DECISION

No. 22/03.09.2010

on approval of the Detailed guideline on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, notification of substantial amendments and declaration of the end of the clinical trial in Romania

The Scientific Council of the National Agency for Medicines and Medical Devices, set up based on Order of the Minister of Public Health No. 1123/18.08.2010, as amended, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 03.09.2010, in accordance with Article 12(5) of Government Ordinance No. 734/2010 related to the set up, organisation and operation of the National Medicines Agency, agrees on the following

DECISION

Art. 1. - The Detailed guideline on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, notification of substantial amendments and declaration of the end of the clinical trial in Romania is approved, in accordance with the Annexes which are integral part of this Decision.

Art. 2. – On the date of the this Decision coming into force, the NMA SCD No. 49/15.12.2006 on approval of the Guidance for the request to the competent authority for authorisation of a clinical trial on a medicinal product for human use, notification of substantial amendments and declaration of the end of the trial in Romania and SCD No. 27/28.09.2007 on approval of modification of the Annex to SCD No. 49/15.09.2006 on approval of the Guidance for the request to the competent authority for authorisation of a clinical trial on a medicinal product for human use, notification of substantial amendments and declaration of the end of the trial in Romania are repealed.

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

ANNEX

Detailed Guideline
on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use to the competent authority, notification of substantial amendments and declaration of the end of the clinical trial in Romania

CHAPTER I
Introduction

Art. 1. – This Guideline is a translation into Romanian and an adaptation of the European Commission Guideline (EC) (2010/C 82/01) on the request for authorisation of a clinical trial on a medicinal product for human use to the competent authority, notification of substantial amendments and declaration of the end of the trial.

I.1 Legal basis

Art. 2. - In Art. 44 of Order of the Minister of Public Health No. 904/2006 on approval of Norms relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use, transposing Art. 8(9) of Directive 2001/20/EC, the publication by the NAMMD of certain detailed Guidelines is expected:

a) the format and contents of the request for authorisation of a clinical trial carried out with medicinal products for human use, as well as the documentation to be submitted to support that request in justification of the quality and manufacture of the investigational medicinal product (IMP), any toxicological and pharmacological tests, the protocol and clinical information about the IMP, including the Investigator's Brochure;

b) the presentation and content of substantial amendment notifications referred to in Art. 45(a) of Order of the Minister of Public Health No. 904/2006, transposing Art. 10(a) of Directive 2001/20/EC related to the substantial amendments brought to the protocol;

c) the declaration of the end of the clinical trial.

Art. 3. – (1) As regards the Ethics Committee, this guidance only addresses related aspects insofar as the provisions contained Order of the Minister of Public Health No. 904/2006, transposing Directive 2001/20/EC, are identical with regard to both the national competent authority and the Ethics Committee. This means that the following sections also apply to the Ethics Committee:

- Procedural aspects of the notification of "substantial amendments" (see sections III.1 – III.3 and III.5 – III.8)
- Declaration of the end of a clinical trial (see Section IV of this Guideline).

Art. 3. – This Guideline must be correlated with provisions of Law No. 95/2006 on healthcare reform, Title XVII-The medicinal product, of Order of the Minister of Public Health No. 904/2006, Order of the Minister of Public Health No. 903/2006 on Principles and detailed Guidelines on Good Clinical Practice for investigational medicinal products for human use, as well as with applications for manufacturing and importation of these medicinal products and other Guidelines on clinical trials.

(2) As regards the other aspects, reference is made to the separate guidance based on the provisions of Chapter X (Detailed guidelines) of Order of the Minister of Public Health No. 904/2006.

Art. 4. – (1) In accordance with provisions of Art. 3 (1) of Directive 2001/20/EC, national provisions referring to clinical trials have t o be consistent with the procedures and timescales established in this Directive related to the procedures and timescales of authorisation of a clinical trial, notification of a substantial amendment and declaration of the end of a clinical trial and this document provides recommendations in that respect.

(2) EU Member States, contracting States of the European Economic Area (EEA)[1] and persons who request authorisation of a clinical trial (applicants), notify substantial amendments, and declare the end of a clinical trial in the EU should consider this guidance when applying provisions of Order of the Minister of Public Health No 904/2006, transposing Directive 2001/20/EC.

I.2 Scope

Art. 5. – (1) This Guideline applies to requests for authorisation of a clinical trial, amendments and a declaration of the end of a clinical trial within the scope of Order of the Minister of Public Health No. 904/2006, applying to all clinical trials as defined in Art. 21(a), Chapter IV "Definitions" of Order of the Minister of Public Health No. 904/2006, transposing Art. 2(a) of Directive 2001/20/EC.

(2) As regards the term "medicinal products", this refers to medicinal products for human use as defined in Art. 695(1) of Law No. 95/2006, Title XVII – The medicinal product[2], transposing Art. 1(2) of Directive 2001/83/EC; these include medicinal products whose pharmacological, immunological or metabolic action is still uncertain and being explored.

Art. 6. – This also refers to medicinal products specifically addressed in EU law on pharmaceutical products, as well as advanced therapy medicinal products[3] or medicinal products derived from human blood or plasma, as defined in Art. 1(9) of Law No. 95/2006, Title XVII – The medicinal product, transposing Art. 1(10) of Directive 2001/83/EC.

Art. 7. – Order of the Minister of Public Health No. 904/2006 also applies to interventional clinical trials with medicinal products for the paediatric population and to interventional clinical trials with medicinal products manufactured or reconstituted at the site of a (hospital) pharmacy, meant for direct supply to the participants in the clinical trial.

Art. 8. – Mention is made to the exclusions in Art. 697 of Law No. 95/2006, Title XVII – The medicinal product, transposing Art. 3 of Directive 2001/83/EC, which are not relevant as regards the scope of Order of the Minister of Public Health No. 904/2006 and of this Guideline.

Art. 9. – Provisions of Order of the Minister of Public Health No. 904/2006 do not apply to:

- medical devices, active implantable medical devices and *in vitro* diagnostic medical devices, as defined in the Community legislation[4,5,6],
- cosmetic products, as defined in the Community legislation[7],

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[1] For the purposes of this document, references to the EU, EU Member States or Member States should be understood to include the EEA or EEA contracting States, unless indicated otherwise.

[2] OJ L 311, 28.11.2001, p. 67.

[3] As defined in Article 2(1)(a) of Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and of Regulation (EC) No. 726/2004 (OJ l 324, 10.12.2007, p. 121) (hereinafter Regulation (EC) No. 1394/2007).

[4] Directive 93/42/EEC of 14 June 1993 concerning medical devices (OJ l 169, 12.7.1993, p. 1).

[5] Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (OJ L 189, 20.7.1990, p. 17)

[6] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (OJ L 331, 7.12.1998, p. 1)

[7] Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (OJ L 262, 27.9.1976, p. 169)

- food, as defined in the Community legislation [8].

Art. 10. – To draw the 'borderline' between these sectoral legislations (e.g. medicinal product/food, medicinal product/cosmetic product, medicinal product/medical device), the criteria established in the case law of the European Court of Justice apply and reference is made to the relevant guidelines[9].

I.3 Definitions

Art. 11. – (1) The definitions established in Order of the Minister of Public Health No. 904/2006, its implementing acts and relevant guidance documents and the relevant regulatory documents also apply in the context of this Guideline.

(2) As regards the implementing guidelines, the following documents contain useful additional definitions:

- The Guideline on the use in clinical trials of investigational medicinal products and other medicinal products, approved through Scientific Council Decision No. 7/26.06.2009;

- Annex to the Guideline on Good Manufacturing Practice for medicinal products for human use (approved through Scientific Council Decision No. 23/03.09.2010) – The manufacturing process of investigational medicinal products;

- European Commission recommendations on pharmacovigilance for medicinal products for human products (on the term "non-interventional clinical trial");

- Questions and Answers Document on Directive 2001/20/EC.

Art. 12. – (1) For the purposes of this Guideline, the term "Member State concerned" refers to the Member States where the clinical trial is intended to be performed.

(2) There may be several Member States concerned in a given clinical trial (multinational clinical trials).

(3) The term "ICH countries" refers to a third country, which is party to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, namely Japan and the United States.

CHAPTER II
Request for authorisation of a clinical trial

II.1 Procedural aspects

II.1.1. Legal basis

Art. 13. – Articles 36(1) and 37 of Order of the Minister of Public Health No. 904/2006 transposing Art. 9 (1), second subparagraph, and (2) of Directive 2001/20/EC reads as follows: "The sponsor may not start a clinical trial until the Ethics Committee has issued a favorable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance", as well as " Before commencing any clinical trial, the sponsor shall be required to submit to the NAMMD application request for authorisation written in a concise and adequate form, expressing their plan to conduct the respective clinical trial" [10].

II.1.2 Request for authorisation, applicable timelines, tacit authorisation

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[8] Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, as amended (OJ L 31, 1.2.2002, p. 1)

[9] Cf., for example, http://ec.europa.eu/enterprise/sectors/cosmetics/cosmetic-products/borderline-products/index_en.htm

[10] Cf. also recital 11 of Directive 2001/20/EC: "As a rule, authorisation should be implicit, i.e. if there has been a vote in favor by the Ethics Committee and the competent authority has not objected within a given period, it should be possible to begin the clinical trials." '

Art. 14. – The applicant submits a request for authorisation of a clinical trial to the National Agency for Medicines and Medical Devices.

