Ministry of Health

ORDER No. 3.390
of 8 November
2022

on approval of the Methodological rules for approval of provisions of Articles 3 (10), 4 (3) and 6 (2) of Emergency Government Ordinance no. 29/2022 regarding the establishment of the institutional framework and the necessary measures to ensure the application of 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, as well as for the amendment of some regulatory acts in the healthcare field*)

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On seeing approval report no. AR/19.966 of 8.11.2022 of the Pharmaceutical and Medical Devices Directorate and notification no. 56.884E of 22.06.2022, of the National Agency for Medicines and Medical Devices of Romania, registered at the Ministry of Health with no. P0743 of 22.06.2022,

taking into account the provisions of:

- Art. 3 paragraph (10), Art. 4 paragraph (3) and Art. 6 paragraph (2) of Emergency Government Ordinance no. 29/2022 regarding the establishment of an institutional framework and necessary measures for implementation of 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, repeal of Directive 2001/20/EC and amendment of certain healthcare regulations, approved as amended and supplemented through Law 249/2022;
- Art. 2 point k), Art. 4 paragraph (3) points 1 and 5 of Law 134/2019 on reorganisation of the National Agency for Medicines and Medical Devices and amendment of further ruling provisions, as further amended and supplemented,

pursuant to Article 7 (4) of Government Decision no. 144/2010 on the organisation and operation of the Ministry of Health, as further amended and supplemented,

the minister of health hereby issues the following order:

Art. 1 - The Methodological rules for approval of provisions of Art. 3 paragraph (10), Art. 4 paragraph (3) and Art. 6 paragraph (2) of Emergency Government Ordinance no. 29/2022 regarding the establishment of an institutional framework and necessary measures for implementation of

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, repeal of Directive 2001/20/EC and amendment of certain healthcare regulations, mentioned in the Annex which is integral part of this Order, are approved.

Art. 2 – The National Agency for Medicines and Medical Devices of Romania, hereinafter the ***NAMMDR***, and the National Bioethics Committee of Medicines and Medical Devices, hereinafter the ***CNBMDM***, shall carry out the provisions of this Order.

Art. 3 - This Order shall be published in the Official Gazette of Romania, Part I.

On behalf of the Minister of Health,
Romică-Andrei Baciu,
Secretary of State

Annex

METHODOLOGICAL RULES

for approval of provisions of Articles 3 (10), 4 (3) and 6 (2) of Emergency Government Ordinance no. 29/2022 regarding the establishment of the institutional framework and the necessary measures to ensure the application of 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, as well as for the amendment of some regulatory acts in the healthcare field

Chapter I
General provisions

Art. 1 - (1) The terms used in this Order have the meaning established by 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, as well as for the amendment of some regulatory acts in the healthcare field, hereinafter the ***Regulation.***

(2) In line with the provisions of this Order, ***public and private healthcare facilities*** are the public and private healthcare facilities mentioned in Art. 30 paragraph (1) and (2) of Law 95/2006 on healthcare reform, republished, as further amended and supplemented, and ***an informed consent*** is understood as defined in Art. 2 paragraph (2) point 21 of the Regulation.

Art. 2 - (1) In order to authorise a clinical trial or a substantial amendment of a clinical trial, in accordance with the provisions of the Regulation, the NAMMDR collaborates with the CNBMDM to analyse the information and documents in the application dossier specified in Art. 4 paragraph (1) of Emergency Government Ordinance no. 29/2022, as further amended and supplemented, and in Section IV of the Regulation.

(2) The NAMMDR is the competent authority in the field of interventional clinical trials with medicinal products for human use and the national contact point facilitating the functioning of the procedures established in Sections II and III of the Regulation, in line with the provisions of Art. 2 paragraph (1) of Emergency Government Ordinance no. 29/2022, as further amended and supplemented.

(3) The NAMMDR and the CNBMDM are responsible for fulfilling the tasks specified by the Regulation, which are incumbent on Romania, according to its specific attributions and they ensure the efficiency of the administrative process.

(4) In order to achieve the purpose set out in paragraph (3), the NAMMDR and the CNBMDM shall establish, by mutual agreement, an electronic communication channel with a high information security level.

Art. 3 - (1) The NAMMDR and the CNBMDM have the following attributions in ensuring the responsibilities mentioned in Art. 2 paragraph (3):

a) The NAMMDR:

1. coordinates at national level, in accordance with the provisions of Art. 4, the second paragraph of the Regulation, the process of analysing the

information and documents contained in the application dossier, specified in Section IV of the Regulation and transmitted by the sponsor through the Clinical Trial Information System, hereinafter the CTIS, specified in Art. 3, paragraph (2) of Emergency Government Ordinance no. 29/2022, as further amended and supplemented, the process of evaluating the aspects covered by Parts I and II of the assessment report, as well as the process of solving the requests received from sponsors, mentioned in Art. 5 and Art. 16 of the Regulation.

2. transmits, through the CTIS, the requested information and documents in line with the provisions of the Regulation, to the other Member States of the European Union, sponsors and the European Commission;

3. participates in the procedure for election of the Rapporteur Member State, hereinafter the ***SMR***, specified in Art. 5 paragraph (1) paragraphs 2 - 7 of the Regulation;

4. validates the application for authorisation of an interventional clinical trial or a substantial amendment, as the case may be, in accordance with the provisions of Art. 5 paragraph (3), Art. 17 paragraph (2) and Art. 20 paragraph (1) - (4) of the Regulation;

5. consolidates the observations and informs the sponsor about the application dossier, through the CTIS, in the situations mentioned in Art. 5 paragraph (5), Art. 17 paragraph (4) and Art. 20 paragraph (3) of the Regulation;

6. scientifically evaluates the aspects covered by Part I of the assessment report;

7. evaluates the aspects covered by Part II of the assessment report, with regard to compliance with Art. 49 and Art. 50 of the Regulation;

8. drafts Part I of the assessment report, both in draft form, in accordance with Art. 6 paragraph (5) point (c) the second paragraph of the Regulation, and in finished form, in accordance with Art. 6 paragraph (6) of the Regulation, in the event that Romania is a SMR;

9. consolidates and transmits to the sponsor, through the CTIS, the requests for additional information, formulated following the assessment process of the aspects covered by Part I of the assessment report, in accordance with the provisions of Art. 6 paragraph (8), Art. 18 paragraph (4) point (c) fourth paragraph of the Regulation, as well as the requests formulated following the assessment process of the aspects covered by Part II of the assessment report, in line with the provisions of Art. 7 paragraph (2) second paragraph and Art. 20 paragraph (3) of the Regulation;

10. sends to the sponsor, through the CTIS, the finished form of Part II of the assessment report, in line with the provisions of Art. 7 paragraph (2) the first paragraph and Art. 20 paragraph (5) of the Regulation;

11. notifies, through the CTIS, the other Member States of the European Union, the sponsor and the European Commission, of the decisions taken by Romania, in accordance with the provisions of Art. 8 paragraph (1) the second paragraph, Art. 14 paragraph (3), Art. 19 paragraph (1) the second paragraph and Art. 23 paragraph (1) the second paragraph of the Regulation;

5. issues the authorisation for conduct of the interventional clinical trial or a substantial amendment of the clinical trial, with or without the reservation of the fulfilment of certain specific conditions, as the case may be, or the NAMMDR decision regarding the refusal to authorise the interventional clinical trial or the substantial amendment of a clinical trial, as the case may be, in compliance with the terms mentioned in Art. 8 paragraph (1) second paragraph, Art. 14

paragraph (3), Art. 19 paragraph (1) second paragraph, Art. 23 paragraph (1) second paragraph of the Regulation.

6. issues the decision for withdrawal of the authorisation of the conduct of an authorised interventional clinical trial, in accordance with the provisions of Art. 77 paragraph (1) point a) of the Regulation;

b) the CNBMDM:

1. carries out the ethical analysis on the aspects covered by parts I and II of the assessment report, in accordance with the second sentence of Art. 4 and Art. 7 paragraph (1) of the Regulation;
2. transmits to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), the observations on the validation of the application as well as the considerations following the ethical analysis of the aspects covered by part I of the assessment report;
3. drafts part II of the assessment report, the draft form and the finished form, in line with the provisions of Art. 7 paragraph (2), Art. 14 paragraph (7) and Art. 20 paragraph (5) of the Regulation;
4. issues and transmits the ethical opinion to the NAMMDR, through the electronic communication channel;
5. approves the electronic information resources regarding the conduct of clinical trials mentioned in Art. 14 paragraph (1) point d).

