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Best Practice Guide for multicentre/multinational veterinary clinical trials

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# Introduction

According to Article 9(1) of the Regulation (EU) 2019/6: ‘‘an application for the approval of a clinical trial (CT) shall be submitted in accordance with the applicable national law to a competent authority of the Member State (MS) in which the clinical trial is to take place”. Consequently, the assessment of the clinical trial application will be done by National Competent Authorities (NCAs) in which the CT application is submitted following rules established in national laws.

However, multicenter/multinational (MCMN) veterinary CT applications submitted in several NCAs at the same time, may require coordination between the Member States involved, as a coordinated approach between NCAs is considered helpful for the companies as well as for the NCAs with respect to the assessment of clinical trial. The Regulation (EU) 2019/6 does not explicitly state whether, how and in which detail the coordination with respect to the approval/refusal of MCMN veterinary clinical trials should be performed by the Member States. Whereas the scientific assessment and the decision on approval/refusal of MCMN veterinary CTs is made by NCAs according to their national legislation, MS had expressed the need for a guidance document on the coordination of the assessment of MCMN veterinary CT application.

# Aim and scope

This BPG has been prepared by the CMDv in order to facilitate the processing of MCMN veterinary CT application. Guidance is provided on the role of the NCAs and the applicant in order to ensure that a consistent, timely and efficient procedural approach is guaranteed for the assessment of MCMN veterinary CT application.

The CMDv has also proposed several documents for handling those MCMN veterinary CT application e.g. an application form, a list of national requirements and clock start dates. These documents should be used for the coordination of MCMN veterinary CT application. However, several NCAs also accept the use of these documents for their national veterinary CT application. Please check NCAs websites (information is published on the CMDv website).

# References and related documents

* Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC.
* International Guideline on Good Clinical Practice of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (‘VICH’) – Guideline 9.
* CMDv documents: Procedural Contact Points, CT application form (AF); CT national requirements, CT clock start dates, template for the compiled list of questions.

# Procedure

According to the Article 9(3) of the Regulation (EU) 2019/6: ‘‘The Competent Authority shall issue a decision to approve or refuse a clinical trial within 60 days of the receipt of a valid application.’

Consequently, the CMDv agreed that the procedure for MCMN veterinary CT application will be divided in several steps to handle this 60-day procedure:

* A submission phase in which a lead authority should be nominated/determined by the applicant.
* A validation step that lasts 15 days during which involved NCAs check that the documentation provided in the application fulfils the requirements of Article 9 of the Regulation.
* There will be one starting date per month as published in the CMDv website.
* The first phase of the assessment will last 30 days. During this period each involved NCA will assess the application separately and will prepare a list of questions.
* Upon request by involved NCAs or the lead authority, a coordination meeting will be organised by the CMDv secretariat to share their viewson the MCMN veterinary CT application and their assessment.
* Once the lists of questions are sent individually by the NCAs, the applicant has 30 days to provide the answers to the questions of all NCAs within one common response document.
* After the clock stop NCAs will have a period of 30 days to assess the answers to their questions individually. The organisation of an informal meeting is possible during this step for NCAs involved to share their views on the answers of the applicant.
* The procedure is considered closed at the end of this period of 30 days. Each NCA should issue a decision to approve or refus*e* the MCMN veterinary CT application.

The procedural steps are summarised in the chart below:

## Submission phase

4.1.1 Selection of the lead authority

The applicant is invited to liaise with NCAs involved prior the submission of MCMN veterinary CT application as those applications are assessed at national level and requirements differ between MSs based on national law.

Before the submission of a MCMN veterinary CT application, a lead authority should be nominated by the applicant amongst the NCAs involved in the MCMN veterinary CT application.

Consequently, the applicant is invited to send the application form to the NCAs proposed as lead authority in order to facilitate the decision of the NCAs. The applicant should also inform the NCAs about its intended starting date. This request should be circulated 2 weeks before the intended submission date.