Art. 15. – In accordance with Art. 39(1) of Order of the Minister of Public Health No. 904/2006, transposing Art. 9(4) of Directive 2001/20/EC, consideration of a valid request for authorisation by the NAMMD, shall be carried out as rapidly as possible and may not exceed 60 calendar days.

Art. 16. – (1) Validation of the request for authorisation is included in the period of 60 calendar days.

(2) Day 0 is the day of receipt of the request.

(3) If the request is valid, and by day 60 no ground for non-acceptance has been raised, the clinical trial is authorised by the national competent authority of the NAMMD (tacit authorisation).[11]

Art. 17. – (1) However, under Art. 40, 41 and 42 of Order of the Minister of Public Health No. 904/2006, transposing Art. 9(4), (5) and (6) of Directive 2001/20/EC, important exceptions to the rules on timelines and tacit authorisation are established, concerning certain medicinal products, including medicinal products whose active substances are biological products of human or animal origin or whose manufacturing process requires such compounds.

(2) Exceptions also apply to medicinal products for gene therapy, somatic cell therapy including xenogeneic cell therapy and all medicinal products containing genetically modified organisms.

II.1.3 Scope of authorisation

Art. 18. – The authorisation of a clinical trial by the NAMMD is valid for a clinical trial conducted in Romania and this authorisation is not to be considered as scientific advice on the development programme of the investigational medicinal product (IMP) tested.

II.1.4 Follow-up to request for authorisation

II.1.4.1 Application is not valid

Art. 19. - If an application is not valid, the NAMMD should inform the applicant of this within the first 10 calendar days of the period referred to in Art. 15. The reasons should be given.

II.1.4.2 Changes to the submitted documentation during the evaluation phase

Art. 20. - Following the submission of a request for authorisation, the submitted documentation may change. This may happen either:

- following information by the NAMMD that the application is not valid (see Section II.1.4.1, "Application is not valid"); in this case, the time limit set out in Article 39(1) of Order of the Minister of Public Health No. 904/2006, transposing Art. 9(4) of Directive 2001/20/EC, starts again when a valid request has been received;
- at the initiative of the applicant. In practice, the applicant may have an interest in changing submitted documentation. This may happen as a consequence of grounds for non-acceptance by the national competent authority of another Member State or a third country concerned if the applicant wants to ensure that the documentation submitted in all Member States/third countries concerned is identical; in this case, the time limit set out in Article 9(4) of Directive 2001/20/EC starts again; or
- following notification of grounds for non-acceptance by the NAMMD: in this case, provisions of Art. 38 of Order of the Minister of Public Health No. 904/2006, transposing Article 9(3) of Directive 2001/20/EC applies.

[11] The term "authorisation" shall be used throughout the entire document.

II.1.4.3 Withdrawals of requests for marketing authorisation

Art. 21. – (1) Unexpected events or additional information may require the applicant to withdraw a request for authorisation before the NAMMD has reached its decision on authorisation.

(2) The applicant should inform the NAMMD as soon as he becomes aware that he intends to withdraw the application, first by fax or e-mail, while specifying the EudraCT number and other data for trial identification.

(3) Where the initial contact is by telephone, this should be followed up, for reasons of traceability, by fax or e-mail.

(4) The initial contact should be followed as soon as possible by a formal letter of withdrawal providing a brief description of the reasons.

Art. 22. – (1) If the applicant wishes to resubmit the application, he must identify the application as a resubmission in the cover letter (resubmission letter) and in the dedicated field of the clinical trial application form.

(2) The initial EudraCT number is used with a letter after the number sequence: A for first resubmission, B for second resubmission, and so on.

II.1.5 Interface with other authorisation requirements in force

Art. 23. - The applicant should also make applications to fulfil other requirements in force that relate to clinical trials with IMPs where applicable; for example, if the IMP is a genetically modified organism (GMO) it may be necessary to obtain permission for its contained use or deliberate release in accordance with Directive 90/219/EEC[12] and/or Directive 2001/18/EC[13] from the National Agency for Environmental Protection.

II.1.6 Other issues

Art. 24. – The application dossier should be submitted as electronic version only, i.e. via telematics system (if nationally available), e-mail, or a posted CD-ROM. If documentation is sent by paper, it should be limited to the signed cover letter only.

Art. 25. - The European Commission encourages the NAMMD to accept the English language in their communication with applicants and for documentation which is not destined for the public or the clinical trial participant, such as scientific documentation.

II.2 Allocation of EudraCT number

Art. 26. – (1) Before submitting an application to the NAMMD, the applicant should obtain a unique EudraCT number from the EudraCT Community Clinical Trial System[14] by the procedure described in the current version of the Detailed guidance for the European clinical trials database[15]; this number identifies the protocol for a trial, whether conducted at a single site or at multiple sites in one or more Member States.

(2) To obtain the EudraCT number automatically from the database the applicant will need to provide a few items of information[16].

II.3 Cover letter

Art. 27. - The applicant should submit a signed cover letter with the application; its subject line should contain the EudraCT number and the invariable sponsor protocol number (if available) with the title of the trial.

Art. 28. - In the cover letter, the applicant should draw attention to peculiarities of the trial.

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[12] OJ L 117, 8.5.1990, p. 1.

[13] OJ L 117, 8.5.1990, p. 1.

[14] http://eudract.ema.europa.eu/

[15] EudraLex, Volume 10; http://ec.europa.eu/enterprise/sectors/ pharmaceuticals/documents/eudralex/vol-10/index_en.htm

[16] Note that paediatric clinical trials included in an agreed PIP and performed in a third country have to be entered into EudraCT as well (cf. point 2.2.1. of Commission Communication 2009/C28/01).

Art. 29. - However, in the cover letter it is not necessary to reproduce information which is already contained in the clinical trial application form, with the following exceptions:

- specific features of the trial population, such as clinical trial participants not able to give informed consent or minors;

- whether the trial involves the first administration of a new active substance to humans;

- whether there is scientific advice related to the trial or IMP given by the European Medicines Agency (EMA- the Agency), the NAMMD or the national competent authority of a Member State or third country; and

- whether the trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3 of Regulation (EC) No 1901/2006 on medicinal products for paediatric use (14); if the Agency has already issued a Decision on the respective PIP, the cover letter should contain the link to the Decision of the Agency on its website (see also Section II.9).

Art. 30. - In the cover letter, the applicant should highlight whether the IMP or NIMP is a narcotic/psychotropic.

Art. 31. - The applicant should indicate where the relevant information is contained in the application dossier.

Art. 32. - The applicant should set out precisely in the cover letter where in the application dossier the reference safety information is contained for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction (SUSAR).

Art. 33. - In the case of a resubmission letter (see Section II.1.4.3, "Recalls of marketing authorisation application"), the applicant should highlight the changes as compared to the previous submission.

II.4 Clinical trial application form

Art. 34. - For clinical trials falling within the scope of Order of the Minister of Public Health No. 904/2006, there is a unique, EU-wide clinical trial application form provided and published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the European Union (14).

Art. 35. - Some of the information in the form, such as information related to the applicant and the name of the investigators, will be relevant in one Member State only.

Art. 36. - The applicant's signature will confirm that the sponsor is satisfied that:

- the information provided is complete,

- the attached documents contain an accurate account of the information available,

- the clinical trial will be conducted in accordance with the protocol, and

- the clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.

Art. 37. - If the form is submitted in paper form (cf. Section II.1.6), the applicant should save the full clinical trial application form data set as an XML file using the utilities feature and submit an electronic copy of this XML file on a CD-ROM.

Art. 38. - More information about the clinical trial application form, and how to fill it in, is available in the current version of these documents:

- Detailed guidance for the European clinical trials database[17],

- EudraCT User Manual[18]

- EudraCT Frequently Asked Questions[19].

Art. 39. - In addition, the Agency operates a help desk to support applicants who have questions related to EudraCT [20].

[17] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm

[18] http://eudract.ema.europa.eu/document.html

[19] http://eudract.ema.europa.eu/document.html

[20] EudraCT Helpdesk, e-mail: eudract@ema.europa.eu; Tel. +44 2075237523; Fax +44 2074188669.

Art. 40. - (1) Certain information contained in the clinical trial application form will be made public, following its entry into EudraCT by the NAMMD.

(2) This is done by rendering certain data fields contained in EudraCT public in accordance with the applicable guidelines published by the European Commission.

II.5 Protocol

Art. 41. - According to Article 21 (h) of Order of the Minister of Public Health No. 904/2006, the protocol is 'a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial.'

Art. 42. - The protocol should be identified by the title, the sponsor's protocol code number specific for all versions of it (if available), a date and number of version that will be updated when it is amended, and a short title or name assigned to it.

Art. 43. - For the content and format of the protocol, reference is made to Section VII of the Guideline on Good Clinical Practice approved through Scientific Council Decision No. 39/2006, transposing Section 6 of Guideline CPMP/ICH/135/95[21] amended in 2002. In particular, the protocol should include:

- a clear and unambiguous definition of the end of the trial in question. In most cases this will be the date of the last visit of the last patient undergoing the trial; any exceptions to this should be justified in the protocol;

- a description of the plan for the provision of any additional care for the trial participants once their participation in the trial has ended, where it differs from what is normally expected according to the medical condition of the clinical trial participant.

Art. 44. - The protocol should clearly address sub-studies conducted at all trial sites or only at specific sites.