(2) In fulfilling the duties specified in paragraph (1), the NAMMDR and the CNBMDM shall examine the documents specified in Annexes I and II to the Regulation, as the case may be, respectively from the list specified in Annex 1 to these Rules.

Art. 4 - (1) In order to make and confirm the payment specified in point Q point 72 of Annex I and point G point 9 of Annex II to the Regulation, as applicable, the sponsor shall send the NAMMDR, through the CTIS, the payment commitment form filled in according to the draft specified in Annex 2 to these Rules.

(2) Immediately after the completion of the SMR selection procedure, through the CTIS, the NAMMDR issues the invoice based on the payment commitment specified in paragraph (1).

(3) The sponsor is obliged to pay the invoice specified in paragraph (2) within maximum 15 days from the date of issuance by the NAMMDR.

(4) The methodology regarding the transfer by the NAMMDR to the CNBMDM of the amount due from the single tariff paid by the sponsor is established by a protocol concluded between the two parties.

Chapter II
Procedure for authorisation of an interventional clinical trial

Section 1
Validation of the request for authorisation of an interventional clinical trial

Art. 5 - (1) The CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), its considerations for the validation of the application within maximum 5 days from the date of submission of the application dossier for authorisation of an

interventional clinical trial through the CTIS.

(2) In the event that the sponsor completes the application dossier or transmits information in response to the observations sent in line with Art. 5 paragraph (5) first paragraph of the Regulation, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel, its conclusion regarding the validation of the application, within maximum 3 days from receipt of the sponsor's response to the observations, through the CTIS.

(3) If Romania is the SMR, the NAMMDR shall notify the sponsor in accordance with the provisions of Art. 5 paragraph (3) of the Regulation.

(4) In the case where Romania is the Member State concerned, hereinafter the SMC, the NAMMDR shall transmit its observations and those of the CNBMDM to the SMR, in accordance with the provisions of Art. 5 paragraph (3) of the Regulation.

Section 2

Assessment of the aspects covered by Part I of the assessment report, according to Art. 6 of the Regulation

Art. 6 - (1) If Romania is the SMR and no other Member State of the European Union is involved in the procedure for authorisation of the interventional clinical trial, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel, its considerations regarding the aspects covered by part I of the assessment report within maximum 21 days from the date of validation, as specified in Art. 5 paragraph (6) of the Regulation.

(2) The CNBMDM shall transmit to the NAMMDR, through the electronic communication channel, the ethical conclusion within maximum 38 days from the date of validation specified in paragraph (1).

(3) When Romania is the SMR and at least one other Member State of the European Union is involved in the procedure for authorisation of the interventional clinical trial, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel, the considerations regarding the aspects covered by part I of the assessment report within maximum 21 days from the date of validation specified in paragraph (1).

(2) In the situations specified in paragraphs (1) and (3), the NAMMDR, after consulting the CNBMDM, may extend the assessment period in accordance with Art. 6 paragraph (7) of the Regulation and communicates the extension of the period to the other Member States, through the CTIS, as well as to the CNBMDM, through the electronic communication channel specified in Art. 2 paragraph (4), for transmission of the conclusion and the ethical opinion, within this period.

(3) If Romania is a SMC, the CNBMDM shall transmit, through the electronic communication channel specified in Art. 2 paragraph (4), its considerations to the NAMMDR within maximum 7 days after the conclusion of the initial assessment phase by the SMR, in line with the provisions of Art. 6 paragraph (5) point a) of the Regulation.

(4) In the event that Romania is a SMR, the NAMMDR shall consult with the

CNBMDM in the consolidation phase, as specified in Art. 6 paragraph (5) point c) of the Regulation. In this case, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), the ethical conclusion within 4 days of the end of the coordinated assessment phase, in accordance with Art. 6 paragraph (5) point b) of the Regulation.

(5) When Romania is the SMR, the NAMMDR may request additional information from the sponsor on the aspects covered by Part I of the assessment report, in accordance with the provisions of Art. 6 paragraph (8) fourth paragraph of the Regulation. In this case, the CNBMDM shall communicate its observations to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), which the latter shall transmit to the sponsor through the CTIS.

(6) Where the SMR has requested additional information from the sponsor in accordance with the first subparagraph of Article 6 paragraph (8) of the Regulation, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Article 2 paragraph (4), its conclusion within maximum 8 days after receipt of the additional information from the sponsor, through the CTIS.

(7) Where Romania is the SMR, the NAMMDR shall consult the CNBMDM in the subsequent consolidation phase, within the meaning of the fourth subparagraph of Article 6 paragraph (8) of the Regulation. The CNBMDM shall transmit to the NAMMDR, through the electronic communication channel, its conclusion, as part of this subsequent consolidation, within maximum 4 days after completion of the coordinated assessment.

Section 3

Assessment of the aspects covered by Part II of the assessment report in line with Art. 7 of the Regulation

Art. 7 - (1) The NAMMDR and the CNBMDM may request additional information from the sponsor regarding the aspects covered by Part II of the assessment report, in accordance with the provisions of Art. 7 paragraph (2) second paragraph and paragraph (3) paragraph 5 of the Regulation.

(2) The CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), the assessment report for Part II, draft form, within a maximum of 21 days from validation and the report for Part II, final form, within a maximum of 15 days from the date of receipt from the sponsor, through the CTIS, of the additional information mentioned in Art. 7 paragraph (2) second paragraph of the Regulation.

(3) The CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), its conclusion on the aspects covered by Part II of the assessment report, namely, acceptable, acceptable subject to fulfilment of specific conditions or unacceptable on duly justified grounds, in accordance with the provisions of Art. 8 paragraph (4) of the Regulation.

(4) The CNBMDM shall issue the ethical opinion and transmit it to the

NAMMDR within maximum two days from the date of the report or the last day of the assessment referred to in Art. 7 of the Regulation.

Section 4
Subsequent addition of a concerned Member State of the European Union

Art. 8 - (1) If the sponsor wishes to extend an authorised interventional clinical trial to Romania as an additional SMC, in accordance with Art. 14 of the Regulation, the CNBMDM transmits its conclusion to the NAMMDR, through the electronic communication channel, within maximum 42 days from the date of submission of the application dossier by the sponsor, through the CTIS.

(2) When the sponsor wishes to extend an authorised interventional clinical trial for which Romania is the SMR, to an additional SMC, in accordance with Art. 14 of the Regulation, only the NAMMDR may request additional information from the sponsor, in accordance with Art. 14 paragraph (6) first paragraph of the Regulation, on the aspects covered by Part I of the assessment report, requested by the additionally added SMC.

(3) In the situation specified in paragraph (1), the NAMMDR may request additional information from the sponsor, taking into account the aspects mentioned in Art. 14 paragraph (5) of the Regulation, through the SMR, in accordance with Art. 14 paragraph (6) paragraph one of the Regulation.

(4) In the situation specified in paragraph (1), the CNBMDM may transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), with justified reasons, the request for additional information regarding the aspects covered by Part II of the assessment report, in accordance with Art. 14 paragraph (7) sentence 2 and paragraph 8 paragraph five of the Regulation, which the NAMMDR shall transmit, through the CTIS, to the sponsor.

(5)The CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), its conclusion on the aspects covered by Part II of the assessment report, namely, acceptable, acceptable subject to fulfilment of specific conditions or unacceptable on the basis of duly justified reasons, in accordance with the provisions of Art. 8 paragraph (4) of the Regulation.

(6) The NAMMDR notifies the sponsor of Romania's decision, through the CTIS, in accordance with the provisions of Art. 14 paragraph (3) of the Regulation.

Chapter III
Procedure for authorisation of a substantial amendment of an interventional clinical trial

Art. 9 - (1) In the case of an application for authorisation of a substantial amendment of a interventional clinical trial, in line with the provisions of Art. 15 - 24 of the Regulation, when Romania is a SMR or SMC, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), its observations on the validation of the application regarding the aspects covered by Part I of the assessment report,

within maximum 3 days from submission of the application dossier by the sponsor, through the CTIS.

(2) If Romania is the SMC, the NAMMDR shall transmit to the SMR, through the CTIS, its observations as well as the observations of the CNBMDM, in accordance with the provisions of Art. 17 paragraph (1) second paragraph of the Regulation.

