

Joint pilot project between federal higher authorities and ethics committees for processing of applications for the authorisation of clinical trials on medicinal products for human use in accordance with Regulation (EU) No. 536/2014 under consideration of the legal stipulations laid down in AMG and GCP-V

Guideline for participating sponsors

Introduction

The pilot project presented in the following was designed by members of the Permanent Working Party of Research Ethics Committees (Arbeitskreis der Medizinischen Ethik-Kommissionen), the German Medical Association (Bundesärztekammer), the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich-Institute (PEI) with the aim of developing, testing and optimising processes for a joint assessment of applications for the authorisation of clinical trials (CTAs) with medicinal products as well as of substantial modifications.

Background

"Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC" (called Clinical Trial Regulation (CTR) in the following) will alter the authorisation procedure for clinical trials in many fields. While the authorisation procedures at the competent federal higher authorities (BfArM and PEI) and the ethics committees stipulated by Land law are currently independent from each other, parts of them will change considerably when the CTR comes into force.

After coming into force of the CTR and the German Medicinal Products Act (*Arzneimittelgesetz*, AMG) amended accordingly (by the Fourth Act to Amend Provisions under the Law Concerning Medicinal Products and other Provisions), the decision on the authorisation of a clinical trial and/or a substantial modification is made by the NCA (national competent authority). In doing so, the NCA must duly consider the opinion of the competent ethics committee with regard to Part I of the dossier and is bound to the opinion of the competent ethics committee with regard to Part II. Thus, a closer cooperation between the NCA and the competent ethics committee in Germany will become necessary in the future. This is all the more true if Germany is the reporting Member State since in these cases NCA (BfArM and PEI) and competent ethics committee have to compile an Assessment Report jointly within a short period of time.

Aims of the project

This pilot project is aimed at the development of processes and procedures for the joint assessment of CTAs as well as for substantial modifications and for the compilation and harmonisation of Assessment Reports with the help of suitable software tools. The process is designed, tested and optimised in a learning-by-doing approach. In order to avoid redundancies, the pilot project will be conducted with selected CTAs.

For a clinical trial authorised within the pilot project, the sponsor may decide whether to submit a substantial modification directly in accordance with current legislation (Section 10 GCP-V) or whether to choose the procedure described in the following for applying for a substantial modification. However, the latter is only feasible for changes that primarily cover substantial modifications subject to approval in the documentation for Part I pursuant to the CTR.

Objectives of the procedure

The pilot project includes a larger number of CTAs. At the beginning, however, only initial CTAs were processed in the pilot project. In the meantime, the processing of substantial modifications for initial CTAs which were already authorised in the pilot project is also possible. Both mono-centre as well as multi-centre CTAs can be included in the assessment. CTAs that are also part of a VHP¹ and CTAs for which the period is reduced to 14 days pursuant to Section 8 sub-section 3 and/or Section 9 sub-section 3 GCP-V are excluded from the pilot project. The Regulation provides the option of separately submitting the documentations for Part I and Part II pursuant to the CTR. However, based on the current legislation, the sponsor cannot make use of this option in the course of the pilot project.

As a matter of principle, the procedures in the pilot project are supposed to follow the provisions and deadlines of the CTR. Since the CTR is currently not legally effective, authorisation and positive opinion are issued on the basis of the AMG and the Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans (*GCP-Verordnung*, GCP-V). This ensures that participation in the pilot project does not entail legal disadvantages for sponsors, authorities or ethics committees concerned. Violation of the deadlines of the CTR by a participating sponsor does not lead to an implicit withdrawal or refusal of the CTA. In turn, violation of the deadlines of the CTR by the NCA or ethics committee does not lead to an assumption of approval unless this would also have existed or already did exist on the basis of current legislation.

CTAs within the pilot procedure have to be submitted in accordance with the current legal framework, therefore, submission of a CTA exclusively via e-mail or the web-portal is currently not possible. Pursuant to Section 7 and/or Section 10 GCP-V, CTAs are to be submitted to NCAs and ethics committees separately and in written form. CTA and documentation shall also be submitted on an electronic data carrier. Communication during the procedure will take place via e-mail. A corresponding e-mail address of the sponsor is to be included in the cover letter of the CTA. For communication with the NCAs, their official e-mail addresses for clinical trials are to be used (ct-pilot@bfarm.de or ct-pilot@pei.de). The e-mail addresses of the participating ethics committees are listed on the internet pages of the NCAs and of the Permanent Working Party of Research Ethics Committees (www.ak-med-ethik-komm.de) and are updated on a regular basis.