Art. 45. – (1) The protocol should also contain the relevant information for the assessment of the clinical trial by the Ethics Committee.

(2) To this end, the protocol should include the following information:

- a discussion of the relevance of the clinical trial and its design to allow assessment in view of Article 28 (3) (a) of Order of the Minister of Public Health No. 904/2006, transposing Art. 6 (3) (a) of Directive 2001/20/EC,

- an evaluation of the anticipated benefits and risks as required in Article 23 (a) of Order of the Minister of Public Health No. 904/2006, transposing Art. 6(3)(b) of Directive 2001/20/EC),

- a justification for including participants who are incapable of giving informed consent or other special populations, such as minors (cf. Article 28 (g) of Order of the Minister of Public Health No. 904/2006, transposing Art. 6 (3) (g) of Directive 2001/20/EC), and

- a detailed description of the recruitment and informed consent procedure, especially when participants are incapable of giving informed consent (cf. Article 28 (k) of Order of the Minister of Public Health No. 904/2006, transposing Art. 6 (3) (k) of Directive 2001/20/EC).

Art. 46. - More details are provided in a separate Guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical on medicinal products for human use in Romania, approved through Scientific Council Decision No. 50/15.12.2006, transposition of Guideline CT-2 of the European Commission, based on Art. 8 of Directive 2001/20/EC.

Art. 47. – (1) A sponsor may wish to conduct a clinical trial with an active substance that is available in the European Union with different trade names in a number of medicines with marketing authorisations in Romania; this may be the case, for example, in order to address local clinical practice at each clinical trial site in Romania.

[21] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/ eudralex/vol-10/index_en.htm

(2) In this case the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 3-5) only and not specify the trade name of each product.

Art. 48. - With regard to notification of adverse events, the protocol:

- may identify serious adverse events which do not require immediate reporting by the investigator (cf. Article 58 (1) of Order of the Minister of Public Health No. 904/2006, transposing Art. 16 (1) of Directive 2001/20/EC), and
- shall identify adverse events or laboratory anomalies critical to safety evaluations to be reported to the sponsor (cf. Article 59 of Order of the Minister of Public Health No. 904/2006, transposing Art. 16 (2) of Directive 2001/20/EC).

Art. 49. - In certain cases, issues of unblinding of IMPs might need to be addressed in the protocol; for details, reference is made to the guidelines on adverse reaction reporting issued from clinical trials performed on medicinal products for human use, approved through Scientific Council Decision No. 26/28.09.2007, transposing the guideline on adverse reaction reporting published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the European Union [22].

Art. 50. - Regarding first-in-human clinical trials, additional guidance is provided in the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products[23].

Art. 51. - The protocol should be accompanied by a synopsis of the protocol.

Art. 52. - The protocol should be signed by the sponsor and:

- the overall coordinating investigator for a multi-centre (incl. multinational) trial, or
- the principal investigator in a single-site trial.

II.6. Investigator's brochure

Art. 53. - According to Article 21 (g) of Order of the Minister of Health No. 904/2006, transposing Art. 2 (g) of Directive 2001/20/EC, the investigator's brochure (IB) is "a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects."

Art. 54. – (1) A request for trial authorisation has to be accompanied by an IB or a document used in place of the IB (see below).

(2) Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

Art. 55. – (1) The content, format and procedures for updating the IB have to comply with Article 21 of Order of the Minister of Public Health No. 903/2006 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, transposing Art. 8 (1) of Directive 2005/28/EC as well as with the Guideline on the Good Clinical Practice approved through Scientific Council Decision No. 39/27.10.2006, transposing Guideline CPMP/ICH/135/95 and with Art. 34 of Order of the Minister of Public Health No. 904/2006.

(2) It should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the IMP in the trial and be presented in the form of summaries.

Art. 56. – (1) The approved summary of product characteristics (SmPC) may be used in place of the IB if the IMP is authorised in any Member State or ICH country and is used according to the terms of the marketing authorisation.

(2) Regarding ICH countries, the document equivalent to the SmPC is used.

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[22] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm

[23] EMEA/CHMP/SWP/28367/07 (see http://www.ema.europa.eu/pdfs/human/swp/2836707enfin.pdf)

(3) If the conditions of use in the clinical trial differ from those authorised, the SmPC should be supplemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in the clinical trial.

(4) Where the IMP is identified in the protocol only by its active substance, the sponsor should elect one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

Art. 57. – (1) For a multinational trial where the medicinal product to be used in each Member State is the one authorised at national level and the SmPC varies among the Member States involved, the sponsor should chose one SmPC to replace the IB for the whole clinical trial.

(2) This SmPC should be the one best suited to ensure patient safety.

Art. 58. - The IB as last amended and approved by the NAMMD or equivalent document (e.g. SmPC for marketed products) serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.

II.7 Investigational Medicinal Product (IMP) Dossier

Art. 59. - In accordance with Article 21 (d) of Order of the Minister of Public Health No. 904/2006, transposing Art. 2 (d) of Directive 2001/20/EC defines an IMP as follows: 'A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used, exposed or assembled in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.'

Art. 60. – (1) The IMP dossier (IMPD) gives information related to the quality, manufacture and control of any IMP (i.e. including reference product and placebo), and data from non-clinical studies and from its clinical use.

(2) However, in many cases where the IMP has a marketing authorisation, an IMPD is not required; reference is made to Section II.7.1 (regarding compliance with Good Manufacturing Practice, GMP) and Section II.7.3 (regarding data).

II.7.1 Good Manufacturing Practice (GMP) compliance

Art. 61. - As regards GMP compliance, in the following cases no documentation needs to be submitted:

- the IMP has a marketing authorisation in the EU or in an ICH country, is not modified, and is manufactured in the EU, or

- the IMP is not manufactured in the EU, but has a marketing authorisation in the EU, and is not modified.

Art. 62. - If the IMP does not have a marketing authorisation in the EU or an ICH country and is not manufactured in the EU, the following documentation should be submitted:

- a copy of the importation authorisation as referred to in Article 48(1) of Order of the Minister of Public Health No. 904/2006, transposing Art. 13 (1) of Directive 2001/20/EC, and

- a certification by the qualified person (QP) in the EU that the manufacturing complies with GMP at least equivalent to the GMP in the EU. Regarding this certification, there are specific arrangements provided for in the Mutual Recognition Agreements between the EU and third countries[24].

[24] For further information, please visit: http://www.ema.europa.eu/Inspections/docs/000204en.pdf

Art. 63. - In all other cases, to document compliance with GMP as set out in Order of the Minister of Public Health No. 905/25.07.2006 on approval of the Principles and guidelines for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, transposing Directive 2003/94/EC and the implementing detailed guideline for IMPs[25], the applicant should submit a copy of the manufacturing/importing authorisation as referred to in Article 48 (1) of Order of the Minister of Public Health No. 904/2006, transposing Art. 13 (1) of Directive 2001/20/EC stating the scope of the manufacturing/importation authorisation.

II.7.2 Data related to the IMP

II.7.2.1 Introductory remarks

Art. 64. - Regarding data, the IMPD can be replaced by other documentation which may be submitted alone or with a simplified IMPD; the details for this 'simplified IMPD' are set out in Section II.7.3.

Art. 65. - The IMPD should be prefaced with a detailed table of contents and a glossary of terms.

Art. 66. – (1) The information in the IMPD should be concise.

(2) The IMPD should not be unnecessarily voluminous.

(3) It is preferable to present data in tabular form accompanied by brief narrative highlighting the main salient points.

Art. 67. - Regarding various specific types of IMPs, guidance is also given by EMA, and made available in Volume 3 of EudraLex — The Rules Governing Medicinal Products in the European Union[26].

II.7.2.2 Quality data

Art. 68. - Quality data should be submitted in a logical structure, such as the headings of the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials[27] approved through SCD No. 15/23.05.2008. This document also contains guidance for quality of placebos.

Art. 69. - As regards biotechnological IMPs, reference is made to the Guideline on virus safety evaluation of biotechnological investigational medicinal products, as amended[28].

Art. 70. – (1) In exceptional cases, where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected, the certificate of analysis for test products should be attached.

(2) Applicants should assess the need to submit a TSE Certificate.

II.7.2.3 Non-clinical pharmacology and toxicology data

Art. 71. – (1) The applicant should also provide summaries of non-clinical pharmacology and toxicology data for any IMP used in the clinical trial; he should also provide a reference list of studies conducted and appropriate literature references.

(2) Full data from the studies and copies of the references should be made available on request.

(3) Wherever appropriate it is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points.

(4) The summaries of the studies conducted should allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol.

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[25] Annex 13 to Volume 4 of EudraLex - The Rules Governing Medicinal Products in the European Union (http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_ en.htm)

[26] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm

[27] CHMP/QWP/185401/2004 final (http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm).

[28] Ref. EMEA/CHMP/BWP/398498/2005 (http://www.ema.europa.eu/pdfs/human/bwp/39849805enfin.pdf)

Art. 72. - Non-clinical pharmacology and toxicology data should be submitted in a logical structure, such as the headings of the current version of Module 4 of the Common Technical Document[29], transposed by Order of the Minister of Public Health No. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, amended by Order of the Minister of Health No. 615/01.06.2010 or of the eCTD format.