(3) If Romania is the SMR, the NAMMDR shall notify the sponsor, through the CTIS, of the aspects mentioned in Art. 17 paragraph (4) first and second paragraphs of the Regulation.

(4) If Romania is the SMR, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), the ethical considerations within maximum 15 days after validation of the application, in line with the provisions of Art. 17 paragraph (5) of the Regulation.

(5) In the situations specified in paragraphs (3) and (4), after consulting with the CNBMDM, the NAMMDR may extend the assessment period, in accordance with the provisions of Art. 18 paragraph (5) of the Regulation and communicates the extension of the period to the other Member States, through the CTIS, as well as to the CNBMDM, through the electronic communication channel specified in Art. 2 paragraph (4), for the transmission of the conclusion and the ethical opinion within this period.

(6) In the event that Romania is a SMC, the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), ethical considerations within maximum 10 days from the conclusion of the initial assessment phase, carried out by the SMR, in accordance with the provisions of Art. 18 paragraph (4) point a) of the Regulation.

(7) If Romania is a SMR, the NAMMDR shall consult with the CNBMDM during the consolidation phase, specified in Art. 18 paragraph (4) point c) of the Regulation, and the CNBMDM shall transmit to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), the ethical considerations within maximum 4 days after the end of the coordinated assessment phase, in accordance with the provisions of Art. 18 paragraph (4) point b) of the Regulation.

(8) When Romania is the SMR, the NAMMDR notifies the sponsor, through the CTIS, of the request for additional information regarding the aspects covered by Part I of the assessment report, in accordance with Art. 18 paragraph (6) of the Regulation.

(9) If the SMR has requested additional information from the sponsor, in accordance with Art. 18 paragraph (6) first paragraph of the Regulation, the CNBMDM shall transmit its conclusion to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), within maximum 8 days after receipt of the additional information from the sponsor through the CTIS, in accordance with the provisions of Art. 18 paragraph (6) fourth and sixth paragraphs of the Regulation.

(10) If Romania is a SMR, the NAMMDR consults the CNBMDM, during the coordinated assessment phase, in accordance with the provisions of Art. 18 paragraph (6) paragraph four of the Regulation, and the CNBMDM transmits to the NAMMDR, through the electronic communication channel specified in Art. 2 paragraph (4), its conclusion within maximum 4 days following

completion of the coordinated assessment, as part of the subsequent consolidation, in line with the provisions of Art. 18 paragraph (6) paragraph four of the Regulation.

(11) The NAMMDR and the CNBMDM may request from the sponsor, through the CTIS, additional information regarding the aspects covered by Part II of the assessment report, in accordance with the provisions of Art. 20 paragraph (6) paragraphs 1 and 6, Art. 22 paragraph (2), paragraph (3) paragraph 5 of the Regulation.

(12) The NAMMDR shall notify the sponsor of Romania's decision, through the CTIS, in accordance with the provisions of Art. 19 paragraph (1), Art. 20 paragraph (5) second paragraph of the Regulation.

(13) The CNBMDM shall issue the ethical opinion and transmit it to the NAMMDR within maximum two days following reporting, in accordance with Art. 18 paragraph (3) paragraph two of the Regulation.

Chapter IV
Notification of the single decision of Romania and issuance of the authorisation for conduct of the clinical trial or a substantial amendment of the clinical trial

Art. 10 - (1) The NAMMDR notifies, through the CTIS, the sponsor, all Member States of the European Union and the European Commission, of the single decision of Romania regarding the authorisation, authorisation subject to the fulfilment of certain conditions or the decision to refuse the authorisation of a interventional clinical trial or of a substantial amendment of the interventional clinical trial, in accordance with the provisions of Art. 8 paragraph (1) second paragraph, Art. 19 paragraph (1) first paragraph and Art. 23 paragraph (1) second paragraph of the Regulation.

(2) The NAMMDR issues: the authorisation for the conduct of the interventional clinical trial, the authorisation of a substantial amendment of the interventional clinical trial, with or without the reservation of the fulfilment of certain specific conditions or the decision regarding the refusal of the authorisation of the interventional clinical trial or of the substantial amendment, as the case may be, within the term specified in Art. 8 paragraph (1) second paragraph, Art. 14 paragraph (3), respectively Art. 19 paragraph (1) second paragraph, Art. 23 paragraph (1) second paragraph of the Regulation, as the case may be.

(3) The authorisation, respectively the decision specified in paragraph (2), shall specify the ethical opinion issued by the CNBMDM.

Chapter V
Compliance with the provisions of Art. 98 of the Regulation

Art. 11 - (1) In accordance with the provisions of Art. 98 paragraphs (1) and (2) of the Regulation, after the expiry of the period of 3 years from the date referred to in Art. 99 second paragraph of the Regulation, a clinical trial authorised under Directive 2001/20/EC may continue to be conducted provided

that, before expiry of this period, the interventional clinical trial is authorised in line with the Regulation.

(2) For the authorisation referred to in paragraph (1), the sponsor shall submit an initial application via the CTIS, comprising the EU application form set out in point C of Annex I to the Regulation, a letter of intent set out in point B of Annex I to the Regulation and an application dossier based on the existing dossier, with documents already examined by Member States, for both Part I and Part II of the assessment report, in accordance with Annex I to the Regulation. In the case of multinational clinical trials, the application dossier shall contain a harmonised or at least consolidated protocol.

(3) The letter of intent referred to in paragraph (2) shall state that the purpose of the application is to authorise an interventional clinical trial in line with the Regulation which has already been authorised and is ongoing under Directive 2001/20/EC.

(4) The NAMMDR and the CNBMDM charge a single fee for the authorisation request under this article, according to Art. 5 paragraph (1) of Emergency Government Ordinance no. 29/2022, as further amended and supplemented.

(5) For payment and confirmation of the fee referred to in paragraph (4), the procedure referred to in Art. 4 shall apply.

(6) The procedure for solving the application referred to in paragraph (2) shall be carried out in accordance with the provisions of Section II of the Regulation and Section II of this Order.

(7) The NAMMDR shall notify the sponsor, through the CTIS, of the national decision on the authorisation in line with the Regulation of the interventional clinical trial already authorised and in progress in line with Directive 2001/20/EC and shall issue the authorisation to conduct the clinical trial in line with the Regulation, specifying the EudraCT number and the fact that the interventional clinical trial is already authorised and in progress in line with Directive 2001/20/EC, or a rejection notice, as the case may be.

Chapter VI
Assessment procedure in accordance with Article 44 of Regulation (EU) 536/2014

Art. 12 - (1) The NAMMDR and the CNBMDM shall cooperate on the procedure for the assessment of yearly safety reports and suspected unexpected serious adverse reactions reported in accordance with Art. 44 paragraph (1) of the Regulation.

(2) The CNBMDM shall transmit to the NAMMDR, through the electronic communication channel, its considerations after the assessment, at least 2 days before the timetable established by the Member State chosen responsible for safety assessment of medicinal products containing the same active substance.

Chapter VII
Persons assessing the application for authorisation of an interventional clinical trial or the application for a substantial amendment

Art. 13 - (1) The NAMMDR and the CNBMDM involve, in the assessment of applications for authorisation of a clinical trial, of applications for a substantial amendment of a clinical trial or of a change in the regulatory framework of a clinical trial, a sufficient number of qualified persons, who jointly have the expertise required in order to analyse the documents and evaluate the information in the application dossier, as well as at least one non-specialist.

(2) Qualified persons participating in the assessment of the application dossier must hold a diploma, certificate or other proof of official qualification acquired upon completion of university studies or a course recognised as equivalent by Romania, in one of the following scientific disciplines: medicine, pharmacy, biology, chemistry, biostatistics, bioethics, as appropriate, and in the case of the CNBMDM, including the specialty of law. The non-specialist is not required to hold a qualification in the fields listed above.

(3) In fulfilling its duties, the NAMMDR involves, in the assessment of applications for authorisation of a interventional clinical trial, applications for a substantial amendment or change in the regulatory framework of a interventional clinical trial, qualified personnel in the fields of medicine, pharmacy, biology, chemistry, biostatistics.

(4) Regarding the authorisation of healthcare facilities where phase I and bioequivalence clinical trials will be conducted, the NAMMDR also involves a legal adviser in the procedure for verification of the documentation.