¹ "Voluntary Harmonisation Procedure":

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2013_06_CTFG_VHP.pdf

The NCA and the competent ethics committee jointly validate and assess CTAs regarding the contents covered by the future Part I of the application. This process is managed by the NCA in close coordination with the respective competent ethics committee.

After successful validation, the CTA is assessed by NCA and competent ethics committee and a joint internal Assessment Report is compiled. The assessment regarding the aspects covered by Part I of the CTA is performed jointly while the aspects covered by Part II are assessed by the competent ethics committee under consideration of possible comments by the concerned (local) ethics committees. The Assessment Report remains exclusively with the NCA and competent ethics committee but is made available for optimisation purposes in pseudonymised² form to all ethics committees participating in the pilot project as well as to the two NCAs. Sponsors who object to this or who will not communicate via (unencrypted) e-mail in the course of the procedure cannot participate in the pilot project. As there is currently no infrastructure for encryption of e-mails between sponsors, ethics committees and NCAs, e-mail transmission is unencrypted. However, the possibility of a safe data transfer for supplementing documents in the ongoing procedure will be offered.

If an initial CTA is not directly granted an authorisation or positive assessment, the sponsor will receive a (harmonised) list of questions and/or deficiencies and will be requested to respond within the maximum time limit specified in the CTR. This response is to be submitted in parallel to the NCA and the competent ethics committee in one single reply. After evaluation of the sponsor's response, the NCA and the competent ethics committee issue their notices separately and in written form.

A separate procedure has been established in the pilot project for the processing of substantial modifications. The content assessment is made by the NCA and competent ethics committee in the course of a consultation (preliminary assessment) preceding the application pursuant to Section 10 sub-section 1 GCP-V. Transmission of the opinion to the applicants is followed by the application phase during which the valid application (if necessary with supplemented information) is conclusively decided upon.

Those contents of a CTA or substantial modification that correspond to the contents of Part I pursuant to the CTR are assessed jointly by NCA and ethics committee with the exception of the documentation concerning the pharmaceutical quality of the investigational medicinal products (chemistry, manufacturing and control, CMC). If necessary for legal reasons, deficiency letters and requests for additional supplements regarding Part I will be sent out separately by NCA and ethics committee but with identical contents as far as possible. CMC aspects will be assessed exclusively by the NCA; questions and assessment regarding CMC aspects are not made known to the ethics committee. The same also applies to supplements and responses by the sponsor.

Contents of a CTA or substantial modification covered by the future Part II of the CTA pursuant to the CTR are assessed in parallel by the competent ethics committee. Questions and/or requests for supplementation regarding these aspects are exclusively raised by the competent ethics committee unless otherwise required for legal reasons.

² Removal of all data related to persons or sponsors, removal of the name of the investigational medicinal products, unless this is permitted.

The ethics committee passes the data to the NCA for information only. In accordance with the current legal situation, the competent ethics committee assesses the suitability of investigators and investigational facilities in consultation with the concerned ethics committees, thus, all these ethics committees support the competent ethics committee in the course of the pilot procedure. Therefore, it is also necessary in the pilot project that all ethics committees concerned receive a copy of the CTA in written form and/or a copy of the application for substantial modification (both for the preliminary consultation (preliminary assessment) as well as for the subsequent application) at the time it is submitted pursuant to Sections 7/10 GCP-V.

After the assessment of the CTA and/or the application phase (in the case of substantial modifications) has been concluded, the sponsor will receive separate notices from the NCA and the ethics committee. If the CTA and/or the application for substantial modification receive an authorisation by the NCA and a positive assessment by the competent ethics committee, the clinical trial can be started and/or the modification can be implemented. Possible other notification obligations, e.g. towards Land authorities, remain unaffected by the pilot project.

After the end of the procedure, the NCA sends all those who participated in the procedure the detailed statistics on the time lines of the current procedure with reference to the maximum time limits specified in the CTR. This statistical information is also made available to all ethics committees participating in the pilot project and the two NCAs under statement of the pilot project number but otherwise pseudonymised.