Art. 73. - Reference is made to the specific Community guidelines contained in Volume 3 of EudraLex[30], and especially the Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, as amended (CPMP/ ICH/286/95).

Art. 74. - This section should provide a critical analysis of the data, including justification for omissions of data, and an assessment of the safety of the medicinal product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

Art. 75. - The protocols should meet the requirements of Good Laboratory Practice (GLP) guidelines where appropriate. The applicant should provide a statement of the GLP status of all studies.

76. – (1) The test material used in the toxicity studies should be representative of that proposed for clinical trial use in terms of qualitative and quantitative impurity profiles.

(2) The preparation of the test material should be subject to the controls necessary to ensure this and thus support the validity of the study.

II.7.2.4 Previous clinical trial and human experience data

Art. 77. - Clinical trial and human experience data should be submitted in a logical structure, such as the headings of the current version of Module 5 of the Common Technical Document[31], transposed by Order of the Minister of Public Health No. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, amended by Order of the Minister of Health No. 615/01.06.2010 or of the eCTD format.

Art. 78. - This section should provide summaries of all available data from previous clinical trials and human experience with the proposed IMPs.

Art. 79. - All studies should have been conducted in accordance with the principles of Good Clinical Practice (GCP). To this end, the applicant should submit the following:

- a statement of the GCP compliance of the clinical trials referred to,
- where a clinical trial referred to has been performed in third countries, a reference to the entry of this clinical trial in a public register, if available; where a clinical trial is not published in a register, this should be explained and justified.

Art. 80. - There are no specific requirements for data from clinical studies that must be provided before a clinical trial authorisation can be granted. Rather, this is to be assessed on a case-by-case basis. In this respect, applicant should nevertheless take into account the provisions of the Guideline on general considerations for clinical trials approved through Scientific Council Decision No. 40/27.10.2006 (transposition of CPMP/ICH/291/95) [32].

II.7.2.5 Overall risk-benefit assessment

Art. 81. – (1) This section should provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the proposed trial unless this information is already provided in the protocol.

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[29] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf
[30] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-3/index_en.htm
[31] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf
[32] http://www.ema.europa.eu/htms/human/ich/ichefficacy.htm

(2) In the latter case, the applicant should cross-refer to the relevant section in the protocol.

(3) The text should identify any studies that were terminated prematurely and discuss the reasons.

(4) Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults, who are not able to express their informed legal consent, should take account of the provisions set out in Chapters V – VII of Order of the Minister of Public Health No. 904/2006, transposing Articles 3 to 5 of Directive 2001/20/EC.

Art. 82. – (1) Where appropriate, the sponsor should discuss safety margins in terms of relative systemic exposure to the IMP, preferably based on area under the curve (AUC) data, or peak concentration (C_{max}) data, whichever is considered more relevant, rather than in terms of administered dose.

(2) The sponsor should also discuss the clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials.

II.7.3 Simplified IMPD by referring to other documentation

Art. 83. - The applicant has the possibility to refer to other documentation which may be submitted alone or with a simplified IMPD to contain the information as set out in Table 1.

II.7.3.1 Possibility to refer to the IB

Art. 84. – (1) The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the preclinical and clinical parts of the IMPD; in the latter case, the summaries of pre-clinical information and clinical information should include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision about the potential toxicity of the IMP and the safety of its use in the proposed trial.

(2) If there is some special aspect of the preclinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the applicant should submit the preclinical and clinical information as part of the IMPD.

II.7.3.2 Possibility to refer to the Summary of Product Characteristics (SmPC) or to the assessment of the IMPD in another clinical trials application

Art. 85. – (1) The applicant may submit the current version of the SmPC (or, as regards ICH countries, the documentation equivalent to the SmPC) as the IMPD if an IMP has a marketing authorisation in any Member State or in an ICH country.

(2) The exact requirements are detailed in Table 1.

Art. 86. – (1) Moreover, the IMPD may have been submitted previously by the same applicant or by another applicant and held by the NAMMD.

(2) In these cases applicants are allowed to cross-refer to the previous submission.

(3) If the submission was made by another applicant, a letter from that applicant should be submitted authorising the NAMMD to cross-refer to that data.

(4) The exact requirements are detailed in Table 1.

Art. 87. – The content of the simplified IMPD is detailed in Table 1.

Table 1

Content of simplified IMPD

<table>
<tr><th>Type of previous information on an IMP</th><th>Quality data</th><th>Non-clinical data</th><th>Clinical data</th></tr>
<tr><td rowspan="3">The IMP has an MA in any EU Member State or ICH country and is used in the trial:
- Within the conditions of the SmPC
- Outside the conditions of the SmPC
- after modification (blinding)</td><td></td><td></td><td></td></tr>
<tr><td colspan="3">SmPC</td></tr>
<tr><td>SmPC

P+A</td><td>If appropriate

SmPC</td><td>If appropriate

SmPC</td></tr>
<tr><td>Another pharmaceutical form or strength of the IMP has an MA in any EU Member State or ICH country and the IMP is supplied by the MA holder</td><td>SmPC +P+A</td><td>YES</td><td>YES</td></tr>
<tr><td>- The IMP has no MA in any EU Member State or ICH country but the active substance is part of a medicinal product with an MA in an EU Member State and
- is supplied by the same manufacturer
- is supplied by another manufacturer</td><td>

SmPC +P+A

SmPC +S+P+A</td><td>

YES

YES</td><td>

YES

YES</td></tr>
<tr><td rowspan="3">The IMP was subject to a previous clinical trial authorisation and authorised in the Member State concerned[33] and has not been modified and
— no new data is available since last amendment to the clinical trial authorisathion
— new data is available since last amendment to the clinical trial authorisation
- is used under different conditions</td><td></td><td></td><td></td></tr>
<tr><td colspan="3">Reference to previous submission</td></tr>
<tr><td>New data

If appropriate</td><td>New data

If appropriate</td><td>New data

If appropriate</td></tr>
<tr><td colspan="4">NOTE: S: Data relating to the active substance; P: Data relating to the IMP; A: Appendices to the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials approved through Scientific Council Decision No. 15/2008 (transposition of Guidleine CHMP/QWP/185401/2004/final)</td></tr>
</table>

[33] The sponsor should provide a letter of authorisation to cross-refer to the data submitted by another applicant.

Art. 88. - If the applicant is the MA holder and he has submitted an application to vary the SmPC, which has not yet been authorised, and which is relevant for the assessment of the IMPD in terms of patient safety, the nature of the variation and the reason for it should be explained.

Art. 89. - If the IMP is defined in the protocol in terms of active substance or ATC code (see above, Section II.5), the applicant may replace the IMPD by one representative SmPC for each active substance/active substance pertaining to that ATC group; alternatively, he may provide a collated document containing information equivalent to that in the representative SmPCs for each active substance that could be used as an IMP in the clinical trial.

II.7.4. IMPD in cases of placebo

Art. 90. - If the IMP is a placebo, the information requirements can be reduced in line with the requirements set out in Table 2.

Art. 91 – Table 2 contains the required documentation for IMPD in cases of placebo.

Table 2

IMPD in cases of placebo

IMPD in for placebo	Quality data	Non-clinical data	Clinical data
The IMP is a placebo	P +A	NO	NO
The IMP is a placebo and has the same composition as the tested IMP, is manufactured by the same manufacturer, and is not sterile	NO	NO	NO
The IMP is a placebo and has been submitted to the NAMMD in a previous CTA	NO	NO	NO

NOTE: (S: Data relating to the active substance; P: Data relating to the IMP; A: Appendices to the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials approved through Scientific Council Decision No. 15/2008 (transposing Guideline CHMP/QWP/185401/2004/final)

II.8 Non-investigational medicinal products (NIMPs) used in the trial

Art. 92. – (1) Medicinal products used in the context of a clinical trial and not falling within the definition of an IMP are non- investigational medicinal products (NIMPs).

(2) The 'borderline' between IMPs and NIMPs is described in the Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials, approved through Scientific Council Decision No. 7/26.06.2009 (transposing the European Commission Guideline[34]).

Art. 93. – (1) It is strongly recommended that NIMPs with marketing authorisation in Romania are used.

(2) When this is not possible, the next choice should be NIMPs with marketing authorisation in another EU Member State.

[34] cf. http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm

(3) When this is not possible, the next choice should be NIMPs with marketing authorisation in an ICH country or a third country having a mutual recognition agreement with the EU (MRA country)[35].

(4) When this is not possible, the next choice should be NIMPs with a marketing authorisation in another third country.

(5) Otherwise, a NIMP with no marketing authorisation may be used.

Art. 94. - For the requirements of the NIMP dossier, reference is made to the applicable guideline published in EudraLex — The Rules Governing Medicinal Products in the European Union, Volume 10[36].

II.9 Other documents to be submitted - Overview

Art. 95. - The following additional documents should be contained in the application dossier submitted to the NAMMD:

1) A copy of the opinion of the Ethics Committee of the Member State concerned, whether the application has been submitted in parallel or in sequence, as soon as it is available, unless the Ethics Committee informs the applicant that it has copied its opinion to the NAMMD; a submission of this document subsequently to the submission of a request for authorisation is not to be considered as a change of the documentation as referred to in Section II.1.4.2.

2) If available, a copy of the summary of scientific advice from any Member State or the EMA with regard to the respective clinical trial; a submission of this document subsequently to the submission of a request for authorisation is not to be considered as a change of the documentation as referred to in Section II.1.4.2.