(5) In carrying out its duties, the CNBMDM shall involve in the assessment of applications for authorisation of a clinical trial, applications for a substantial amendment or change to the regulatory framework of a clinical trial, qualified personnel in the fields of medicine, pharmacy, biology, biostatistics, law, as well as at least one non-specialist. The latter is not required to be qualified in any of the fields listed in paragraph (2).

(6) The NAMMDR and the CNBMDM shall develop procedures for verifying and monitoring the persons who validate and assess the applications for authorisation of a clinical trial, the applications for a substantial amendment or change in the regulatory framework of a clinical trial, which they publish on their own website, so as to ensure that they are not subject to conflicts of interest, are independent of the sponsor, the location of the clinical trial, the investigators involved and the persons financing the clinical trial and are free from any other undue influence.

Chapter VIII
Methods of recruiting and obtaining informed consent from subjects for enrolment in interventional clinical trials

Art. 14 - (1) Recruitment of subjects, patients or healthy volunteers, for enrolment in interventional clinical trials, in accordance with Annex I point K of the Regulation, can be achieved through the following methods:

a) through patients under the care of the investigators or the healthcare facility where the clinical trial will be conducted;

b) through specialist physicians who are not part of the investigation teams in the trial in question, family physicians or pharmacists;

c) by displaying, in healthcare facilities, an announcement/poster regarding the conduct of a clinical trial;
d) through electronic resources regarding the conduct of interventional clinical trials, approved by the CNBMDM in advance, in compliance with certain information requirements and indicating contact persons who can provide additional details;
e) through nationally recognised patient organisations, in compliance with certain information requirements and indicating contact persons who can provide additional details;
f) through a non-governmental organisation in the medical and healthcare field.

(2) By way of exception to the provisions of paragraph (1), recruitment for phase I and bioequivalence studies may be carried out from among the persons in the databases of phase I or bioequivalence units and of healthcare units, in compliance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), as well as subsequent legislation in the field, provided that the informed consent of the person who participated in a clinical trial exists, in order to be stored in a database for future recruitment.

(3) If the recruitment of subjects is carried out by the methods referred to in paragraph (1), the application dossier for the authorisation of an interventional clinical trial must include:

a) the recruitment and informed consent procedure, according to the draft in Annex 3 to these Rules;

b) recruitment materials in Romanian, if provided.

(4) The procedure for recruiting subjects in orders to participate in interventional clinical trials should include information regarding the management of responses to recruitment materials, information regarding counselling of subjects who did not qualify for participation in the trial, and a description of the personnel involved in conducting the recruitment interview, if applicable.

(5) The procedure specified in paragraph (3) must be carried out in compliance with the General Data Protection Regulation, as well as subsequent legislation in the field.

Art. 15 - (1) The person conducting the interview in order to obtain informed consent must be a physician, a member of the investigation team, appropriately trained on the protocol and good clinical trial practice.

(2) In the case of minors, in addition to the informed consent of the legal representative, according to the legal provisions in force, or of the legal representative appointed under the law, the agreement of minors to participate in the interventional clinical trial, minors who are capable of forming an opinion and evaluating the information provided to them, is mandatory.

(3) In the case of incapacitated persons who are able to form an opinion and evaluate the information referred to in Art. 29 paragraph (2) of the Regulation, both their signature and that of the legal representative, or the legal representative appointed under the law, are mandatory on the informed consent form, according to the legal provisions in force.

Section IX
Investigators and investigation centres

Art. 16 - (1) In line with the provisions of Art. 49 of the Regulation, in order to assess the adequacy of the investigational sites where the interventional clinical trial is to be conducted and of the investigators selected by the sponsor, the NAMMDR and the CNBMDM evaluate the following documents submitted by the sponsor, through the CTIS:

a) the list of sites for planned interventional clinical trials, in accordance with Annex I, point M point 64 of the Regulation;

b) the curriculum vitae of the main investigator, in accordance with the form in Annex 4 to these rules;

c) the declaration of interests of the main investigator, in accordance with the form in Annex 5 to these rules;

d) description of the investigation centre's facilities for participation in the trial, signed by the main investigator, the head of the department and the manager of the healthcare unit, according to the form provided in Annex 6 to these Rules; in the case of phase I or bioequivalence clinical trials, this form specifies the number and date of the authorisation issued by the NAMMDR to the healthcare unit for conducting phase I and bioequivalence clinical trials.

e) the form describing the financial compensation for participants in the interventional clinical trial, according to the form provided in Annex 7 to these rules;

f) the unsigned form of the contract between the sponsor and the clinical trial centre/investigator, which should include general clauses referring to payments to centres and investigators;

(2) The investigator, respectively the main investigator, must be a specialist physician, with more than 3 years of experience in the specialty, or a primary care physician.

(3) (3) The investigation team may include, in addition to investigators, other suitably qualified natural persons, in accordance with the provisions of Art. 49, second paragraph of the Regulation.

(4) The natural persons referred to in paragraph (3) must have one of the following professions, as well as the qualifications necessary to exercise it: resident physician, researcher, pharmacist, physicist, biologist, chemist, medical assistant, psychologist or IT specialist.

(5) In the case of clinical trials involving the paediatric population, the team of investigators must include a paediatrician.

Chapter X
Authorisation of healthcare facilities where phase I clinical trials and bioequivalence shall be conducted

Art. 17 - In order to implement the provisions of Art. 15 paragraph (5) of Emergency Government Ordinance no. 29/2022, as further amended and supplemented, in order to obtain the authorisation for conducting phase I and bioequivalence clinical trials, the applicant shall submit to the NAMMDR an

authorisation application according to the form provided in Annex 8 to these Rules, accompanied by the following documents:

1) proof of payment of the authorisation fee;

2) documents regarding the premises, utilities and equipment;

a) health authorisation to operate as a health unit with beds;

b) description of the ward specially designed for simultaneous hospitalisation of at least 8 or 12 subjects;

c) description of the conditions for medical examination and supervision of subjects participating in the trial, for collection of biological samples and their storage;

d) description of the infrastructure of the emergency service, according to the form provided in Annex 9 to these Rules;

e) the contract for ensuring emergency medical care with the public or private ambulance service for assisted medical transport and with the nearest county hospital/regional emergency hospital. In the event that the phase I health unit operates within a hospital, an internal decision/procedure/written agreement with the intensive care unit (ICU) is required to ensure emergencies that may contract research organisationur;

f) description of the spaces for storing clinical investigational medicinal products, respectively the pharmaceutical unit;

g) description of the spaces for archiving dossiers of phase I and bioequivalence clinical trials;

h) if the healthcare unit intends to use its own bioanalytical laboratory, specialised for pharmacokinetic determinations, in clinical trials, or to collaborate with such a laboratory located on Romanian territory, these laboratories must hold a Good Laboratory Practice certificate, issued by the NAMMDR, in accordance with the provisions of Government Decision no. 63/2002 on approval of the Principles of Good Laboratory Practice, as well as the inspection and verification of compliance with them, in the case of testing performed on chemical substances, as further amended and supplemented. Specialised bioanalytical laboratories for pharmacokinetic determinations, which are not located on Romanian territory, must hold valid certification or accreditation.

3) documents regarding the healthcare unit staff:

a) list of available personnel and their qualifications. Healthcare facilities requesting authorisation to conduct phase I or bioequivalence clinical trials must employ qualified personnel to conduct clinical trials, namely: primary care physicians, specialist physicians with at least 3 years of experience, qualified according to the trial type, pharmacists, appropriate auxiliary personnel, as appropriate;

b) proof of employment of a clinical pharmacologist;

c) proof of employment of personnel in the ICU or emergency medicine specialty.

4) documents regarding certification of implementation of a quality management system, in accordance with ISO standards in force, applicable to clinical trials;

5) protocol for transferring subjects to the nearest county hospital/regional emergency hospital and providing the hospital with relevant medical information regarding the subjects' participation in the phase I or bioequivalence trial.

Art. 18 - (1) Within maximum 45 calendar days as of the date of submission of the application for authorisation of the phase I or bioequivalence unit, the NAMMDR checks whether the documentation is complete, compliant and issues the authorisation of the healthcare unit that meets all the requirements mentioned in Art. 17.

Art. 19 - If the dossier is incomplete or certain documents in the dossier are not compliant, the NAMMDR shall notify these aspects to the applicant within maximum 30 days as of the date of submission of the authorisation application mentioned in Art. 17, and the healthcare unit is obliged to send the response to the NAMMDR upon request for clarifications and/or supplementations, as the case may be, within maximum 15 days.

