DECISION

No. 6/05.06.2014

on approval of Regulations for authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 374/02.04.2014, in accordance with the Regulation on organisation and operation of the NAMMD Scientific Council, Article 8 (1), adopts through written procedure the following

DECISION

Article 1. - The Regulations for authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania are approved, in accordance with the Annexes which are integral parts of this Decision.

Article 2. – On this Decision coming into force, the following are repealed:

- SCD no. 29/16.12.2010 on approval of regulations on authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies conducted on medicinal products for human use in Romania;
- SCD no. 26/13.12.2011 on approval of amendment of Scientific Council Decision no. 29/16.12.2010 on approval of regulations on authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies conducted on medicinal products for human use in Romania
- SCD no. 8/17.04.2012 on approval of amendment of the Annex to Scientific Council Decision no. 29/16.12.2010 on approval of the Regulations on the authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX to SCD no. 6/05.06.2014

REGULATIONS
for authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania

CHAPTER I
General principles

Article 1. - (1) Clinical trials undertaken in Romania are authorised by the National Agency for Medicines and Medical Devices (NAMMD) in accordance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, Government Decision no. 734/21.07.2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, and Order of the Minister of Public Health no. 904/2006 on the approval of the Norms on the implementation of GMP rules in clinical trials carried out on medicinal products for human use.

(2) Non-interventional studies are an exception to provisions of paragraph (1), as defined in Order of the Minister of Health no. 904/2006, which shall be notified to the NAMMD.

Article 2. - Clinical trials must be conducted in accordance with all clinical trial regulations in force.

CHAPTER II
Clinical trial authorisation procedure

Article 3. - (1) For initiation of a clinical trial authorisation procedure, the applicant shall pay the clinical trial authorisation fee, established through Order of the Minister of Health in force concerning NAMMD fees.

(2) To perform the payment, at least 2 weeks in advance of submission of the application for clinical trial authorisation, the applicant shall submit to the NAMMD a cover letter related to the payment of the clinical trial fee, accompanied by the filled-in clinical trial fee payment form.

(3) The fee is to be paid to the accounts published on the NAMMD website.

(4) The NAMMD confirms the respective payment by e-mail.

Article 4. - (1) Following fee payment confirmation, the applicant may submit to the NAMMD an application for authorisation, using the format shown in SCD No. 22/2010 on approval of the Guidance for the request for authorisation of a clinical trial on a medicinal product for human use, addressed to the competent authority, notification of substantial amendments and declaration of the end of the trial in Romania.

(2) At the same time with submission of the application, the applicant shall also forward a signed cover letter, on paper, as shown in SCD no. 22/2010.

(3) On request, the documents mentioned in Annex 1, which is integral part of these regulations, shall be attached and forwarded in electronic format (on CD/DVD), structured in accordance with Annex 2.

Article 5. – The assessment period starts on submission of the documentation (day 0).

Article 6. - (1) The NAMMD reviews the validity of all documents required under Annex 1 (validation stage) and in 10 days forwards to the applicant a letter of information on validation of the application.

(2) If the documentation submitted by the applicant is complete, the application is considered valid and the assessment period is continued.

(3) If the documentation submitted by the applicant contains the essential documents related to the trial and supplementations are however necessary, requests for supplementation of the documentation are made; the assessment period is stopped until the date of submission of the required supplementations.

(4) If the documentation does not comprise the essential trial documents, the application for authorisation is rejected.

Article 7. - Documents under Article 4 (3) must be drawn up in accordance with provisions of SCD No. 22/2010.

Article 8. - The documentation is submitted in either English or Romanian.

Article 9. – (1) Labelling of medicinal products used in clinical trials is either Romanian or English (only for NAMMD use, for translation checking purposes);

(2) If the sponsor is Romanian, the label is submitted in Romanian only.

(3) Labelling is submitted in Romanian only for clinical trials performed in Romania.