3) If the clinical trial is part of an agreed Paediatric Investigation Plan (PIP), a copy of EMA's Decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet; in the latter case, the link to this documentation in the cover letter is sufficient; a submission of this document subsequently to the submission of a request for authorisation is not to be considered as a change of the documentation as referred to in Section II.1.4.2.

4) The content of the labelling of the IMP.

5) The fee setting sheet for assessment of documentation for authorisation of conduct of a clinical trial on medicinal products for human use, in accordance with provisions of Order of the Minister of Public Health No. 716/11.06.2009.

Art. 96. - Table 3 contains the final overview of the documentation to be submitted.

Table 3

List of documentation to be provided to the NAMMD in accordance with this detailed guidance

- Cover letter with the contents set out in Section II.3,
- Clinical trial application form,
- Protocol with the contents set out in Section II.5,
- IB, or document replacing the IB, as set out in Section II.6,
- IMPD/simplified IMPD, as set out in Sections II.7 and II.7.3,
- NIMP dossier as set out in Section II.8,
- The additional pieces of documentation as set out in Section II.9.

[35] These third countries are Australia, Canada, Japan, New Zealand and Switzerland.

[36] cf. http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm

CHAPTER III

Notification of amendments and related measures

III.1 Legal basis and scope

Art. 97. - Art. 45 of Chapter XII 'Conducting a clinical trial' of Order of the Minister of Public Health No. 904/2006 (transposing Art. 10(a) of Directive 20/2001/EC, states the following: 'After the commencement of the clinical trial, the sponsor may make amendments to the protocol; if those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the NAMMD of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned in accordance with Chapter VIII 'Ethics Committee' and XI 'Commencement of a clinical trial' of Order of the Minister of Public Health No. 904/2006, transposing Art. 6 and 9 of Directive 20/2001/EC.'

Art. 98. - In view of the identical legal consequences of an amendment that is 'substantial and likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial' and an amendment that is 'otherwise significant', the term 'substantial amendment' used in this guidance refers to both types of amendments.

Art. 99. – (1) Notification/submission of information is only obligatory if the amendment is a substantial amendment[37].

(2) Order of the Minister of Public Health No. 904/2006 does not require notification, nor immediate submission of information of non-substantial amendments.

(3) Neither the NAMMD, nor its Ethics Committee can oblige the sponsor to submit non-substantial amendments; in this regard, the rules for non-substantial amendments (cf. Section II.6) apply.

III.2 The notion of "amendment"

Art. 100. - The following changes do not count as an 'amendment' as referred to in Article 45(a) of Order of the Minister of Public Health No. 904/2006, transposing Art. 10(a) of Directive 2001/20/EC:

- a change to the documentation submitted to the NAMMD during the ongoing assessment of the request for authorisation by the national competent authority (for these aspects see Section II.1.4.2), and
- a change to the documentation submitted to the Ethics Committee during the ongoing assessment of the request for authorisation by the Ethics Committee.

Art. 101. - Article 45(a) of Order of the Minister of Public Health No. 904/2006, transposing Article 10(a) of Directive 2001/20/EC refers only to amendments to the approved protocol. This is to be understood as encompassing all documentation submitted in the context of the approved protocol.

Art. 102. – (1) The annual safety report (ASR) submitted in accordance with Article 63 of Order of the Minister of Public Health No. 904/2006, transposing Article 17(2) of Directive 2001/20/EC is not per se an amendment and thus does not have to be notified as a substantial amendment to the NAMMD.

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[37] Directive 2001/20/EC makes a difference between the notification of the national competent authority and the submission of information to the Ethics Committee. Envisaging this Guideline's purpose, both means of information shall be referred to as 'notification'.

(2) However, the sponsor has to verify whether the data presented in the ASR requires a change to the documentation submitted with the request for authorisation of a clinical trial.

(3) If this amendment is substantial, the rules for notification of substantial amendments apply to these changes.

Art. 103. – (1) A change of the contact person or in the contact details of the contact person (e.g. a change of e-mail or postal address) is not considered as an amendment, if the sponsor and legal representative remain identical.

(2) However, the sponsor should ensure that the NAMMD is aware of this change as soon as possible, in order to allow the national competent authority to exercise its supervisory function.

III.3 The notion of "substantial"

Art. 104. - Amendments to the trial are regarded as 'substantial' where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the clinical trial participants, or
- the scientific value of the trial.

Art. 105. - In all cases, an amendment is only to be regarded as 'substantial' when one or both of the above criteria are met.

Art. 106. – (1) It is up to the sponsor to assess whether an amendment is to be regarded as 'substantial', according to the aforementioned criteria.

(2) In cases where the sponsor consults the NAMMD, advice should be given without delay and free of charge.

Art. 107. - In applying these criteria, however, care has to be taken to avoid over-reporting, since not every change to the clinical trial application form is by default to be considered as a 'substantial' amendment.

Art. 108. – (1) The annual update of the IB in accordance with Article 23 of Order of the Minister of Public Health No. 903/25.07.2006, transposing Art. 8 of Directive 2005/28/EC is not per se a substantial amendment.

(2) However, it is up to the sponsor to assess whether updated data refer to substantial amendments.

(3) In that case, the rules for notification of substantial amendments apply to the change.

Art. 109. - The sponsor should assess also whether the combination of substantial amendments lead to changes of the clinical trial to an extent that it has to be considered as a completely new clinical trial, which would then be subject to a new authorisation procedure.

III.4 Examples

Art. 110. – (1) In view of these criteria the following examples should serve as guidance for the case-by-case decision of the sponsor.

(2) These examples relate only to the aspects assessed by the NAMMD.

(3) For aspects considered by the Ethics Committee, reference is made to the Commission guidance based on Article 8 of Directive 2001/20/EC, as well as to Chapter X, Detailed guidelines of Order of the Minister of Public Health No. 904/2006.

III.4.1 Amendments as regards the clinical trials protocol

Art. 111. - With regard to the protocol, the following is a non-exhaustive list of amendments that are typically 'substantial':

a) change of main objective of the clinical trial;

b) change of primary or secondary endpoint which is likely to have a significant impact on the safety or scientific value of the clinical trial;

c) use of a new measurement for the primary endpoint;

d) new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk/benefit assessment;

e) a change in the definition of the end of the trial, even if the trial has in practice already ended;

f) addition of a trial arm or placebo group;

g) change of inclusion or exclusion criteria, such as changes to age range, if these changes are likely to have a significant impact on the safety or scientific value of the clinical trial;

h) reducing the number of monitoring visits;

i) change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the clinical trial;

j) withdrawal of an independent data monitoring board;

k) change of IMPs;

l) change of dosing of IMPs;

m) change of mode of administration of IMPs;

n) a change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment.

Art. 112. - With regard to the protocol, the following is a non- exhaustive list of amendments that are typically not 'substantial':

a) changes to the identification of the trial (e.g. change of title etc.);

b) the addition/deletion of exploratory/tertiary endpoints;

c) a minor increase in the duration of the trial (< 10 % of the overall time of the trial);

d) an increase in duration of > 10 % of the overall time of the trial, provided that:

- the exposure to treatment with the IMP is not extended,
- the definition of the end of the trial is unchanged, and
- monitoring arrangements are unchanged;

e) a change in the number of clinical trial participants per trial site, if the total number of Romanian participants is identical or the increase/decrease is insignificant in view of the absolute number of participants;

f) a change in the number of clinical trial participants in Romania, if the total number of participants is identical or the increase/decrease is insignificant in view of the absolute number of participants;

g) a change in the documentation used by the research team for recording study data (e.g. case report form or data collection form);

h) additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis;

i) minor clarifications to the protocol;

j) correction of typographical errors.

III.4.2 Amendments as regards the IMPD

Art. 113. - With regard to changes in the IMPD, guidance is contained in Scientific Council Decision No. 15/23.05.2008 on approval of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials[38].

III.4.3 Amendments as regards the IB

Art. 114. - With regard to the IB, the following is a non-exhaustive list of amendments that are typically 'substantial':

a) new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data of relevance for the investigator;

b) changes to the reference safety information for the annual safety report.

[38] (CHMP/QWP/185401/2004 final (http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm).

III.4.4 Amendments as regards other initial documents supporting the request for authorisation of the clinical trial

Art. 115. - With regard to other initial documents, the following is a non-exhaustive list of amendments that are typically 'substantial':

- a change of sponsor or the sponsor's legal representative in Romania;
- the revocation or suspension of the IMP's marketing authorisation.

Art. 116. - With regard to other initial documents, the following is a list of amendments that are typically *not* 'substantial':

a) Any change of persons other than the sponsor or his legal representative, for example applicant, clinical research associates (CRAs) who monitor the clinical trial for the investigator, and clinical research organisations (CROs) (note that the responsibility vis-à-vis the NAMMD for the clinical trial is always with the sponsor or his legal representative);

b) any change in the contact details of persons referred to in the documentation (see, however, Section III.2 as regards contact details of the contact person);

c) changes to the internal organisation of the sponsor or of the persons to whom certain tasks have been delegated;

d) changes in the logistical arrangements for storing/ transporting samples;

e) change of technical equipment;

f) addition or deletion per se of another Member State or third country concerned.

III.5 Who should be notified?

Art. 117. - Substantial amendments may relate to information relevant for assessment by the NAMMD, the Ethics Committee, or both.