Art. 20 - (1) If the authorisation application does not meet the requirements mentioned in Art. 17, and if the applicant does not respond to the NAMMDR notification within the period provided for in Art. 19, the NAMMDR issues a decision rejecting the application, which it communicates to the applicant.

(2) The NAMMDR decision provided for in paragraph (1) may be appealed within 30 days of its receipt by the issuing institution.

(3) The decision issued in resolving the appeal provided for in paragraph (2) may be appealed to the Administrative Court of Appeal.

Art. 21 - (1) The NAMMDR issues the authorisation for the conduct of phase I and bioequivalence clinical trials by healthcare facilities, which is valid for 3 years.

(2) The authorisation provided for in paragraph (1) may be withdrawn by the NAMMDR whenever it finds, following an inspection carried out by authorised personnel, non-compliance with the requirements of Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections, in particular with regard to respect for the rights and well-being of clinical trial subjects, the quality and integrity of data generated within the clinical trial, compliance with the principles of Good Clinical Practice in clinical trials, as well as relevant national legislation, including these rules.

Chapter XI
Surveillance

Art. 22 - Inspections surveilling the conduct of interventional clinical trials and the adequacy of the sites for conducting interventional clinical trials, in compliance with the mechanisms provided for by the provisions of the Regulation, are carried out by authorised personnel within the NAMMDR, with an appropriate frequency, depending on the risk, whenever necessary.

Chapter XII
Manufacturing and import authorisation

Art. 23 - The manufacture and import of investigational medicinal products in

Romania is carried out only on the basis of holding a manufacturing and/or import authorisation, issued by the NAMMDR.

Art. 24 - The NAMMDR shall make sure, through periodic inspections, with an appropriate frequency, depending on the risk, whenever necessary, that the processes mentioned in Art. 61 paragraph (5) and Art. 63 paragraph (4) of the Regulation comply with appropriate and proportionate requirements to ensure the safety of the subjects, the reliability and robustness of the data generated within the interventional clinical trial.

Chapter XIII
Withdrawal of authorisation to conduct a clinical trial

Art. 25 - In line with Art. 77 paragraph (1) point a) of the Regulation, the NAMMDR may withdraw the authorisation to conduct a clinical trial, as a corrective measure, in compliance with the mechanisms provided for in Art. 77 paragraph (2) - (4) of the Regulation.

Chapter XIV
Transitional and final provisions

Art. 26 - (1) Within maximum 30 days from registration of the appeal with the NAMMDR or the CNBMDM, as the case may be, against the refusal provided for in Art. 16 paragraph (1) of Emergency Government Ordinance no. 29/2022, as further amended and supplemented, the appeals resolution committee shall meet in session to resolve the appeal.

(2) The Appeals Resolution Commission is appointed by decision of the NAMMDR President or by Order of the Minister of Health, for the CNBMDM, as the case may be, and consists of at least 3 members, a secretary and their deputies from the NAMMDR or the CNBMDM, as the case may be, who did not participate in the assessment process. The President of the Appeals Resolution Commission is elected from among its members and convenes the members or their alternates, as the case may be, to a meeting through the Commission's Secretariat.

(3) The convening of the members of the committee referred to in paragraph (2) or their alternates and all correspondence regarding the meeting shall be carried out via electronic mail.

(4)The agenda of the meetings is established by the commission's chairman.

(5)For the meeting of the commission provided for in paragraph (2), the presence of all members or their alternates, as the case may be, is required. If one of the members is unable to attend the meetings, he/she shall immediately inform the commission's chairman in order to convene the alternate to the meeting.

(6)The decisions of the appeals resolution committee are taken by open vote, by simple majority, and are recorded in the minutes of the meeting.

(7) The secretary of the appeals committee is responsible for the efficient organisation and conduct of appeals hearings and draws up minutes.

(8)Based on the decision of the appeals resolution committee recorded in the

minutes provided for in paragraph (7), the decision of the president of the NAMMDR or the decision of the CNBMDM shall be issued, as the case may be, of accepting/rejecting the appeal, which is officially communicated to the appellant, within maximum 7 days from the date of the appeals resolution committee's meeting.

Art. 27 - (1) Annexes 1 - 10 are an integral part of these methodological Rules.

(2) The forms in Annexes 2 - 8 provided for in paragraph (1) shall be published on the NAMMDR website whenever they are updated by the European Commission in EudraLex vol. 10 on the webpage: https://www.anm.ro/medicamente-de-uz-uman/studii-clinice/.

Art. 28 - During the period provided for in Art. 98 paragraph (2) of the Regulation, for applications for authorisation of an interventional clinical trial submitted on the basis of Directive 20/2001/EC, the forms provided for in Annexes 3 - 8 shall be used.

Annex 1
to the methodological rules

LIST
of documents provided for in Annexes I and II to the Regulation and in the Annexes to the methodological rules

a) The NAMMDR examines the following documents provided for in Annexes I and II to the Regulation:

1. The cover letter, as set out in point B of Annex I to the Regulation;
2. The EU application form, as set out in point C of Annex I to the Regulation;
3. The protocol, as set out in point D of Annex I to the Regulation and, where applicable, the document referred to in point D, point 17 (s) of Annex I to the Regulation, according to the draft in Annex 10 to these Rules;
4. Investigator's Brochure (IB), as set out in point E of Annex I to the Regulation;
5. Documentation on compliance with Good Manufacturing Practice (GMP) of the investigational medicinal product, as set out in point F of Annex I to the Regulation;
6. Investigational medicinal product dossier (IMPD), as set out in point G of Annex I to the Regulation;
7. Auxiliary medicinal product dossier, as set out in point H of Annex I to the Regulation;
8. Scientific advice and paediatric investigation plan (PIP), as set out in point I of Annex I to the Regulation;
9. Content of the label of the investigational medicinal product, as set out in point J of Annex I to the Regulation;
10. Suitability of the investigator, as set out in point M of Annex I to the Regulation, namely the list of sites of planned interventional clinical trials, specifying the name and function of the main investigators, as well as the planned number of subjects for each site;

1. The suitability of the venues, as provided for in point N of Annex I to the Regulation, namely:

- the document containing the description of the medical unit's facilities for participation in the clinical trial, according to Annex 6 to the methodological rules;
- the authorisation regarding the location of clinical trials for medicinal products for human use issued for phase I and bioequivalence medical units according to the provisions of Art. 15 paragraph (5) of Emergency Government Ordinance no. 29/2022, as further amended and supplemented;

2. The payment commitment form according to Annex 2 to the methodological rules and the proof of payment of the fee, provided for in point Q point 72 of Annex I to the Regulation;

3. Proof that the data will be processed in accordance with Union data protection legislation - the declaration provided for in point R of Annex I to

the Regulation;

14. Cover letter, as set out in point B of Annex II to the Regulation;

15. Variation application form, as set out in point C of Annex II to the Regulation;

16. Documents as set out in point D of Annex II to the Regulation (taking into account the responsibilities set out in point a) for the initial application for authorisation of the clinical trial;

17. Supporting information as set out in point E of Annex II to the Regulation;

18. EU application form, updated where applicable, as set out in point F of Annex II to the Regulation;

19. Payment commitment form as set out in Annex 2 to the methodological rules and proof of payment of the fee as set out in point G point 9 of Annex II to the Regulation.

b) The CNBMDM examines the following documents provided for in Annexes I and II to the Regulation:

1. Cover letter, as set out in point B - Annex I to the Regulation;

2. EU application form, as set out in point C - Annex I to the Regulation;

3. Protocol, as set out in point D - Annex I to the Regulation;

4. Investigator's brochure (IB), as set out in point E - Annex I to the Regulation;

5. Scientific advice and paediatric investigation plan (PIP), as set out in point I - Annex I to the Regulation;

6. Recruitment arrangements - recruitment procedure and consent, as set out in point K - Annex I to the Regulation;

7. Notification of subjects, informed consent form and procedure for obtaining the informed consent (notifications per Member State concerned), as set out in point L - Annex I to the Regulation;

8. Suitability of the investigator, as set out in point M - Annex I to the Regulation, namely:

- curriculum vitae for the main investigator, according to Annex 4 to the methodological rules;

- declaration of interests, according to Annex 5 to the methodological rules, for the main investigator;

1. The suitability of the venues, provided for in point N - Annex I to the Regulation, namely:

- the document containing the description of the healthcare unit's facilities for participation in the clinical study, according to Annex 6 to these Rules;

