepare our internal support documents in due time. Could you organise a specific info session for academic sponsors?

The FAMHP has decided to provide the information to all stakeholders by the means of several info sessions, accessible to all interested.

The first one has been organised on 23 September 2021. The next one will be organised on 15 December 2021.

Please follow the news on our website to be informed on the info sessions what will be organised by our agency.

Moreover, there are some other tools available for your support:

- [training and support information](#) is available on the European Medicines Agency (EMA) website;
- [set of training modules](#) has been prepared by the EMA and is available on EMA's website. Please note that module 19 has been specifically prepared for training of SMEs and academic sponsors.
- a specific webinar for SMEs and academia on key aspects of the Clinical Trials Regulation and the new processes via CTIS for clinical trial applications submission for small and medium-sized enterprises (SMEs) and academia on the Clinical Trials Regulation and the Clinical Trials Information System (CTIS) was organised on 29 November 2021. Please consult the [CTIS highlights of October](#) available on the EMA website. The recording will be published on the EMA website after the event.
- a [sponsor's handbook](#) has also been developed by the EMA, available in the section 'Handbook for clinical trial sponsors' on the EMA website.

89. How should the non-substantial annual update of the IB be submitted in CTIS?

The IB must be submitted once a year even if there is no modification or if the modifications are non-substantial. This should be submitted as an 81.9NSM (see page 120 in "Annex III. Classification of changes to ongoing clinical trials" in the [CTR Q&A](#) in EudraLex volume 10.

90. Can we have early discussions with the agency with regards to RMS?

We would encourage you to pro-actively contact us with regard to the intended applications where BE would be proposed as RMS.

In general, we can confirm that the strategic lines, established by the FAMHP so far, will remain: i.e. the domains such as vaccines, first in human trials, oncology, ATMP's but the application of RMS will not be limited to these.

91. When will the ICF template for healthy volunteers be finalised?

Response of College: See above, question 47. The ICF template is currently under revision. Discussions with the BAREC are ongoing.

92. How will the role of the CRO be delegated in the CTIS system? Do we, as CRO, also need to be registered as a separate organisation? Or can the sponsor delegate certain tasks to the CRO? From the training material already available, it is not clear what the role will be for the CRO.

Response of College: The CRO must register first in OMS. They can then create an account for CTIS, link their account to their organisation (registered in OMS). Then CRO can request for roles to the sponsor admin within CTIS. Sponsors can assign roles according to the agreements concluded between the CRO and the sponsor.

93. Are the fees already available for the submission of new trials, amendments, etc. Will it be one fixed fee? Or will it depend on how many MS are involved?

There will be a fee defined for each country and the proof of payment of the fee must be part of the submission dossier.

For Belgium, the submission of CTA dossiers following the CTR process will be free of charge. As the proof of payment is an obligatory document, a blank document or document stating that the application is free of charge in Belgium should be uploaded.

94. In the next webinar, could we see a list of advantages and disadvantages of transitioning to the CTR?

Yes, this will be taken into account for the next info session in December 2021.

95. For ongoing trials approved in VHP process, how should substantial amendments be submitted after 15 October 2021?

If it would not be possible to wait for the implementation of the CTR and the switch of the trial from the Directive to the CTR, the substantial amendments will have to be submitted nationally separately in each concerned member state.