When accepted by the NCAs involved, the lead authority of upcoming MCMN veterinary CT application should fill in the CT tracking table stored in HMA Data Management System (DMS) with all the available information and allocate a procedure number. This procedure number should be conveyed to the applicant for the insertion in the application (including the application form) and for any future communication. Then this NCA will be considered as the lead-authority for this MCMN veterinary CT procedure.

In case the favoured NCA cannot accept to be the lead authority, the applicant should be informed immediately. The applicant should propose another NCA to be the lead authority. In any case, the lead authority should be determined before the submission of the MCMN veterinary CT application.

4.1.2 Duties of the lead authority

The lead authority will have to:

* allocate the procedure number (consecutive number ‘‘MCMN/Year/Ordinal number” taken from the CT tracking table), fill in the tracking table before the start of the procedure (outcome of the procedure and the date of decision will be self-included in the table by each NCA involved),
* liaise with CMDv secretariat for the organisation of the coordination meeting: list the NCAs involved and provide information on the CT application (information taken from the tracking table),
* chair the coordination meeting and prepare the summarising minutes of the meeting.

4.1.3 Numbering of the procedure

The format of the MCMN veterinary CT procedure number is: ‘‘MCMN/YYYY/Number’ as for instance ‘MCMN/2023/001”. Where:

* ‘‘YYYY’ is the year when the MCMN veterinary CT application is submitted and
* ‘‘Number’ is the number allocated to the procedure. This number is incremented from the tracking table listing all MCMN veterinary CT application (ordinal number associated procedure in the present year).
* In case of update of the MCMN veterinary CT application (see 4.7), an extension of the procedure number should be added: MCMN/YYYY/Number\_VAR\_Number. For instance: MCMN/2024/412\_VAR1.

4.1.4 Submission and validation

The MCMN veterinary CT application should be simultaneously submitted electronically by CESP or by the national system in place in the NCAs concerned (see CMDv document ‘‘Procedural Contact Points” for the preferred submission type of NCAs as well as national contact points for advice on CT application).

The MCMN veterinary CT application should contain the application form prepared by CMDv and all necessary documents/information according to national requirements of the NCAs involved (see CMDv documents ‘CT application form’ and ‘’CT national requirements”).

NCAs have 15 days to check the presence of the required documentation. Consequently, the applicant should submit its MCMN veterinary CT application at least 15 days before the intended clock start date (day 0) according to the clock start dates published in the CMDv website.

The CT application is considered invalid at the same time in all NCAs involved if one of the requirements that are mandatory for all MS has not been fulfilled. The ‘‘mandatory requirements” are those mentioned in the list of national requirements as requirements mandatory for all EU MS (see CMDv website).

All other validation issues, which are not common to all EU MS and which are considered as country-specific validation issues, can be managed outside of the validation period and will not avoid the start of the procedure in all NCAs.Those issues should be solved during the assessment step I.

In case of country-specific requirements that prevents the start of the MCMN procedure, the applicant is invited to withdraw the NCAs concerned from the MCMN procedure and proceed nationally with the assessment of the CT application. If the issue is solved quickly, the NCAs can re-integrate the MCMN procedure if desired. Requested missing information/documentation are prerequisites for a positive validation and must be provided by the applicant within the validation phase. The applicant should complete the application with the missing documentation accordingly and the procedure will start at next possible clock start date. No response from the NCAs involved in the MCMN veterinary CT application is considered as validation of the application.

Some NCAs may request that an updated (consolidated) application is submitted at the start of the procedure. Applicants are invited to check the national requirements.

The CT tracking table contains the following information:

* Submission date,
* MCMN veterinary CT Procedure number ‘MCMN/YYYY/Number’ and applicant procedure code/number,
* Name of applicant, name of active substance(s), target species,
* List of EU NCAs concerned by the MCMN veterinary CT application, lead authority,
* Conclusion on the MCMN veterinary CT application per NCAs involved,
* Date of the start of the procedure,
* Date of the end of the procedure.