Article 10. Applicants are advised to submit substantial amendments to the main trial documentation within 50 days as of payment confirmation; otherwise, the time for assessment of documentation is extended accordingly.

Article 11. - NAMMD examination of an accurate and properly formatted application for authorisation is to be completed as soon as possible, in line with the deadline set in Order of the Minister of Public Health no. 904/2006.

Article 12. - In case of documentation set up compliant with regulations in force and sufficiently substantiated, the NAMMD grants the authorisation for the performance of the clinical trial in the format mentioned in Annex 3, which is integral part of these regulations.

Article 13. - (1) If, following assessment of documentation, additional information or key clarifications to trial documentation is found necessary, the NAMMD notifies the applicant thereof.

(2) The deadline for assessment for clinical trial authorisation/refusal as specified in Order of the Minister of Public Health no. 904/2006 is extended with the time from applicant receipt of the NAMMD notification to receipt by NAMMD of the information required.

Article 14. - If, following assessment, documentation is found noncompliant with regulations in force and insufficiently substantiated, within the deadline provided in Order of the Minister of Public Health no. 904/2006, the NAMMD notifies the applicant on rejection of authorisation, accompanied by an explanatory report.

Article 15. - (1) The applicant may require revision of the refusal decision within 30 days as of issuance of the NAMMD decision; the application for revision must be accompanied by supporting documentation.

(2) The NAMMD examines the application and formulates an opinion within 30 days as of admission of the application for revision.

Article 16. - (1) The authorisation covers the entire conduct of a clinical trial, approved by the NAMMD; the trial starts within 1 year after the date of approval, otherwise the authorisation is no longer valid and the application must be resubmitted.

(2) The applicant informs the NAMMD about start of the trial in Romania (date of inclusion of the first patient/subject).

(3) In the end of the trial, the applicant informs the NAMMD about start of the trial, as shown in SCD no. 22/2010 and informs the NAMMD about the number of subjects enrolled in Romania.

Article 17. – The applicant submits to the NAMMD a copy of the National Ethics Commission/Institutional Ethics Commission opinion as soon as it becomes available.

Article 18. - A clinical trial may only start on condition the NAMMD has granted the authorisation for clinical trial conduct and after grant of the favourable opinion of the National

Ethics Commission, for multicentre trials, or the Institutional Ethics Commission, for single-centre trials.

CHAPTER III
Procedure for notification of amendments

Article 19. – In accordance with Order of the Minister of Health no. 904/2006, after start of the trial, the sponsor may amend the clinical trial documentation.

Article 20. - (1) The notification is mandatory only in case of substantial amendments (in accordance with SCD No. 22/2010).

(1) Immediate notification/submission of non-substantial amendments is not necessary (as under Minister of Public Health Order No. 904/2006).

Article 21. - (1) To start an authorisation procedure for a substantial amendment, the applicant must pay the fee for assessment of amendments, as established through the Minister of Health Order in force concerning NAMMD fees.

(2) To pay the fee, the applicant submits a cover letter to the NAMMD, accompanied by a filled-in form for payment of amendment fee, at least 2 weeks prior to the submission of the application for clinical trial authorisation.

(3) The NAMMD confirms the respective payment by e-mail.

Article 22. - (1) After confirmation of the payment, the applicant submits to the NAMMD a notification in the format provided in SCD No. 22/2010.

(2) At the same time with the application, the applicant also submits a signed cover letter.

(3) On request, the documents mentioned in SCD No. 22/2010, section III.7, Form and content of the notification, are attached.

Article 23. - (1) The period for assessment of amendments starts with submission of documentation (day 0).

(2) The NAMMD responds to the notification of an amendment within 35 calendar days as of receipt of a valid notification.

Article 24. - (1) The NAMMD assesses the validity of the notification.

(2) When the submission of the amendment is not considered valid (e.g. the dossier does not contain the necessary as per SCD No. 22/2010), the NAMMD informs the applicant within 10 calendar days of the aforementioned 35-day period, while stating the grounds for this decision.