The pilot project is of a more experimental nature and is mainly designed to organise the process between NCAs and ethics committees. For sponsors, participation is voluntary and without disadvantages. A legal entitlement to participation in the pilot project does not exist. The NCAs and the respective competent ethics committees decide on a case-by-case basis whether a CTA can be processed in the pilot project. Therefore, a letter of intent is required prior to beginning the pilot procedure (see below) in order to allow coordination of those participating in the procedure.

[Start and duration of the entire pilot project](#)

The pilot project was started on 1 October 2015. The ethics committees participating in the pilot project are listed on the websites of BfArM (www.bfarm.de), PEI (www.pei.de) and the Permanent Working Party of Research Ethics Committees (www.ak-med-ethik-komm.de). This list will be updated on a regular basis. Currently, the duration of the entire pilot project has not been specified. However, it is intended to assess a larger number of clinical trials in the project in order to involve all participating ethics committees if possible. The end of the pilot project will be published in due time on the a.m. internet pages.

Description of the procedure for sponsors

I. Initial authorisation

I.A. Preparation of the initial CTA

Prior to initiating a procedure, the sponsor must first determine whether the ethics committee responsible for the co-ordinating investigator of the clinical trial and thus competent for the CTA is participating in the pilot project. If this is the case, an application for participation in the pilot project can be submitted (see below). An up-to-date list of the ethics committees participating in the pilot project will be published on the websites of the NCAs and the Permanent Working Party of Research Ethics Committees (see above).

Sponsors wishing to participate in the pilot project with their CTA will send an e-mail ("letter of intent") to the NCA (BfArM or PEI) competent pursuant to Section 77 AMG and at the same time to the ethics committee competent for the co-ordinating investigator of the clinical trial pursuant to Section 42 AMG 14 days prior to the planned submission of the CTA requesting participation in the pilot project with that specific CTA. This e-mail must contain the following information:

- EUDRA-CT number of the clinical trial
- sponsor's trial code as stated when applying for the EUDRA-CT number
- title of the clinical trial
- name and official address of the co-ordinating investigator of the clinical trial
- name and address of the ethics committee competent for the co-ordinating investigator of the clinical trial
- number of planned trial centres in Germany
- planned date of submission to the NCA and ethics committee (at the earliest 14 days after having sent the e-mail)
- list of concerned ethics committees as an attachment.

The NCA and the competent ethics committee come to an agreement with regard to their capacities and the NCA informs the sponsor whether the CTA can be processed in the pilot project. A legal entitlement to participation in the pilot project does not exist. If the decision is positive, the NCA will send the sponsor a pilot project number and will confirm the date of submission. In any communication between sponsor and NCA or competent ethics committee, this pilot project number must be the first entry in the subject line of e-mails or letters in order to allow internal allocation. Should it not be possible to process the CTA within the pilot project, the NCA will inform the sponsor at the latest within one week. In case of a rejection, the sponsor can submit a regular CTA in accordance with AMG and GCP-V separately with the NCA and the competent ethics committee. The letter of intent does not pose a formal CTA.

I.B. Submission of the CTA (Day 0 initial CTA)

On the intended and confirmed date, the sponsor submits the complete CTA simultaneously to

- the NCA
- the competent ethics committee and
- all concerned ethics committees.

The cover letter is to point out that participation in the pilot project has been confirmed and must contain the pilot project number. Submission should be made in such a manner as to ensure that the copies of the CTA reach all concerned parties at the same time. The submission must completely fulfil the specifications in Section 7 GCP-V with regard to form and extent.

I.C. Validation phase of the initial CTA

The day after receipt of the CTA marks the beginning of the validation phase at the NCA and the competent ethics committee. If one of the two institutions receives the CTA with a delay of more than two days, a timely processing within the pilot project cannot be ensured. If NCA or ethics committee come to the conclusion that joint processing in due time will not be possible because they have received the CTAs at different times, the NCA informs the sponsor and the competent ethics committee of this. The authorisation procedure will then take its regular course outside the pilot project separately for each institution in accordance with the specifications of AMG and GCP-V.

