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.

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 mostly independent from each other, parts of them will change considerably when the CTR comes into force. The requisite national legislation for conducting the authorisation procedures is not yet completed; nevertheless, the basic principle of a parallel assessment by ethics committee and national competent authorities (NCAs) can be expected. Articles 8 and 9 of the regulation stipulate that a "single decision" per Member State is to be reached within a short period of time and that the assessment is done jointly by a reasonable number of sufficiently qualified and experienced persons. Based on these requirements it is obvious that a closer cooperation between the NCA and the competent ethics committee in Germany will become necessary. 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 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.

Objectives of the procedure

The pilot project will include a larger number of CTAs. At the beginning, however, only initial CTAs will be processed in the pilot project in order to establish the corresponding processes. Then, at a later time it is intended to also include the substantial modifications the initial CTAs of which were already authorised in the pilot project. Both mono-centre as well as multi-centre CTAs can be included in the assessment. CTAs that are also part of a VHP[1] 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 German Medicinal Products Act (*Arzneimittelgesetz*, 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 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.

The NCA and the 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 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 ethics committee but is made

[1] "Voluntary Harmonisation Procedure": http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2013_06_CTFG_VHP.pdf

available for optimisation purposes in pseudonymised[2] 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 a CTA is not directly granted an authorisation or positive assessment, the sponsor will receive a (harmonised) list of questions and/or deficits 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 ethics committee in one single reply. After evaluation of the sponsor's response, the NCA and the ethics committee issue their notices separately and in written form.

Those contents of a CTA 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 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. The ethics committee passes the data to the relevant 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 at the time it is submitted pursuant to 7 GCP-V.

After the assessment has been concluded, the sponsor will receive separate notices from the NCA and the ethics committee. If the CTA receives an authorisation by the NCA and a positive assessment by the competent ethics committee, the clinical trial can be started. 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

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

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

It is intended to start the pilot project at the end of the third quarter of 2015. BfArM (www.bfarm.de), PEI (www.pei.de) and the Permanent Working Party of Research Ethics Committees (www.ak-med-ethik-komm.de) will be publishing the exact starting date of the pilot project on their websites. They will also publish a list of the ethics committees participating in the pilot project which 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

Preparation

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 responsible 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 responsible 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 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 relevant 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 relevant 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 ethics committee. The letter of intent does not pose a formal CTA.

Submission of the CTA (Day 0)

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.

Validation phase

The day after receipt of the CTA marks the beginning of the validation phase at the NCA and the 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 relevant 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 notice of validation additionally includes aspects in accordance with Part II of the CTR. NCA and ethics committee send each other the validation notices (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 relevant 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 relevant documents regarding Part II, the absence of which makes an assessment of the entire CTA impossible, continue to be missing despite the supplement, the relevant 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.

Assessment phase

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 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 relevant 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.

Issuing notices

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.

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 **Fehler! Textmarke nicht definiert.**

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