Article 25. - If documentation is set up in accordance with legal provisions in force and sufficiently substantiated, the NAMMD notifies approval of the amendment.

Article 26. - (1) If, following assessment of the documentation, the NAMMD ascertains that additional information or essential clarifications to the documentation submitted are required, the NAMMD notifies the applicant in writing.

(2) The assessment period until approval/refusal of the amendment is extended with the time from applicant receipt of the request notification to NAMMD receipt of the information required.

Article 27. – If, following assessment of documentation, this is found not to be compliant with regulations in force and not satisfactorily substantiated, this leads to rejection of the proposed amendment.

Article 28. - (1) The applicant may require revision of the rejection decision within 30 days as of issuance of the NAMMD decision; the application for revision must be accompanied by supporting documentation.

(2) The NAMMD examines the application and formulates an opinion within 30 days as of receipt of the application for revision.

Article 29. – An amendment may only be implemented if:

- The NAMMD has notified its approval of the amendment and the CNBMDM has expressed its favourable opinion (if the amendment requires both NAMMD approval and CNBMDM opinion);
- The NAMMD has forwarded the approval of the amendment (if the amendment only requires NAMMD approval);
- The CNBMDM has expressed a favourable opinion (if the amendment only requires CNBMDM opinion).

CHAPTER IV
Importation of investigational medicinal products

Article 30. - The notification of investigational medicinal products (IMPs) importation is performed in compliance with legislation in force.

CHAPTER V
Analysis of biological samples

Article 31. - Analysis of biological samples collected during clinical trials are carried out in certified or accredited laboratories in Romania or other countries.

Article 32. - In case the analysis of biological samples is not performed in Romania, these shall be sent to other member states/exportation in third countries shall be done in compliance with legal provisions in force.

CHAPTER VI
Good Clinical Practice (GCP) inspection

Article 33. - GCP inspection is conducted in accordance with legal provisions in force.

CHAPTER VII
Requests concerning manner of trial subjects recruitment

Article 34. – (1) Recruitment of subjects for clinical trials conducted in Romania may only be done through healthcare professionals (physicians and pharmacists), except for healthy volunteers, who may also be recruited by other means.

(2) The media may not be used for recruitment.

CHAPTER VIII
Reporting of adverse reactions occurring in clinical trials

Article 35. - It is the sponsor’s obligation to report to the NAMMD adverse reactions and other information according to provisions of SCD No. 27/2011 on approval of the Guidance on the collection, verification and presentation of adverse reaction/event reports arising from clinical trials on medicinal products for human use.

CHAPTER IX
Requirements regarding investigator’s qualification

Article 36. – In order to fulfil provisions of Article 13 of Order of the Minister of Public Health no. 904/2006 and Articles 37 and 39 of SCD no. 39/2006 on qualification and training of investigators and knowledge of and compliance with Good Clinical Practice (GCP)

Regulations and other legal regulations in the field, the application for authorisation of a clinical trial is accompanied by the documents specified in Annex 1, which are integral part of these Regulations.

CHAPTER X
Authorisation of sites for conduct of clinical trials

Article 37. – Clinical trials may only be conducted on sites authorised by the Ministry of Public Health, in accordance with provisions of SCD no. 2/22.04.2014 on approval of Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use.

Article 38. – The authorisation is granted by the NAMMD on request by the interested site, in accordance with legal regulations in force.

Article 39. – (1) The amendments concerning investigation centres refer to the initial documents submitted for support of the application for authorisation for conduct of a clinical trial, as described under Section III.4.4 of SCD no. 22/2010.

(2) Non-exhaustive list of amendments typically considered important:

- addition of new centres;
- change of the new investigator from an already authorised site;
- change of the investigation site from an already authorised site (clinic/medical unit).