At the end of the **validation phase** which will last a maximum of **ten days**, the sponsor will receive separate notices of validation from the NCA and the competent ethics committee. The contents of the notices with regard to Part I are harmonised between NCA and ethics committee (with the exception of the CMC aspects). The ethics committee's notification of validation additionally includes aspects in accordance with Part II of the CTR. NCA and ethics committee send each other the notification of validation (with CMC aspects made illegible) for information.

If the CTA was already valid in all aspects at the time of submission, the deadlines are adjusted in accordance with AMG and GCP-V. If the validation shows that deficiencies are present or that relevant documentation is missing, leading to the CTA itself not being valid, the sponsor is granted a **10-day** period to remove the deficiencies. The corresponding response by the sponsor (e-mail) is to be sent to the competent ethics committee, all concerned ethics committees and the NCA at the same time.

The NCA and the competent ethics committee evaluate the supplemented documentation within five calendar days after receipt of the comments or the amended application dossier and exchange views and information with each other. If NCA and ethics committee come to the conclusion that the documentation regarding Part I is still not valid despite the supplement or if the sponsor neglects timely submission of the supplement, the NCA informs the sponsor after agreement with the competent ethics committee that the CTA can no longer be processed within the pilot project, as it would have lapsed pursuant to the CTR due to incompleteness. In this case, the sponsor can decide to either withdraw the CTA and submit a new application in the course of the pilot project at a later time, or to maintain the CTA within the regular procedure (separately with NCA and ethics committees). An extension of the deadline for supplements if the CTA is not valid is not envisaged in the CTR and is therefore also not granted within the pilot project.

If the CTA regarding the documents in accordance with Part I is complete, but documents regarding Part II, the absence of which makes an assessment of the entire CTA impossible, continue to be missing despite the supplement, the NCA informs the sponsor after agreement with the competent ethics committee that the CTA is not suited for the pilot project. The sponsor can then withdraw the CTA or maintain it within the regular (separate) procedure pursuant to AMG and GCP-V. Should the sponsor not withdraw the CTA, the assessments are made and notices are sent out separately by the two institutions according to national law.

I.D. Assessment phase of the initial CTA

If the CTA is valid, it is assessed by the NCA and the competent ethics committee. Both will compile an internal Assessment Report at the latest within **26 days** after receipt of a valid application at which time the sponsor will either receive separate positive notices from the two institutions or he will receive a deficiency letter in accordance with AMG and GCP-V. If a deficiency letter becomes necessary in the case of mono-centre clinical trials, the sponsor will receive this at the most after **23 days**. If the deficiencies concern the contents covered by the future Part I of the CTA according to the CTR, the contents of the deficiency letters are harmonised between NCA and ethics committee (with the exception of CMC aspects). If the deficiencies refer exclusively to Part II aspects, the notice is only issued by the competent ethics committee. In such cases, the NCA already grants its authorisation at this point and only continues to play an administrative role during the rest of the pilot procedure.

In the case of a deficiency letter, the sponsor is called upon to remedy the deficiencies noted or to supply the requested information within **12 days at the most** in order to comply with the deadlines specified in the CTR. As before, the answer here should also be as a single response sent in parallel to both institutions. Responses pertaining exclusively to the contents of Part II only have to be submitted to the competent ethics committee; however, the NCA should also receive this data for information. If the deficiencies concern CMC aspects, the response can be made illegible for the ethics committee. Should the sponsor be uncertain regarding requests/deficiency letter of NCA or competent ethics committee it is recommended to contact the corresponding institution by e-mail prior to sending the response.

If the sponsor is not able to provide the requested information or changes within **12 days**, the pilot procedure is terminated as the CTA has lapsed pursuant to the specifications of the CTR. In such cases, the two institutions further assess the CTA and send out notices separately pursuant to AMG and GCP-V.

I.E. Issuing notices for the initial CTA

The NCA and the competent ethics committee compile their final notices on the basis of the internal Assessment Report on Part I and Part II of the CTA. If they agree on Part I of the CTA, NCA and ethics committee separately issue notices with the same contents, if they disagree on this issue, each sends out a different notice. The competent ethics committee also adds the assessment regarding Part II and here especially information with regard to the suitability of the individual investigators and trial centres to its notice.