## Start of procedure (Day 0)

Once the received application has been validated, the lead authority will inform by e-mail all NCAs involved and the applicant (as mentioned in the AF of the MCMN veterinary CT application) about the start of the procedure. This e-mail will be sent by the list ‘list-v-clinical-trials@eudra.org’ notifying the proposed starting dates according to the MCMN veterinary CT clock start dates published on the CMDv website. The lead authority will also inform NCAs involved that the CT tracking table was updated.

The communication between NCAs should be done according to the list of NCAs procedural contact points as long as the EU CT mailing list is not available.

## During the procedure

### Assessment Step I

The assessment is conducted by each NCA individually according to their national law and in conformity with the VICH Guideline 9 Good Clinical Practices EMEA/CVMP/VICH/595/98. NCAs will prepare their assessment e.g. based on an AR or a checklist and a list of questions will be drawn up, if the assessment of the application raises questions, according to their national requirements.

NCAs will share their lists of questions by e-mail (confidential contact points as long as the EU CT list is not available) with the other NCAs involved in the MCMN veterinary CT application before day 26/27.

### Coordination meeting

If required by NCAs involved, a coordination meeting could be organised at day 26/27 before the questions will be sent to the applicant. The aim of this meeting is not to achieve a harmonised opinion, but to exchange on the application and to clarify possible scientific issues of the individual NCAs.

The coordination meeting is organised by the CMDv secretariat by Webex on the same day as the product discussion as part of the Webex schedule MRP/DCP discussion(s). The lead authority will inform the CMDv secretariat in advance of the meeting about the list of participants (names and e-mail addresses). All participants should be registered in the list of experts and have a valid declaration of interest (DoI).

The lead authority will chair the discussion and will prepare summarising minutes that will be circulated to the NCAs involved in the MCMN veterinary CT application.

Each NCA will send their questions individually to the applicant at day 30 by e-mail. In its AR/list of questions, the lead authority is invited to mention all the administrative information mentioned in the template that will be used by the applicant for the compilation of questions (please see the template for the compiled list of questions).

### Clock Stop

During the clock stop the applicant has 30 days to respond to all NCAs involved by CESP/National system.

The answers to all questions raised by NCAs should be provided in one common document. The template for the compiled list of questions is available on the CMDv website. The applicant will find information on how to fill in the template in the template itself.

The original numbering of the questions raised by NCAs should be maintained in the Applicant’s response document.

### Assessment Step II

Each NCA will assess the answers received to their questions individually (NCAs only to assess and comment responses to the question they have asked) and will circulate their conclusion (and if applicable, further comments/recommendations for the applicants) to the other NCAs concerned at day 58/59. If considered necessary, NCAs involved can organise an informal virtual meeting. This meeting will be organised by the lead authority.

At day 58/59 all NCAs involved should fill in the CT tracking table with their decision on the MCMN veterinary CT application.

## Outcome of the procedure

The procedure will be closed at day 60 and the applicant will be informed about the outcome of the procedure (approved/refused) in each MS directly by the respective NCAs.

Each NCA involved finalises the CT tracking table with its decision on the outcome of the CT application and the date of the decision.

## CMDv plenary meeting

A hyperlink to the CT tracking table stored in HMA-DMS is available in the agenda of the CMDv plenary, so that each month all CMDv members have the possibility to check the list of MCMN veterinary CT applications.

## Duties of the applicant once the MCMN veterinary CT is approved

Once the MCMN veterinary CT is approved, the applicant must report at the end of the study, and any reason for an early termination.

With regard to any further national requirements after approval of the CT application (e.g. reporting of end of CT, early termination of CT, the reporting of adverse events (AEs) for (un)authorised IVPs etc.), the applicant is invited to consult the list of national requirements published on the CMDv website.

## Update the MCMN veterinary CT application

Once authorized, protocol modifications should be notified to the NCAs without delay. In some NCAs, each change to the submitted application should be approved before implementation. In those NCAs, the applicant will be informed by the NCAs about the approval/rejection of the change.