Art. 118. - For substantial amendments to information that is assessed only by the NAMMD, the sponsor should only notify the amendment to the NAMMD.

Art. 119. - For substantial amendments to information that is assessed, according to Order of the Minister of Public Health No. 904/2006, only by the Ethics Committee, the sponsor should only notify the amendment to the Ethics Committee; this is in particular of relevance for the information relating to:

- the clinical trial site (according to Article 28 (3)(f) of Order of the Minister of Public Health No. 904/2006, transposing Art. 6(3) of Directive 2001/20/EC),
- the written information to be given to the clinical trial participant in order to obtain informed consent (Article 28(3)(g) of Public Health Order No. 904/2006, transposing Art. 6(3) (g) of Directive 2001/20/EC), and
- the investigator (Article 28(3)(d) of Order of the Minister of Public Health No. 904/2006, transposing Art. 6(3)(d) of Directive 2001/20/EC).

Art. 120. - These aspects are addressed in the separate Commission guidance based on Article 8 of Directive 2001/20/EC and are referred to in Chapter X, Detailed guidelines, of Order of the Minister of Public Health No. 904/2006.

Art. 121. - In the case of substantial amendments that affect information assessed by the NAMMD and the Ethics Committee of Romania, the sponsor should submit the notifications in parallel.

Art. 122. - There is no need to notify 'for information only' substantial amendments to one body (the NAMMD or Ethics Committee), if this information is assessed by the respective other body.

Art. 123. - In practice, it is necessary that the NAMMD and the Ethics Committee in Romania communicate with each other in order to ensure the exchange of expertise or information; this may be in particular relevant, for example, for:

- assessing scientific information requiring specific expertise,
- ensuring effective inspections of clinical trials sites, and
- updating relevant information in EudraCT.

III.6 Non-substantial amendments

Art. 124. – (1) The sponsor does not have to notify non-substantial amendments to the NAMMD or the Ethics Committee.

(2) However, non-substantial amendments should be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment.

(3) This is of particular relevance for the Clinical Trial Application Form, which should be updated in its entirety at the occasion of a substantial amendment.

(4) Documentation of non-substantial amendments should also be available on request for inspection at the trial site or the sponsor premises as appropriate.

III.7 Format and content of notification

Art. 125. – The notification of a substantial amendment should include the following:

a) a signed cover letter, including:

- in its subject line the EudraCT number and the sponsor protocol number (if available) with the title of the trial and the sponsor's amendment code number allowing unique identification of the substantial amendment; care should be taken to use the code number consistently;
- identification of the applicant;
- identification of the amendment (sponsor's substantial amendment code number[39] and date); one amendment could refer to several changes in the protocol or scientific supporting documents;
- a highlighted indication of any special issues related to the amendment and indication where the relevant information or text is in the original application dossier;
- identification of any information not contained in the Amendment Notification Form that might impact on the risk to trial participants;
- where applicable, a list of all affected clinical trials with EudraCT numbers and respective amendment code numbers (see above);

b) the Amendment Notification Form, as amended, which is published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the European Union[40]; only this Amendment Notification Form should be used;

c) a description of the amendment;

- an extract from the amended documents showing previous and new wording in track changes, as well as the extract only showing the new wording;
- notwithstanding the previous point, if the changes are so widespread or far-reaching that they justify an entire new version of the document, a new version of the entire document. In this case, an additional table should list the amendments to the documents; in this list, identical changes can be grouped.

The new version should be identified with the date and an updated version number.

d) supporting information including, where applicable:

- summaries of data,
- an updated overall risk/benefit assessment,
- possible consequences for subjects already included in the trial,
- possible consequences for the evaluation of the results;

[39] The code number identifies the amendment and refers to all the documents submitted. The sponsor decides which code to be used. Section E1 of the amendment form should be completed with the date and version of the new amendment to which this form relates.

[40] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/ eudralex/vol-10/index_en.htm

e) if a substantial amendment involves changes to entries on the clinical trial application form, a revised copy of the XML file incorporating amended data; if the form is not submitted via a telematics system, the fields affected by the substantial amendment should be highlighted in the revised form[41].

Art. 126. – (1) Where a substantial amendment affects more than one clinical trial of the same sponsor and the same IMP, the sponsor may make a single notification to the NAMMD/Ethics Committee concerned.

(2) The cover letter and the notification should contain a list of all clinical trials affected with their EudraCT numbers and respective amendment code numbers.

(3) If the substantial amendment involves changes to several clinical trial application forms, all forms should be updated (see Section III.7).

III.8 Time for response, implementation

Art. 127. – (1) In accordance with the provisions of Art. 45 of Chapter XII "Conducting a clinical trial" of Order of the Minister of Public Health No. 904/2006, transposing Art. 10(a) of Directive 2001/20/EC, based on the issues mentioned in Art. 28 (3) and in accordance with Chapter IX (transposing Art. 6(3) and Art. 7), the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form.

(2) If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

(3) If the opinion of the Ethics Committee is favourable and the NAMMD has raised no grounds for non-acceptance, the sponsor shall proceed to conduct the clinical trial following the amended protocol.

(4) Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment.

Art. 128. – (1) Accordingly, the Ethics Committee has to give within 35 calendar days an opinion on a valid submission of a proposed substantial amendment.

(2) If a submission is not considered as valid by the Ethics Committee, the Ethics Committee should inform the applicant of this within the first 10 calendar days of this 35-day period. The reasons should be given.

Art. 129. – (1) With regard to the NAMMD, it should respond to an amendment notification within 35 calendar days of receipt of the valid notification of an amendment, period which comprises the validation term.

(2) If a submission is not valid (for example, the dossier does not contain the documentation required according to this guidance), the NAMMD is invited to inform the applicant of this within the first 10 calendar days of this 35-day period. The reasons should be given.

(3) This response time may be extended if such extension is justified in view of the nature of the substantial amendment, for example if the NAMMD has to consult an expert group or committee; in such cases, the NAMMD should notify the sponsor of the duration of the extension and its reasons.

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[41] Section A4 of the Application form for marketing authorisation of a clinical trial should contain the version and date of the initially authorised protocol, which should not be modified once new amendments are introduced in the protocol. Section B4 of the Amendment form should contain the version and date of the currently approved protocol.
Note: section H of the Application form for marketing authorisation of a clinical trial does not require modification, since it refers to the status of the application for authorization of a clinical trial forwarded to the ethics committee at the moment of submission of the respective application at the NAMMD (the competent authority).

(4) If the NAMMD states that it raises no grounds for non-acceptance, the sponsor can implement the changes, even if fewer than 35 days have elapsed since the filing of the substantial amendment.

Art. 130. - For amendments submitted to either the Ethics Committee alone or to the NAMMD alone, the sponsor may implement the amendment when the Ethics Committee opinion is favourable or the competent national authority has raised no grounds for non-acceptance.

Art. 131. - Up until then, the trial can continue on the basis of the original documentation, unless the rules for urgent safety measures apply.

Art. 132. – (1) Applicants should be aware that these procedures are intended to ensure rapid and efficient processing of substantial amendments.

(2) Against this background, unsatisfactory documentation is likely to lead to non-acceptance of the substantial amendment.

(3) Non-acceptance does not prejudice the applicant's right to resubmission.

Art. 133. - Upon approval, it is the sponsor's responsibility to ensure communication of the changes to the investigators.

III.9 Notification of urgent safety measures

Art. 134. – (1) 'In accordance with Art. 45 (b) of Order of the Minister of Public Health No. 904/2006 (transposing Art. 10(b) of Directive 2001/20/EC), without being non-compliant with the provisions of Art.45 (a) (transposing Art. 10 (a) of Directive 2001/20/EC) and in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where the new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.

(2) The sponsor shall forthwith inform the NAMMD of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time.'

Art. 135. - Examples of urgent safety measures are if, for reasons of safety of the clinical trial participants, a trial is temporarily halted (see Section III.10) or additional monitoring measures are set up.

Art. 136. – (1) Urgent safety measures may be taken without prior notification to the NAMMD.

(2) However, the sponsor must inform *ex post* the NAMMD and the Ethics Committee of the new events, the measures taken and the plan for further action as soon as possible; where the initial contact is by telephone, this should be followed up, for reasons of traceability, by fax or e-mail. It should be followed by a written report.

Art. 137. - The *ex post* notification of urgent safety measure is independent of the obligation to:

- notify substantial amendments (see above),
- notify early termination of the trial within 15 days in accordance with Article 45 (c) of Order of the Minister of Public Health No. 904/2006, transposing Art. 10(c) of Directive 2001/20/EC (see below, Section IV.2.2), and
- notify adverse events and serious adverse reactions in accordance with Chapter XVII – 'Notification of serious adverse reactions' of Order of the Minister of Public Health No. 904/2006 (transposing Articles 16 and 17 of Directive 2001/20/EC).

III.10 Temporary halt of a trial

Art. 138. - A temporary halt of a trial is a stoppage of the trial which is not envisaged in the approved protocol and where there is an intention to resume it.

Art. 139. - A temporary halt can be:

- a substantial amendment, or

- part of an urgent safety measure as referred to in Article 45(b) of Order of the Minister of Public Health No. 904/2006 (transposing Art. 10(b) of Directive 2001/20/EC); in this case, the notification of the temporary halt of a trial should be made immediately and, at the latest, in accordance with the deadline set out in Article 45(c) of Order of the Minister of Health No. 904/2006 (transposing Art. 10(c) of Directive 2001/20/EC, within 15 days from when the trial is temporarily halted.