CHAPTER XI
Notification procedure for non-interventional studies

Article 40. - Notification of non-interventional studies consists of submission to the NAMMD by an applicant of a notification address, set up according to provisions of Annex 6, which is integral part of these Regulations, accompanied by the following documents:

- copy of the trial design;
- list of the sites where the trial will be conducted;
- information on the duration of the trial and the number of patients to be enrolled;
- list of the investigators containing their names, surnames and workplaces;
- trial endpoints:
    a) The scientific endpoints of the trial must be clearly stated, as well as the relevance for the medical practice of the data obtained during the trial conduct;
    b) The indicators for assessment of trial endpoints must be specified.

Article 41. - The clinical trial applicant is responsible for transmitting to the NAMMD the results of the non-interventional study, as well as for interpretation and statistical significance of results in one year as of trial ending.

Article 42. - In case of non-interventional studies, the NAMMD does not request fees for activities undertaken.

Article 43. - The NAMMD maintains a separate database of non-interventional studies, also including the results of non-interventional studies carried out in Romania.

Article 44. – The NAMMD notifies the applicant about the approval, rejection or need for completion of the documentation in 60 days as of submission of the notification.

ANNEX 1
to Regulations

DOCUMENTS
Accompanying the application to the NAMMD for authorisation of a clinical trial

KEY DOCUMENTATION
1. General information
1.1. Cover letter
1.2. Application form
1.3. Confirmation of EudraCT number receipt
1.4. If the applicant is different from the sponsor, a legal authorisation letter from the sponsor, empowering the applicant to act on behalf of the sponsor

2. Information on the protocol
2.1. Protocol containing all amendments
2.2. Summary of the protocol in Romanian
2.3. Opinion of the main investigator/coordinator on the ethical aspects of the trial

3. Investigator's Brochure (IB) or Document replacing the IB, in accordance with the content established in subsection II.6 of SCD no. 22/2010.

4. Investigational Medicinal Product Dossier (IMPD)/simplified IMPD
In accordance with the content established in subsections II.7 and II.7.3 of SCD no. 22/2010
The Investigational Medicinal Product Dossier (IMPD) includes:
- Evidence of GMP compliance
- Examples of labels in Romanian and English

5. The NIMPD dossier, in accordance with the content established in subsection II.8 of SCD no. 22/2010

6. Information on the staff and facilities
- Facilities made available for the trial:
  - Authorisation of the healthcare unit for the conduct of clinical trials,
  - Consent of the healthcare unit's director on conduct of the clinical trial
- CVs of the main investigator and subinvestigators;
- CV of the coordinator-investigator in Romania (for multicentre trials), if appointed;
- Copy of the confirmation order in the specialised field for the main investigator;
- Form attesting the qualification of the main investigator, containing the List of subinvestigators, of whom at least one is a physician;
- Proof of graduation from a course referring to Good Clinical Trial Practice for all investigators and subinvestigators;
- Any other documents attesting the qualification and training of investigators in accordance with the area of the study.

7. Confirmation of payment

ADDITIONAL DOCUMENTATION
1. Copy of the National Bioethics Committee of Medicines and Medical Devices, if available;
2. Copy/Summary of any scientific counselling, if any;

3. Copy of the EMA decision concerning agreement expressed concerning the PIP, as well as the opinion of the Paediatric Committee, if any;
4. List of competent authorities (CAs) in the EU to whom the application and decision details have been submitted;
5. Information about all active clinical trials on the same PIP.

ANNEX 2
to Regulations

- **1. General information**
- **2. Protocol-related information**
- **3. Investigator's brochure or document replacing the IB**
- **4. Investigational Medicinal Product Dossier (IMPD) /simplified IMPD**
- **5. NIMPD dossier**
- **6. Information on the staff and facilities**
- **7. Additional documents**

ANNEX 3
to Regulations

THE MINISTRY OF HERALTH
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES
48 Av. Sănătescu street, sector 1
011478 Bucharest
Tel.: +40-21.317.11.02
Fax:+40-21.316.34.97

AUTHORISATION
for conduct of a clinical trial

The National Agency for Medicines and Medical Devices, based on Article 4 (2) d) of Government Decision no. 734/21.07.2010, as amended, and on Article 37 of Order of the Minister of Public Health no. 904/2006, hereby authorises conduct of the clinical trial according to Protocol No.:

EudraCT No.:

Title:

Sponsor:

Investigators:

Institution (trial site):

Remarks:

PRESIDENT,
.....