II. Substantial modifications

In order to give sponsors the opportunity to have substantial modifications of clinical trials which were authorised in the pilot project also assessed during the pilot project, it was extended to include substantial modifications. The prerequisites for such an assessment during the pilot project are

- a) initial authorisation of the clinical trial in the pilot project
- b) the contents of the modifications applied for fall primarily under Part I of the Assessment Report in accordance with the CTR and do not exclusively concern CMC contents.

Thus, modifications relating exclusively to CMC aspects of the dossier or to contents of Part II of the Assessment Report (e.g. patient information) are not subject to authorisation or assessment of modifications within the pilot project, as they are not subject to the joint assessment by NCA and ethics committee.

Contrary to current ruling in accordance with Section 10 GCP-V, substantial modifications in accordance with Chapter III of the CTR are designed in three phases with a validation phase, an assessment phase and a decision phase.

In order to facilitate processing during the pilot project especially in view of possible questions or requests for supplementation (while considering the current legal situation at the same time), the procedure for a substantial modification within the pilot project is divided into the following three phases:

- validation phase
- a preceding consultation procedure (consultation phase, referred to as preliminary assessment in the following) and
- an application phase in the course of which the valid application, possibly with supplemented information, is then conclusively decided upon.

Submission of an application for substantial modification at the beginning of the validation and preliminary assessment does not correspond with the submission of an application for substantial modification in accordance with Section 10 GCP-V. The purpose of the preliminary assessment is the joint (preliminary) evaluation of the documentation by NCA and competent ethics committee. It replaces the validation and assessment phase provided for in the CTR.

At the **end** of the **preliminary assessment**, the sponsor is advised to **officially request** the modification **by telefax** (beginning of the **application phase**) with **full reference** to the documentation submitted for consultation or supplemented based on validation and/or preliminary assessment. The subsequent submission then corresponds with the submission of an application for substantial modification in accordance with 10 GCP-V.

II.A Preparation of submission of an application for modification

The sponsor ensures that the following prerequisites have been fulfilled:

- The modification concerns the documentation for Part I pursuant to the CTR that affects both the NCA as well as the competent ethics committee.
- The modification does **not exclusively** concern the documentation regarding Part II pursuant to the CTR or the CMC part of the IMPD.

- The modification does **not** concern changes regarding investigators or clinical trial sites, recruitment material or contracts (such modifications are to be submitted separately within a regular application for substantial modification in accordance with Section 10 GCP-V).
- The sponsor agrees to the processing of the application for substantial modification in the course of a preliminary assessment and a subsequent application phase.
- The application for substantial modification does **not** concern xenogenic medicinal products.

II.B Submission of an application for modification for preliminary assessment (Day 0 preliminary assessment)

Provided the above-mentioned prerequisites have been fulfilled, the sponsor will **simultaneously** send the application for modification including a data CD by post to:

- the **NCA** and
- the competent ethics committee; in the case of multi-centre clinical trials, to competent and concerned ethics committee.

The cover letter shall contain the following information:

- pilot project number and internal procedure number of NCA and/or ethics committee
- Eudra-CT number
- Title of the study
- Name of the competent ethics committee

The documents must include a fully completed EudraCT form module II.

The documentation should be transmitted in such a manner that ensures that all parties concerned receive it at the same time. Form and scope of the submission must be in full compliance with the provisions of Section 10 GCP-V. In particular, a reasoning for the modification is to be given and changes are to be marked in accordance with the CT-1 Guideline.

II.C Preliminary assessment

The preliminary assessment is split into a validation phase and an assessment phase.

II.C.1 Preliminary assessment - validation

The day after receipt of the documentation relating to an intended modification, NCA and competent ethics committee enter into the validation phase. Should one of the two institutions receive the documents with a delay of more than two days, NCA and ethics committee will jointly respecify Day 0 of the procedure. In such cases, the NCA will inform the sponsor accordingly.

At the end of the **validation phase** which will last a maximum of **six days**, the sponsor will receive separate information by e-mail from the NCA and the competent ethics committee on the results of the validation, the contents of which have been harmonised between NCA and ethics committee regarding aspects of Part I (with the exception of CMC aspects).

In the case of multi-centre clinical trials, the ethics committees concerned can transmit comments on the validation to the competent ethics committee **within four days**. Additionally, the ethics committee's notification of validation may also include aspects regarding the contents in accordance with Part II of the CTR resulting from the modification (e.g. necessary changes in the patient information resulting from an updated investigator's brochure). NCA and ethics committee send each other the notification of validation (with CMC aspects made illegible) for information.