2. Proof of insurance or compensation, as provided for in point N - Annex I to the Regulation;

3. Financial and other agreements, provided for in point P - Annex I to the Regulation, namely:

- description of the financing of the trial;

- compensation for subjects, according to Annex 7 to the methodological rules;

- unsigned form of the contract between the sponsor and the clinical investigation centre/investigator, which should include general clauses about payments to centres and investigators;

12. Proof of payment of the fee, as provided for in point Q point 72 - Annex I to the Regulation;

13. Proof that the data will be processed in accordance with Union data protection law - the declaration as provided for in point R - Annex I to the Regulation;

14. Covering letter, as provided for in point B of Annex II to the Regulation;

15. Amendment request form, as provided for in point C of Annex II to the Regulation;

16. Documents referred to in point D of Annex II to the Regulation (taking into account the responsibilities referred to in point b) for the initial application for authorisation of the clinical trial;

17. Supporting information referred to in point E of Annex II to the Regulation;

18. The updated EU application form, if applicable, referred to in point F of Annex II to the Regulation;

19. Proof of payment of the fee referred to in point G point 9 of Annex II to the Regulation.

Annex 2
to the methodological rules

RO_ Commitment form for payment of the invoice issued by the NAMMDR _V1_May 2022

Company .....

PAYMENT COMMITMENT

By this commitment, we hereby confirm that we shall cover all fees related to the submission of the application dossier for the clinical trial/substantial amendment indicated below, within 15 days of receipt of the invoice.

Sponsor:	
Contract research organisation:	
Protocol:	
Country:	
Short description of the clinical trial:	
Company:	
Address:	
City and postal code:	
Country:	
E-mail:	
Fax number:	
Fiscal code:	
Trade Register registration number:	
IBAN account:	
Bank:	
Due date:	15 days

*) Protocol - EU CT protocol code and number, as well as a minimum of information necessary to identify them when applicable
**) CRO - Contract research organisation

Invoices relating to the above clinical study will be issued and sent to:

The signatories assume responsibility that the data in this form is correct.

Annex 3
to the methodological rules

RO_ Recruitment and informed consent procedure*) _V1_May 2022

**) The phrase "Informed Consent" is equivalent to "Informed Consent" defined in Art. 2 paragraph (2) point 21 of the Regulation, Romanian version.*

1. ***All clinical trials (this section must be filled in for all clinical trials)***

1.1	*How will potential subjects be identified? (e.g., through advertising the clinical trial or through existing patient lists)*
enter text here	
1.2	What resources will be used for recruitment? *(describe the format of the resources, e.g., paper or electronic, and how they will be presented to potential subjects, e.g., by mail, in the clinic, via social media or mass media)*
enter text here	
1.3	Will the identification of potential subjects involve access to identification data? If so, describe what measures will be taken to confirm that access to this data will be lawful, in accordance with applicable requirements in Romania.
enter text here	
1.4	Who will approach potential subjects and obtain the informed consent?
enter text here - describe the professional role and whether there is a previous clinical relationship with potential participants	
1.5	When will free and informed consent be obtained?
enter text here - describe when and where the informed consent will be obtained and how confidentiality will be ensured	
1.6	How much time will potential subjects (or their legal representative) be given to decide whether to participate?
enter text here	
1.7	How will it be ensured that potential subjects (or their legal representative) have understood the information and that the informed consent is given?
enter text here - the description should include how the information needs of individuals will be identified and addressed	
1.8	What measures are applied to obtain informed consent from potential subjects (or their legal representative) who do not speak the national language?
enter text here	
1.9	How will it be ensured that participants can withdraw their consent at any time? *(This should include how any consequences of withdrawing the consent will be dealt with)*
enter text here	

1.10	Please provide any additional information regarding the recruitment and informed consent procedure for the clinical trial that has not been provided elsewhere in this document. *(It is recommended to consult national guidelines to ensure that all necessary information has been provided)*
enter text here	
1.11	If this form is also used to describe recruitment procedures (Annex I K59 to the Regulation), please provide a clear indication of the first act of recruitment
enter text here	

2. Clinical trials that will recruit adults with disabilities

Adults with disabilities may only be recruited into clinical trials if consent has been obtained from a legal representative, and data of comparable validity cannot be obtained from clinical trials involving participants who are able to give informed consent. Where potential participants are unable to consent, methods should be in place to involve them as much as possible in the decision to participate in the clinical trial.

2.1	*Provide justification for recruiting adults with disabilities (This should include details of the nature of the condition that caused the person's disability and the relevance of this condition to the clinical trial)*
enter text here	
2.2	Who will assess and confirm whether a potential participant has the capacity to consent?
enter text here	
2.3	Where capacity to consent will fluctuate or be at a limit, how will potential subjects be involved in the decision to participate in the clinical trial? *(This should include how information will be adapted to ensure that (potential and existing) participants are able to understand the information and also how participants who regain capacity will be asked for consent to carry on with the clinical trial)*
enter text here	
2.4	How will a legal representative be identified? *(This should also include identifying the role they will have as a legal representative for this clinical trial)*
enter text here	

3. For clinical trials involving minors

Minors may be recruited into clinical trials only if consent has been obtained from a legal representative and if the clinical trial is of such a nature that it can only be conducted on minors. The minor should take part in the informed consent procedure to the extent appropriate to their age and mental maturity. Where appropriate, please specify any methods for different age categories.

3.1	Provide justification for recruiting minors
enter text here	
3.2	How will potential subjects be involved in the decision to participate in the clinical trial? (Describe the procedures for obtaining and recording consent, including who will obtain the consent and details of their training and experience with children)
enter text here	
3.3	How will a legal representative be identified? (This should include in what capacity they could act as a legal representative for this clinical trial)
enter text here	

3.3	How will the subjects' consent be obtained for continued participation in the clinical trial, when they reach the age at which they become legally competent?
enter text here	

4. Clinical trials in which informed consent is likely to be used by an impartial witness.

If a participant is unable to write, consent may be obtained and recorded by appropriate alternative means, in the presence of at least one impartial witness. The witness is required to sign and date the informed consent document.

4.1	Why is an impartial witness expected to be necessary?
enter text here	
4.2	How will an impartial witness be identified?
enter text here	
4.3	How will it be known if the potential subject gives informed consent?
enter text here	

5. Clinical trials in an emergency situation

Information about the clinical trial may be provided and the informed consent may be obtained after the decision to include the participant in the clinical trial. This is the situation where the decision is made at the time of the first intervention according to the protocol and, due to the urgency of the situation, the person cannot give consent nor can a legal representative be identified.

5.1	Describe why it would not be possible to obtain consent from potential subjects or a legal representative before they are recruited into the clinical trial.
enter text here	
5.2	What procedures will be in place to obtain informed consent from the subject or a legal representative, whichever is most likely to be sooner obtained? *(If a legal representative is expected to be required because the participant lacks capacity to consent, please complete Section 2 of this document as well)*
enter text here	
5.3	How will it be ensured that a potential subject has not expressed any prior objection to participating in the clinical trial?
enter text here	

6. For cluster-randomised controlled trials

Informed consent may be obtained by simplified means if this is not contrary to national law, the study methodology requires randomisation of groups (not individuals), the investigational medicinal product is used in accordance with the terms of the marketing authorisation and there are no interventions other than standard treatment. A clear justification for simplified consent should also be included in the protocol.

6.1	Describe how the simplified informed consent will be obtained.

Sections which are not applicable should either be deleted or marked as Not Applicable/NA.