Depending on the nature of the change, two scenarios are possible:

1. When the necessary changes to an approved protocol are substantial, they should be assessed within a new 60-day procedure during that each NCA assesses the change(s) before its implementation. Substantial changes affect pivotal aspects of the study e.g. that could potentially derive in a significant impact on the efficacy or safety of the studied animals, or the quality of the investigational veterinary medicinal product. For these kind of changes, the applicant should submit the appropriate documentation to all NCAs involved in the original MCMN CT veterinary application. The lead authority of this procedure should be the same as in the initial procedure. The procedure number should be updated with an extension ‘VAR’ (see section 4.1.3). The NCAs assess the documentation provided individually and share the result of their assessment at day 26/27. In case there is no question from NCAs, the procedure can be closed earlier at day 30 and no coordination meeting will be organised.
2. For formal changes of the approved clinical trial protocol other than those listed above (e.g. change in the address of the sponsor, adding new study site…): the applicant submits the appropriate documentation to all NCAs at the same time so that the documentation is assessed according to national rules. There is no need for NCAs to share their assessment on this documentation.

## Pharmacovigilance

Furthermore, any suspected adverse events in CTs using authorised VMPs shall be included in the Union PHV Database in accordance with the requirements of Article 76(1) and (2) of Regulation (EU) 2019/6 and the Guideline on Veterinary Good Pharmacovigilance Practices (VGVP), Modules: ‘Collection and recording of suspected adverse events for VMPs’ etc…

The reporting timeframe and the way to report for any suspected AEs observed in CTs using Investigational Veterinary Medicinal Product (IVPs) not yet authorised can be decided and regulated nationally. However, the EudraVigilance database should not be used for reporting AEs of unauthorised products used in clinical trials.

# ANNEXES

## ANNEX 1: Flow chart for MCMN veterinary clinical trials application

|  |
| --- |
| **Submission Phase** |
| Prior Day -15 | The MCMN veterinary CT application should be submitted to all NCAs simultaneously.The lead authority should be determined before the submission of the veterinary CT application. |
| **Validation** |
| D - 15 | NCAs involved have 15 days to validate the MCMN veterinary CT application. |
| **Assessment Step I – 30 days for** NCAs |
| Day 0 | If the application is considered valid, the procedure can start. |
| Before day 26/27 | NCAs will assess the application individually. A list of questions is prepared by each NCA.  |
| **Coordination Meeting** |
| Day 26/27 | A meeting can be organised for NCAs involved to share on their assessment before questions are sent to the applicant. |
| Day 30 | Questions are sent to the applicant. |
| **Clock Stop – 30 days for applicant** |
|  | Answers should be sent within 30 days to all NCAs within one common response document. |
| **Assessment step II – 30 days for** NCA |
| Day 31 | Procedure re-start, NCAs have 30 days to assess the answers provided by the applicant.  |
| Day 58/59 | NCAs circulate their conclusion to the other NCA concerned. |
| Before day 60 | NCAs communicate to other NCAs on their decision. |
| **End of the procedure** |
| Day 60 | At day 60 NCAs involved should approve/refuse the MCMN veterinary CT application. |

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## ANNEX 2: List of used abbreviations

|  |  |
| --- | --- |
| AE | Adverse events |
| AF | Application form |
| AR | Assessment report |
| BPG  | Best practice guide |
| CESP | Common European Submission Portal |
| CMDv  | Coordination group for mutual recognition and decentralised procedures for veterinary medicinal products |
| CT | Clinical trials |
| DCP | Decentralised procedure |
| DoI | Declaration of interests |
| EMA  | European Medicines Agency |
| HMA DMS | Heads of Medicines Agencies Data Management System |
| IVP | Investigational Veterinary Medicinal Product |
| MS  | Member State(s) |
| MCMN | MultiCenter/MultiNational veterinary clinical trial application |
| MRP | Mutual recognition procedure |
| NCA | National competent authority |
| VGVP | Veterinary Good Pharmacovigilance Practices |
| VICH | International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (‘VICH’) |