Art. 140. - The reasons and scope, e.g. stopping recruitment or interrupting treatment of subjects already included, should be clearly explained in the notification (in case of substantial amendment, see Section III.7) or in the *ex post* information (in case of urgent safety measures, see Section III.9).

Art. 141. - The restart of the trial should be treated as a substantial amendment providing evidence that it is safe to restart the trial.

Art. 142. - If the sponsor decides not to recommence a temporarily halted trial he should notify the NAMMD within 15 days of his decision in accordance with Article 45(c) of Order of the Minister of Public Health No. 904/2006 (transposing Art. 10(c) of Directive 2001/20/EC) (see Section IV.2).

III.11 Suspension/prohibition of a clinical trial performed by the NAMMD in case of doubts about safety or scientific validity

Art. 143. – (1) According to Art. 46(1) of Order of the Minister of Public Health No. 904/2006 (transposing Art. 12(1) of Directive 2001/20/EC), 'where the NAMMD has objective grounds for considering that the conditions in the request for authorisation referred to in Article 37 (transposing Art. 9(2) of Directive 2001/20/EC) are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof.

(2) Before the Member State reaches its decision it shall, except where there is imminent risk, the NAMMD should ask the sponsor and/or the investigator for their opinion, to be delivered within one week.

(3) In this case, the NAMMD shall forthwith inform the other competent authorities, the Ethics Committee concerned, and the EMA of its decision to suspend or prohibit the trial and of the reasons for the decision.'

Art. 144. – If the trial is terminated following a suspension, the rules on end of trial notification apply (see below, Section IV.2).

III.12 Non-compliance with the applicable rules on clinical trials

Art. 145. – (1) In accordance with Art. 46 of Order of the Minister of Public Health No. 904/2006 (transposing Art. 12(1) of Directive 2001/20/EC), if the NAMMD has objective grounds to consider that the sponsor/investigator/ any other person involved in the trial no longer meets the established prerequisites, it immediately informs the respective person about this and establishes a set of measures to be considered in view of solving similar situations.

(2) The NAMMD should immediately inform the involved competent authorities, ethics committees and the European Commission concerning the implementation of this set of rules.

Art. 146. - The set of rules established by the NAMMD should include an implementation schedule and a date when the sponsor reports to the NAMMD the status of implementation of measures and their completion.

Art. 147. – The sponsor's responsibility is to ensure the immediate implementation of the measures imposed by the NAMMD, and should communicate to the NAMMD the progresses achieved and the end of the measure program in accordance with the established timetable.

Art. 148. – The NAMMD should inform the other competent authorities, ethics committees involved and the European Commission about the development of this measure program.

CHAPTER IV

Declaration of the end of a clinical trial

IV.1 Legal basis and scope

Art. 149. – (1) In accordance with Art. 45 (c) of Order of the Minister of Public Health No. 904/2006 (transposing Art. 10 (c) of Directive 2001/20/EC), the sponsor shall notify the NAMMD and the Ethics Committee that the clinical trial has ended within 90 days of the end of a clinical trial .

(2) If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.'

Art. 150. – (1) 'End of the trial' is not defined in Directive 2001/20/EC. The definition of the end of the trial should be provided in the protocol (for guidance, see Section II.5).

(2) For changes to the definition, see under Section III.4.1.

IV.2 Procedure for declaring the end of the trial

IV.2.1 General rules

Art. 151. – (1) The sponsor has to make an end of trial declaration when the complete trial has ended in all Member States/third countries concerned.

(2) The end of the clinical trial is defined in the protocol (see Section IV.1).

Art. 152. – (1) This declaration has to be made to the NAMMD and the Ethics Committee of all Member States concerned within 90 days of the end of the clinical trial.

(2) To this end, the form published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the European Union[42] should be used.

Art. 153. – The NAMMD is responsible for entering this information into the EudraCT database.

IV.2.2 Shortened deadline for early termination of a clinical trial

Art. 154. - An earlier end of the clinical trial which is not based on grounds of safety, but on other grounds, such as faster recruitment than anticipated, is not considered as 'early termination'.

Art. 155. - In the case of early termination, the sponsor must notify the end of the trial to the NAMMD and the Ethics Committee immediately and at the latest within 15 days after the trial is halted, clearly explain the reasons, and describe follow- up measures, if any, taken for safety reasons.

IV.3 Clinical trial summary report

Art. 156. – (1) The clinical trial summary report is part of the end of trial notification, albeit usually submitted only subsequently to the end of trial notification.

(2) The sponsor should provide this summary report within one year of the end of the complete trial for non-paediatric clinical trials.

(3) For paediatric clinical trials, the timelines are set out in the Commission Communication 2009/C28/01.

(4) Regarding the arrangements for submitting the clinical trial summary report, its format, content, and its accessibility for the public, reference is made to the Commission Communications 2009/C28/01 and 2008/C168/02 and their implementing technical guidance documents[43].

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[42] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/ eudralex/vol-10/index_en.htm

[43] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/ eudralex/vol-10/index_en.htm

ANNEX 1
to the Guideline

REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE, TO THE NAMMD AND FOR OPINION OF THE ETHICS COMMITTEE (EC)

To be filled by the NAMMD/EC:

Date of receiving the request: Date of request for information to make it valid:	Date of request for additional information:	Grounds for non-acceptance/ negative opinion ☐ Date:
Date of valid application: **Date of start of procedure:**	Date of receipt of additional/amended information:	*Authorisation/Positive opinion:* ☐ Date*:*
NAMMD, EC registration number:		*Withdrawal of application:* ☐ Date:

To be filled in by the applicant:
This sections in this form for request for authorisation from the NAMMD are also relevant for the opinion from the Ethics Committee (which represents module 1 of the application form submitted to the Ethics Committee) and may be used as part of that application. The relevant purpose must be indicated by checking the appropriate box:

REQUEST FOR AUTHORISATION TO THE NAMMD: ☐
REQUEST FOR OPINION OF THE ETHICS COMMITTEE: ☐

A. TRIAL IDENTIFICATION

A.1	The state where the application is being submitted:
A.2	EudraCT number:
A.3	Full title of the trial:
A.3.1	Title of the trial for non-professionals, in easily accessible language (non-technical terms):
A.3.2	Abbreviated title of the trial, where available:
A.4	Sponsor's protocol code number, version and date [44]:
A.5	Additional international identifiers (given by the WHO, ISRCTN[45], US RCT[46] numbers, if available:
A.6	Is this a resubmission? yes ☐ no ☐ If yes, please attach the resubmission letter[47]

[44] Any translation of the protocol is to be assigned the same date and version as those of the original document
[45] The International Standard Randomised Controlled Trial Number. Sponsors may use the ISRCTN to identify their trials in addition to the EudraCT number; e.g. if this trial is part of a multinational trial being conducted in non-EU countries. The number and guidance may be obtained from the Current Controlled Trials website, namely at http://www.controlled-trials.com/isrctn, to which there is a link from the EudraCT database website: http://www.eudract.emea.europa.eu. When this number is available, sponsors should present it in section A.6 of the application form.
[46] US National Clinical Trial Numbers (NCT numbers) are required on the FDA application form
[47] For a resubmission following a previous withdrawal of an application for authorisation/an unfavourable opinion of an Ethics Committee/a previous withdrawal of an application for authorisation/refusal of request for authorisation by the competent authority, a letter shall be entered for the resubmission letter, as follows: A for the first resubmission, B for the second, C for the third and so on

A.7	Is this study a part of the Paediatric Investigation Plan?	yes ☐ no ☐
A.8	Number of the EMA Decision of the Paediatric Investigation Plan	

B. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

B.1 Sponsor
B1.1 Name of organisation:
B1.2 Name of the contact person:
B1.3 Address:
B.1.2.2 Middle name:
B.1.2.3 Name:
B.1.3 Address:
B.1.3.1 Street:
B.1.3.2 City
B.1.3.3 Post code:
B.1.3.4 Country:
B.1.4 Telephone number:
B.1.5 Fax number:
B.1.6 E-mail:

B.2 Legal representative[48] of the EU sponsor for the purpose of this trial (if different from the sponsor)
B.2.1 Name of organisation:
B.2.2 Name of the contact person:
B.2.2.1 First name
B.2.2.2 Middle name:
B.2.2.3 Name:
B.2.3 Address:
B.2.3.1 Street:
B.2.3.2 City:
B.2.3.3 Post code:
B.2.3.4 Country:
B.2.4 Telephone number:
B.2.5 Fax number:
B.2.6 e-mail:

B.3 STATUS OF THE SPONSOR:	
B.3.1 Commercial	☐
B.3.2 Non-commercial	☐

B.4 Source(s) of monetary or material support for the clinical trial (repeat as necessary):
B.4.1 Name of organisation:
B.4.2 Country:
B.5 Contact point[49] assigned by the sponsor for further information on the trial

[48] In accordance with provisions of Art. 67 and Art. 68 of Minister of Public Health Order NoMinister of Public Health Order NoMinister of Public Health Order No. 904/25.07.2006 transposing Art. 19 of Directive 2001/20/EC

[49] In order to avoid the need for permanent update of the respective contact data, the contact point should ensure operational information rather than details relating to one "person"