Annex 4
to the methodological rules

RO_Investigator CV Form_V1_May 2022

Curriculum Vitae of the Investigator

Personal data	
Name	*enter text here*
Title	*enter text here*
Specialisation	*enter text here*
Current position	*enter text here*

Professional certification	
Professional college membership certificate:	*enter text here*
Issuing professional college:	*enter text here*
Certificate expiration date:	*enter text here*

Education and qualifications		
Institution	**Qualification**	**Year**
enter text here	*enter text here*	*enter text here*
enter text here	*enter text here*	*enter text here*
enter text here	*enter text here*	*enter text here*

Confirmation certificate in the specialty	
Professional degree and specialty	*enter text here*
Issuing institution	*enter text here*
Certificate number and series	*enter text here*
Date of issuance	*enter text here*

Current employer	
Institution:	*enter text here*
Department:	*enter text here*
Institution's address:	*enter text here*
Telephone number:	*enter text here*
E-mail address:	*enter text here*

Professional experience			
Position	**Name of institution and department**	**Starting year**	**Year of completion**
enter text here	*enter text here*	*enter text here*	*enter text here*

Relevant experience in clinical trials

Investigator's role	Therapeutic area	Trial type	Starting year	Phase	Progress
enter text here	*enter text here*	*enter text here*	*enter text here*	*enter text here*	*enter text here*

Research training	Company name	Year of acquisition
enter text here	*enter text here*	*enter text here*
GCP training	**Supplier and certificate number obtained**	**Year of acquisition**
enter text here	*enter text here*	*enter text here*

Date:

Signature:

Annex 5
to the methodological rules

RO_Form_Main investigator's declaration of interests_ V1_ May 2022

The following statement is applicable to the clinical trial
[*enter full title, protocol code and EU CT number below*]

Are there any interests, such as economic interests, institutional affiliations, or personal interests, that may influence your impartiality?
Yes |¯| No |¯|

If yes, please provide details of all interests:

I declare that the information provided above is accurate.
Name of Investigator:
Company name:
Signature:
Date:

A separate declaration must be completed and submitted for each principal investigator at each clinical trial site.
This model was developed and approved by the EU Clinical Trials Expert Group to meet the requirements of Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use.

Annex 6
to the methodological rules
RO- Form regarding the description of investigation centre facilities for participation in the trial _ V1_May 2022

Protocol title:
Protocol code:
EU CT number:

- *name of the healthcare facility, department/clinic/section, postal address*

Main investigator *name of the main investigator*

Section 1
a) Please provide a written statement regarding the suitability of the investigational site, adapted to the nature and use of the investigational medicinal product.

- provide the motivation for choosing the healthcare facility/medical department based on the specifics of the trial, including the healthcare facility's certifications
ASF: *insert the number and date of issue of the sanitary operating authorisation of the sanitary unit.*
Bioequivalence/phase I authorisation: - *in the case of a phase I or bioequivalence trial, please specify the number and date of issue of the phase I or bioequivalence authorisation issued by the NAMMDR or N/A if not applicable.*

Quality assurance at the investigation site

Please specify and confirm the existence, at the investigation site, of specific Standard Operating Procedures for activities corresponding to clinical trials, including a description of the investigator's specific tasks (informed consent, selection of team members, archiving of study documents, management of study medication, etc.).

b) Please describe the facilities for determining suitability
enter text here
The investigation site has: - Facilities for patient admission Yes/No - Specialised outpatient clinic Yes/No - Immediate access to the ICUs Yes/No - Immediate access to emergency medical service Yes/No - Own testing laboratory Yes/No
- Pharmacy/adequate facilities for managing trial medication Yes/No Is it clearly established who is responsible for the study medication and the accounting for the medication? Yes/No Is it clearly established who is responsible for processing biological samples for laboratory analysis? Yes/No Are source documents kept in a secure location and does the investigator have access to source documents at all times? Yes/No

Source documents: *specify here how to generate source documents*

- Please provide additional information regarding the investigational centre, if necessary for a specific clinical trial

c) Please describe the adequacy of the medical equipment

enter text here

d) Please provide a description of all study procedures that will be performed at the investigational site.

enter text here

e) Information regarding Human Resources and expertise at the investigational centre

Main investigator - *name of the main investigator, specifying the qualification and professional degree*

Investigators:

- Please provide the name list of the investigators (physicians), accompanied by a statement of their qualifications and, if applicable, participation as an unblinded investigator.

Note:

- It is necessary that all members of the investigation team be trained to comply with the GCP rules, the Regulation and the national legal framework for conducting clinical trials, as well as with the provisions of the protocol

- The investigator, respectively the main investigator, must be a specialist physician, with more than 3 years of experience in the specialty, or a primary care physician.

- Members of the investigational team are usually individuals who are required to be familiar with the clinical trial protocol, investigator's brochure and/or other aspects of clinical trial specifications in order to perform assigned activities and/or to correctly evaluate diagnostic findings and in line with GCP standards. Individuals who perform routine medical measurements on a daily basis (e.g., blood pressure measurement; standard diagnostic investigations) are not necessarily members of the investigation team.

- The information must be valid for the entire duration of this clinical trial, even in the event of a personnel change.

Section 2

By authorising this document, I confirm that the necessary facilities and equipment available at the investigational centre and that the investigation team is adequately structured and trained to conduct the clinical trial, in accordance with Regulation (EU) 536/2014. I confirm that all identified conditions which could influence the impartiality of any investigators have been addressed.

Main investigator *name of the main investigator*
Data:
Signature: _____

Head of department/clinic/section name: name of the head of department/clinic/section

Data:
Signature: _____

Manager/General Manager/General Director: *name of the Manager/General Manager/General Director*
Data:
Signature: _____

- please ensure that you have consulted any national instructions before submitting this form.
- text in italics in this form shall be removed and replaced with the requested information.

Annex 7
to the methodological rules

RO_Form_Financial compensation for clinical trial participants V1_May 2022

1. **Shall financial compensation be provided? (fill in a single blank)**
No | | Please explain why not.
Yes |¯| Please fill in sections 2-5

2. **Who will be offered compensation and in what format? (select all blanks which apply)**

	subiecţi	părinţi/îngrijitori	reprezentant legal	alţii
Travel expenses	|¯|	|¯|	|¯|	|¯|
Accommodation expenses	|¯|	|¯|	|¯|	|¯|
Food expenses	|¯|	|¯|	|¯|	|¯|
Income losses	|¯|	|¯|	|¯|	|¯|
Monetary payments	|¯|	|¯|	|¯|	|¯|
Non-monetary payments	|¯|	|¯|	|¯|	|¯|
Other	|¯|	|¯|	|¯|	|¯|

If this information is included in another document in the application dossier (e.g. the Subject Information Sheet), a reference to this document is sufficient: *enter text here*

If you enter "other persons", please specify who will be the beneficiary of the compensation or the type of compensation.

If income loss is compensated, please explain how the amount is calculated, with justification: *enter text here*

If monetary payment is offered, please specify the amount, with justification.: *enter text here*

If non-monetary payment is offered, please specify the type and amount of the benefit, with justification: *enter text here*

3. Are there any conditions attached to the payment of compensation? (e.g. if the clinical trial or trial steps must be completed)

	No ⎕ Yes ⎕	If yes, please describe below.

Please note that for clinical trials involving incapacitated adults, minors or breastfeeding women, no financial or other types of incentives may be given to subjects or their legal representatives, except for compensation for expenses or income loss directly related to participation in the clinical trial. A small token of appreciation is not considered an incentive, but must be explicitly assessed and approved by the CNBMDM (see also Eudralex vol. 10, Regulation (EU) No. 536/2014 Questions and Answers, April 2022, 9.1).

Annex 8
to the methodological rules

RO_ Application form for authorisation of healthcare facilities for conducting phase I or bioequivalence clinical trials_ V1_May 2022

Applicant's header **Exit number and date: .....**

To,
The National Agency for Medicines and Medical Devices

- Applicant's name
- Address of the administrative headquarters and address of the work points
- Legally represented by the Director (name),

In accordance with provisions of Order of the Minister of Health no. ……., we hereby request the release of the authorisation for conduct of phase I/bioequivalence clinical trials:

In order to support our application, we hereby submit the following documents:

a) a duly justified written statement on the suitability of the sites for conducting the clinical trial, adapted to the nature and use of the investigational medicinal product and including a description of the adequate quality of the facilities, equipment, human resources and a description of the expertise, issued by the head of the clinic/institution at the site of the interventional clinical trial or by another responsible person, as appropriate;

b) healthcare authorisation to operate as a medical unit with beds (including annexes, if any);

c) description of the ward specially designed for simultaneous admission of at least 8 or 12 subjects;

d) description of the conditions for medical examination and supervision of subjects participating in the study, for taking biological samples and storing them;

e) description of the infrastructure of the own emergency service for ensuring medical assistance in emergency situations, in line with the form provided in Annex 9 to this Order of the Minister of Health.

f) the contract for ensuring emergency medical care with the public or private ambulance service for assisted medical transport and with the nearest county hospital/regional emergency hospital. If the phase I medical unit operates within a hospital, an internal decision/procedure/written agreement with the intensive care unit (ICU) is required to ensure emergencies that may occur;

g) description of the spaces for storing medicinal products for clinical investigation, respectively of the pharmaceutical unit;

h) description of the spaces for archiving clinical trial dossiers;

i) copy of the certificate of Good Laboratory Practice for the bioanalytical laboratory specialised for pharmacokinetic determinations issued by the

NAMMDR for specialised bioanalytical laboratories, for pharmacokinetic determinations on the Romanian territory/proof of valid certification or accreditation of specialised bioanalytical laboratories for pharmacokinetic determinations, which are not located on the Romanian territory;

j) list of available personnel and proof of their qualifications (CV, up-to-date medical college certificate with free practice permit);

k) proof of employment of a clinical pharmacologist;

l) proof of employment of personnel in the ICU or emergency medicine specialty;

m) certification of implementation of a quality management system in line with ISO standards in force, applicable to clinical trials;

n) protocol for transferring subjects to the nearest county hospital/regional emergency hospital and providing the hospital with relevant medical information regarding the participation of volunteers in the phase I study.