If deficiencies are found during the validation or if relevant documentation is missing, leading to the application for substantial modification itself not being valid, the sponsor is granted a **10 day** period to remove the deficiencies. The corresponding response by the sponsor (e-mail) is to be sent to the competent ethics committee and the NCA at the same time.

The NCA and the competent ethics committee evaluate the supplemented documentation within **five calendar days** after receipt of the comments or the supplemented documents and exchange views and information with each other. If NCA and ethics committee come to the conclusion that the documentation regarding Part I is still not valid despite the supplement or if the sponsor neglects timely submission of the supplement, the administrative NCA informs the sponsor after agreement with the competent ethics committee that the application for substantial modification can no longer be processed in the pilot project, as it would have lapsed pursuant to the CTR due to incompleteness. In this case, the sponsor can decide to submit a new application at a later time in the course of the pilot project or to submit the application for substantial modification in the regular procedure in accordance with Section 10 GCP-V separately to NCA and ethics committees. An extension of the deadline for supplements if the application for substantial modification is not valid is not envisaged in the CTR and is therefore also not granted within the pilot project.

II.C.2 Preliminary assessment – Content assessment

If the application for substantial modification is formally valid, the assessment is performed by the NCA and the competent ethics committee. In the case of multi-centre clinical trials, the ethics committee concerned can transmit comments on the content assessment of the application for substantial modification to the competent ethics committee within 10 days, especially if this leads to consequences regarding the suitability of the clinical trial site within the respective remit. At the latest after **15 days** following positive conclusion of the (re-)validation phase the NCA and the competent ethics committee compile an internal Assessment Report. No later than **15 days** after the positive conclusion of the (re-)validation phase, the sponsor will receive separate communications regarding the opinion by e-mail.

Together with the communication of the opinion at the end of the preliminary assessment, the sponsor is requested to officially submit the application for substantial modification within a **maximum of 12 days** with reference to the preliminary assessment pursuant to Section 10 GCP-V (see below).

If deficiencies were found regarding the Part I documentation, the contents of the list of these deficiencies has been agreed upon between NCA and ethics committee (with the exception of CMC aspects). If, by way of exception, the deficiencies found refer exclusively to the contents of Part II, the list is only compiled by the competent ethics committee and transmitted to the NCA for information only.

If the sponsor is uncertain with regard to the requests/deficiency letters from NCA or competent ethics committee it is recommended to contact the corresponding institution by e-mail – prior to submitting the application for substantial modification.

If the sponsor is not able to provide the requested information or changes within **12 days**, the processing of the application for substantial modification within the pilot procedure is terminated, as the change would have lapsed pursuant to the specifications of the CTR. In this case, the sponsor can decide to submit a new application at a later time in the course of the pilot project or to submit the application for substantial modification in a regular procedure in accordance with Section 10 GCP-V separately to NCA and ethics committees.

II.D Application phase

Within a **maximum of 12 days** after receipt of the opinion, the sponsor shall **simultaneously** officially send the application for substantial modification including the documents submitted in the course of the preliminary assessment and, if applicable, the documents/information required for removal of the deficiencies in accordance with Section 10 GCP-V to:

- the NCA and
- the competent ethics committee or, in the case of multi-centre clinical trials, to competent and concerned ethics committee.

It is to be ensured that the application for substantial modification includes exactly those modifications that were evaluated and requested by NCA and competent ethics committee in the preliminary assessment. This is to be confirmed in the cover letter.

In cases where the preliminary assessment was concluded with a list of content-related deficiencies, the following is to be observed for submission:

- The answer regarding the removal of the deficiencies should be sent as a single response in parallel to both institutions. By way of exception, responses pertaining exclusively to the contents of Part II only have to be submitted to the competent ethics committee; however, the NCA should be included for information only. If the deficiencies concern CMC aspects, the response can be made illegible for the ethics committee.
- If deficiencies have been determined in the preliminary assessment, submission of data/documents changed as compared to those presented for preliminary assessment may be required. In such cases it is to be ensured that the changes made are to be indicated (e.g. by submission of a list of the changes or of an additional version of the new document with track changes).