ANNEX 4
to Regulations

FORM
for reporting serious unexpected suspected adverse reactions

Suspected adverse reaction Protocol no. Notification no.

Investigational medicinal product Patient no.

I. Information on the adverse reaction

1.Patient's initials	1.Country	2. Birthdate			2.a. Age	3.Gender	4-6 Manifestation of the adverse reaction			8-12 Fill in accordingly
		Day	Month	Year			Day	Month	Year	[ ] Death [ ] Life-threatening [ ] Hospitalisation/Prolonging hospitalisation [ ] Major or chronic handicap/disability [ ] Congenital disorder/disease
7.Reaction's description (including relevant outcomes/laboratory testings)										

II. Information about the suspected investigational medicinal product

14. Name of the investigational medicinal product		20. The adverse reaction has subsided after the discontinuation of the trial [ ] Yes [ ] No
15. Daily dose	16. Route of administration	21. The adverse reaction has reoccurred after the second administration of the investigational medicinal product [ ] Yes [ ] No
17. Administration indication(s)		
18. Period of administration (from/until)	19. Duration of administration	

III. Concomitant indication and history

22. Concomitant medication and administration dates (excluding that meant for treatment of the reaction)
23. Other relevant medical history data (such as diagnosis, allergic reactions, pregnancies etc.)

IV. Information about the sponsor and the investigator

24.a. Name and address of the sponsor	24.b. Name of the investigator

24.c. Date of receipt by the sponsor	25.a. Type of information [ ] Initial [ ] Sequential	25.b. Manner of informing the sponsor
Date of notification	Date of receipt	[ ] Additional information is to be attached

Sponsor’s signature

ANNEX 5
to Regulations

FORM
for main investigator/coordinator qualification and arrangements made for participation in the clinical trial

Investigational medicinal product ……..... Protocol No. .....…
Name of the main investigator/coordinator .....….....
Investigator's address
…….....….....……
Curriculum Vitae/summary: ..... Attached YES [ ]
Qualification (profession)
…….....
Experience in clinical trials:
.....
Experience with other medicinal products relevant to the proposed trial
…….....
.

Regular duties:
Involvement in other clinical trials:
Time necessary for this protocol:
Availability of subjects suitable for the clinical trial:
I hereby accept to participate as main investigator/coordinator in the clinical trial mentioned:
I hereby agree to allow control of all documents:
I hereby agree to allow access to basic documentation:
I hereby agree to sign the commitment form and conduct the trial according to the approved protocol, in compliance with the revised Helsinki Declaration of Human Rights and Good Clinical Practice in Romania.
During the trial, the following will participate as sub-investigators:

Signature Date.....
(day/month/year)
Title

Monitor

(Name)

ANNEX 6
to Regulations

NOTIFICATION
on conduct of a non-interventional study in Romania

To

THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

APPLICANT SPONSOR ☐ INVESTIGATOR ☐ CRO* ☐

Name and surname

Profession

Institution

Address

Telephone/fax number

*) Contract research organisation

We are hereby notifying conduct of a non-interventional study on a medicinal product authorised for marketing in Romania:

- Title of the clinical trial: .....

Information about the investigational medicinal product
- Trade name/code
- Active substance
- ATC code
- Pharmaceutical form
- Doses
- Route of administration
- Marketing Authorisation Holder
- Country

This notification is accompanied by:

- ❑ Copy of the study design
- ❑ Study endpoints
- ❑ List of the sites where the study is conducted;
- ❑ Information about trial duration and number of patients to be enrolled.
- ❑ List of investigators containing the names and surnames of the investigators and their workplaces