For any additional information you can contact us at:
Contact person:
Telephone number:
Fax number:
E-mail address:
Director's name in clear script

Signature:
Stamp of the medical facility

Annex 9
to the methodological rules

RO_Description of the infrastructure of emergency service of centres

1. Vital signs monitor (BP, EKG, pulse oximeter);
2. Defibrillator (with battery);
3. Injector/Infusion pump;
4. External cardiac pacemaker;
5. Medical oxygen source;
6. Cardiopulmonary resuscitation kit;
7. Ventilator with PEEP (Positive End Expiratory Pressure);
8. Surgical aspirator;
9. Stethoscope and blood pressure monitor;
10. Glucometer and glucose test;
11. Ophthalmoscope;
12. Reflex hammer;
13. Consumables necessary for the treatment of medical emergencies (syringes, sterile and non-sterile surgical gloves, peripheral catheters, intubation tubes, laryngeal mask (G&G Errata: laryngeal), suction tubes, gastric/duodenal tubes, Foley catheters, tracheostomy cannulas, scalpel, infusors, etc.);
14. Adjustable beds;
15. Alarm system (for requesting qualified assistance);
16. Telephone line with direct access to the outside;
17. Medicinal products and solutions for infusion or parenteral administration, unless otherwise specified, necessary for the treatment of medical emergencies (saline, Ringer's solution, glucose 5%, 10%, 33%, colloidal solutions, mannitol, analgesics, inhaled bronchodilators, adrenaline, atropine, diazepam, ketamine, succinylcholine, long-acting muscle paralyzers, hydrocortisone hemisuccinate, dexamethasone, nitro-glycerine, dobutamine, metoprolol, amiodarone, xylene, heparin, antiemetics, furosemide, vitamins B1, B6, sodium bicarbonate, insulin, aminophylline, antihypertensives, clonidine, antispasmodics).

Annex 10
to the methodological rules

Form regarding compliance with national legislation on the collection, storage and subsequent use of human biological samples - RO Version 1.0

Compliance with the regulations applicable in the Member State for collection, storage and future use of biological samples of human origin (Article 7.1 h)

Full title of the clinical trial	**EU name of the clinical trial**
enter text here	*enter text here*
Entity responsible for evidence (legally): *enter text here*	

How to use this document

This form may be used by sponsors of clinical trials in Part II of the application dossier to provide information on "compliance with the applicable rules for collection, storage and further use of biological samples from clinical trial subjects" (Regulation (EU) No. 536/2014, Article 7.1(h)). This is not a mandatory form and different national provisions may be in force, which should be confirmed before submission.

If the information is already provided elsewhere in the Application Dossier, a reference must be provided.
To facilitate the use of the template, each section can be collapsed by clicking on the title.

I - Description of biological samples collected in the clinical trial **Section 1. Does the clinical trial involve new samples from subjects (newly collected samples)?** **☐ Yes, the information requested in Section 1 shall be provided.** **☐ No, not applicable. Please carry on with Section 2**
1.1 What type(s) of sample(s) will be collected from the subject? ***Specify the original material which is collected from the patient, e.g. blood, tissue (specify tissue type), urine, saliva, etc. Do not include information on sample preparation.*** *enter text here*
1.2 Total number of samples, fragments (e.g. aliquots, tissue blocks, sections) and total volume (if applicable) for each individual subject. *enter text here*
1.3 Maximum number of samples and maximum volume (if applicable) during a single collection: *enter text here*
1.4 Will samples be collected as part of routine medical care? *enter text here*
Section 2. Does the clinical trial involve the collection of existing, preserved samples (e.g. preserved diagnostic material or other material from the biobank)? **☐ Yes, the information requested in Section 2 shall be provided.** **☐ No, not applicable. Please carry on with Section 3** ***Note: The sponsor must complete at least one of Sections 1 or 2***
2.1 What type(s) of preserved material/samples will be used? *enter text here*
2.2 Specify the total number of samples, fragments (e.g. aliquots, tissue blocks, sections) and total volume (if applicable) to which the sponsor requires access from each subject. ***Example: 20 sections are required per biopsy from each subject*** *enter text here*
2.3 Will new consent be obtained for the use of archival samples in the clinical trial (if in accordance with national legislation)? If not, explain. **(if applicable, add the text of the initial consent)** *enter text here*
II - Use, storage and transfer of biological samples **Section 3. Use of samples for a purpose that falls within the objective of this clinical trial (i.e. for the use described in the protocol)**

Note: This section must be completed for both newly collected and existing archival samples.

3.1 Where will the samples be analysed?

Within the clinical laboratory, within/outside the sponsor's organisation, within/outside the Member State where it was collected, or within/outside the EU/EEA.

enter text here

3.2

If samples are to be sent to another organisation for analysis (as part of the trial), how will they be managed after analysis?
Destroyed, returned to the entity responsible for the samples (legally), stored at the site where they are analysed, anonymised, etc.
Note: An agreement is established with the recipient (material transfer agreement or equivalent) governing how the sample is to be managed
enter text here

3.3 Where will the samples be stored?
Inside/outside the sponsor's organisation, inside/outside the Member State where they were collected or inside/outside the EU/EEA
enter text here

3.4 How long will the samples be stored?
enter text here

3.5 What type of connection is available between samples and individual subjects?
☐ Direct connection (samples marked with, for example, initials, date of birth)
☐ Pseudonymised connection (samples marked with code)
☐ No connection, samples are anonymised (i.e. samples can neither directly nor indirectly, with reasonably means according to recital 26 of the General Data Protection Regulation (EU) 2016/679, be linked to the sample donor)

3.6 Who will have access to the samples?
enter text here

3.7 Who will have access to the sample code list (if applicable)?
enter text here

Section 4. Will newly collected samples or existing archive samples be stored for future use?

For other use than described in the protocol. Note that some purposes (secondary use of samples) may require additional approval, in Most Member States by an ethics committee
☐ Yes, please fill in the requested information in this section
☐ No, samples will be destroyed, please continue with section 5

4.1 What is the purpose of the future use?
enter text here

4.2 How long will the samples be stored?
enter text here

4.3 Where will the samples be stored?
enter text here

4.4 What type of connection is available between samples and individual subject?
☐ *Direct connection (samples marked with e.g. initials, date of birth)*
☐ *Pseudonymised connection (samples marked with code)*
☐ No connection, samples are anonymised (i.e. samples can neither directly nor indirectly, with reasonably means according to recital 26 of the General Data Protection Regulation (EU) 2016/679, be linked to the sample donor)

4.5 Who will have access to the samples?
enter text here

4.6 Who will have access to the sample code list (if applicable)?
enter text here

4.7 Will the donor be recontacted to give new consent to the use of the samples in future research? If not, explain *enter text here*
4.8 If secondary future use of the samples will be in question, will an ethics committee or biobank committee be reviewing whether the purpose of the new study is within the scope of the original provided consent (if applicable according to national legislation)? *enter text here*
4.9 Who will be able to make use of the samples? *enter text here*
4.10 How will unsolicited findings be handled? *enter text here*
III - Additional information
Section 5. Additional information that is required by the current Member States national arrangements and regulations. The sponsor should confirm this prior to submission ***Note: This section will only be filled in if applicable***
5.1 Provide any information (not described above) that is of relevance to the Member State applicable rules on collection, storage, transport and future use of the samples, e.g. on specific national arrangements and regulations regarding the use of human biological samples. *enter text here*