The day after receipt of the official application for substantial modification according to Section 10 sub-section 1 GCP-V, the NCA and the competent ethics committee start their review and decision process.

Processing of the officially submitted application for substantial modification is based on the following prerequisites:

- simultaneous receipt of the official application for substantial modification by NCA and ethics committee (delay of no more than 2 days)
- modifications in the official application for substantial modification correspond exactly with those evaluated during the preliminary assessment (no deviations whatsoever permitted)
- All data/information within the official submission are presented exclusively for removal of deficiencies observed in the preliminary assessment and are suited and sufficient for this purpose.

Should NCA and ethics committee come to the conclusion that a timely joint assessment is not possible due to varying dates of receipt of the application for substantial modification or deviating modifications, the application is processed separately by both institutions outside the pilot project as laid down in AMG and GCP-V (duration: 20 days).

In accordance with AMG and GCP-V, the sponsor will receive separate notices regarding the application for substantial modification from the two institutions at the latest **14 days** after receipt of the official application.

If, after evaluation of the official application for substantial modification, NCA and competent ethics committee come to the conclusion that the supplemented documents are not suited or sufficient to remove the deficiencies found during the preliminary assessment, this will lead a notice of refusal.

II.E Issuing notices for applications for substantial modification

The NCA and the competent ethics committee compile their final notices for the application for substantial modification on the basis of the internal Assessment Report on the application from the preliminary assessment which was possibly adjusted during the evaluation in the application phase. If they agree on Part I of the CTA, NCA and ethics committee separately issue notices with the same contents, if they disagree on this issue, each sends out a different notice. The competent ethics committee also adds the assessment regarding Part II and here, if necessary, information with regard to the suitability of the individual investigators and trial centres to its notice.

II. F. Withdrawal of the application for substantial modification

If the sponsor withdraws an application for modification after submission for preliminary assessment but prior to submission of the official application for modification, a fee will be charged for the scientific assessment/advice rendered up to that point. The amount charged depends on the fees regulations of NCA and ethics committee and is at least 50% of the fee payable for the corresponding application for modification. If the processing effort is lower, a further fee reduction may be possible. The sponsor must declare his agreement with this procedure in the cover letter for the application.

Other information

Sponsors participate in the pilot project on a voluntary basis and without additional costs. However, only sponsors should participate who are willing to act within the short time lines of the CTR and who agree to a communication throughout the procedure via (unencrypted) e-mail as well as with a pseudonymised exchange of information between the participating institutions. The participation in the pilot project gives sponsors the opportunity of adjusting and testing their own processes with regard to the time lines and procedures of the CTR. Furthermore, participating sponsors could possibly profit from shorter deadlines as compared to the customary procedure pursuant to AMG and GCP-V.

Annex

Sample letter for letter of intent

<Sender>

To

<competent federal higher authority> and
<competent ethics committee>

*Application for participation in the joint pilot project of federal higher authority and ethics committees
"Processing of applications for the authorisation of clinical trials on medicinal products for human use in
accordance with Regulation (EU) No. 536/2014 under consideration of the legal stipulations laid down in
AMG and GCP-V"*

Dear Sir or Madam

We kindly ask you to assess the following clinical trial within the above-mentioned pilot project.

*EUDRA-CT Number: 201x-xxxxxx-yy
Sponsor's trial code: XXX-YYY
Title of the study: "Randomised, placebo-controlled, double-blind Trial in ..."*

*Co-ordinating investigator of the clinical trial:
Dr. med. Renate Mustermann Krankenhaus Musterstadt
Mustergasse 123
12345 Musterstadt*

*Name and address of the ethics committee responsible for the co-ordinating investigator
of the clinical trial: Ethik-Kommission der Landesärztekammer XXX
Musterstraße 123
12345 Musterstadt*

*Number of planned trial centres
in Germany: 15*

*Planned date of submission to the NCA and all ethics committees
concerned: xx.yy.2015*

*We have read the guideline for participating sponsors. We are aware of the fact that the ethics
committees and NCAs participating in the pilot project will exchange pseudonymised information for
assessment of our CTA in the course of the project. We accept communication throughout the procedure
via unencrypted e-mail.*

Date and signature

*Enclosure:
List of concerned ethics committees*