B.5.1 Name of organisation:
B.5.2 Official name of the contact point (e.g., " Clinical Trial Information Desk")
B.5.3 Address:
B.5.3.1 Street:
B.5.3.2 City
B.5.3.3 Post code:
B.5.3.4 Country:

B.5.4 Telephone number:
B.2.5 Fax number:
B.5.6 E-mail: (use an operational e-mail address rather than a personal one)

C. APPLICANT IDENTIFICATION (fill in appropriately)

C1. REQUEST TO THE NAMMD ☐

C.1.1 Sponsor ☐
C.1.2 Legal representative of the sponsor: ☐
C.1.3 Person or organisation authorised by the sponsor to make the application ☐
C.1.4 In this case, the below details of the applicant shall be provided, even if also provided elsewhere on the form:
- C.1.4.1 Name of organisation:
- C.1.4.2 Name of the contact person:
  - C.1.4.2.1 First name:
  - C.1.4.2.2 Middle name:
  - C.1.4.2.3 Name:
- C.1.4.3 Address:
  - C.1.4.3.1 Street
  - C.1.4.3.2 City
  - C.1.4.3.3 Post code
  - C.1.4.3.4 Country
- C.1.4.4 Telephone number:
- C.1.4.5 Fax number:
- C.1.4.6 E-mail:

C.1.5 Request to receive an .xml copy of the information on the application for clinical trial authorisation (ACTA)
C.1.5.1 Request for an .xml copy of the folder the ACTA data saved in the EudraCT database?
yes ☐ no ☐
C.1.5.1.1 If yes, please specify the e-mail address(es) where it should be sent (up to 5 addresses)
C.1.5.1.2 Request for transmission of this copy via password-protected link(s)[50] ? yes ☐ no ☐
If the answer to question C.1.5.1.2 is no, the .xml file is to be transmitted via less secure e-mail link(s).

C2. REQUEST FOR THE ETHICS COMMITTEE (EC) ☐

[50] An EudraLink account is required for this (for further details, see https://eudract.emea.europa.eu/document.html)

C.2.1 Sponsor ☐

C.2.2 Legal representative of the sponsor: ☐

C.2.3 Person or organisation authorised by the sponsor to submit the application ☐

C.2.4 Investigator in charge of the application, if needed[51]:

- Coordinating investigator (for multicentre trials) ☐
- Principal investigator (for single centre trials) ☐

C.2.5 Fill in with the following contact details of the applicant, even if also provided elsewhere on the form:

C.2.5.1 Name of organisation:

C.2.5.2 Name of the contact person:

C.2.5.2.1 First name

C.2.5.2.2 Middle name:

C.2.5.2.3 Name:

C.2.5.3 Address:

C. 2.5.3.1 Street:

C. 2.5.3.2 City

C. 2.5.3.3 Post code:

C. 2.5.3.4 Country:

C.2.5.4 Telephone number:

C.2.5.5 Fax number:

C.2.5.6 E-mail:

D. INFORMATION ON EACH INVESTIGATIONAL MEDICINAL PRODUCT

This section contains information on each "bulk medicinal product" prior to trial-specific operations (blinding, trial specific packaging and labelling) for each IMP being tested, including each comparator and each placebo, if applicable. ***For placebo medicinal products, go directly to section D.8.*** *If the trial is performed with several medicinal products, additional sheets are to be used and each medicinal product is to be given a sequential number, in section D.1.1. If the medicinal product is a combination of several active substances, information should be specified for each active substance.*

D.1 IMP identification

Indicate which of the following IMP is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):

D.1.1 This refers to the IMP number: (..)

D.1.2 IMP being tested ☐

D.1.3 IMP used as comparator ☐

D.2. Status of the IMP

[51] In accordance with national legislation

D.2.1 The IMP to be used in this trial has a marketing authorisation (MA) yes ☐ no ☐

If the IMP has an MA in a Member State where this application is submitted, but the trade name and Marketing Authorisation Holder are not established in the protocol, go to section D.2.2

D.2.1.1 If yes, please specify the following for the medicinal product to be used in the clinical trial:
D.2.1.1.1 Trade name[52]
D.2.1.1.1.1 EV Product Code (where applicable)
D.2.1.1.2 Name of the MAH:
D.2.1.1.3 MA number (if the MA has been granted by an EEA Member State)
D.2.1.1.4 Is the IMP modified in relation to its marketing authorisation? yes ☐ no ☐
D.2.1.1.4.1 If yes, please specify:
D.2.1.2 Country that granted the MA (……)
D.2.1.2.1 This is the Member State concerned with this application yes ☐ no ☐

D.2.2 Situations where the IMP to be used in the trial has MA in Romania but the protocol allows that any brand of the IMP with a MA in Romania be administered to the trial subjects and it is not possible to clearly identify the IMP in advance of the trial start

D.2.2.1 In the protocol, is treatment defined only by the active substance? yes ☐ no ☐
D.2.2.1 1 If yes, specify the active substance in D.3.8 or D.3.9

D.2.2.2 In the protocol, treatment regimens allow different combinations of marketed products used according to the local clinical practice at some or all investigator sites in Romania yes ☐ no ☐
D.2.2.2.1 If yes, specify the active substance in D.3.8 or D.3.9

D.2.2.3 The products to be administered as IMPs are defined as belonging to an ATC group[6] yes ☐ no ☐
D.2.3.3.1 If yes, give the ATC group (level 3 or maximum level that can be defined) in D.3.3

D.2.2.4 Other: yes ☐ no ☐
D.2.2.4.1 If yes, specify which:

D.2.3 IMPD

D.2.3.1 Full IMPD yes ☐ no ☐
D.2.3.2 Simplified IMPD yes ☐ no ☐
D.2.3.3 Summary of Product Characteristics (SmPC) only yes ☐ no ☐

D.2.4 The use of the IMP has been previously authorised in a clinical trial conducted by the sponsor in the EU? yes ☐ no ☐

D.2.4.1 If yes, specify which MS

D.2.5 The IMP indicated has been designated as an orphan medicinal product in the EU**?**
yes ☐ no ☐

D.2.5.1 If yes, specify the orphan drug designation number, if available[53]: ( )

D.2.6 The IMP has been subject of scientific advice related to this clinical trial? yes ☐ no ☐

D.2.6.1 If yes, specify the source of scientific advice and attach a copy in the ACTA request:

D.2.6.1.1 The CHMP[54]?	yes ☐	no ☐

[52] From the Summary of Product Characteristics (SmPC)
[53] In accordance with the Community Register for orphan medicinal products (Regulation No. 141/2000: http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm

D.2.6.1.2 The Competent Authority of a MS?	yes ☐	no ☐

D.3 DESCRIPTION OF THE IMP

D.3.1 Name of the medicinal product, where applicable[55]:

D.3.2 Code of the medicinal product, where applicable [56]:

D.3.3 ATC code, if officially registered[57]:

D.3.4 Pharmaceutical form (use standard terms):

D.3.4.1 This is a paediatric formulation? yes ☐ no☐

D.3.5 Maximum duration of treatment of a subject according to the protocol:

D.3.6 Dose allowed:

D.3.6.1 First dose used for first-in-human clinical trial (please specify: per day or total dose; units and route of administration):

D.3.6.2 Maximum dose allowed (specify: daily or total; units and route of administration):

D.3.7 Route of administration (use standard terms):

D.3.8 Name of each active substance (INN or proposed INN if available):

D.3.9 Other available names of each active substance (all shall be mentioned, if available)

D.3.9.1 CAS[58] Number

D.3.9.2 Current sponsor code(s)

D.3.9.3 Other descriptive names

D.3.9.4 EV substance code

D.3.9.5 Full molecular formula

D.3.9.6 Chemical/Biological description of the active substance

D.3.10 Strength (specify all strengths to be used):

D.3.10.1 Concentration unit:

D.3.10.2 Concentration type ("exact number", "range", "more than", "up to"):

D.3.10.3 Concentration (number).

D.3.11 Type of IMP

The IMP contains an active substance:

D.3.11.1 Of chemical origin yes ☐ no ☐

D.3.11.2 Of biological/biotechnological origin (other than Advanced Therapy investigational medicinal products – ATIMPs) yes ☐ no ☐

This is a/an:

[54] Committee for Medicinal Products for Human Use of the European Medicines Agency

[55] To be specified only when there is no trade name. This is the name routinely used by the sponsor to identify the IMP in the trial documentation (protocol, IB etc).

[56] To be specified only when there is no trade name. This is the code designated by the sponsor which represents the name routinely used by the sponsor to identify the IMP in the trial documentation. For example, a code may be used for a combination of medicinal products or medicinal products and medical devices.

[57] Available inside the SPC

[58] Chemical Abstracts Service (CAS)

D.3.11.3 Advanced Therapy Investigational Medicinal Product (ATIMP)	
D.3.11.3.1 Somatic cell therapy medicinal product [59]	
D.3.11.3.2 Gene therapy medicinal product [60]	
D.3.11.3.3 Tissue engineering medicinal product[61]	yes ☐ no ☐
D.3.11.3.4 ATIMP combination (involving a medical device?[62])	yes ☐ no ☐
D.3.11.3.5 The Committee for Advanced Therapies has issued a classification for this medicinal product	yes ☐ no ☐
	yes ☐ no ☐
D.3.11.3.5.1 If yes, please specify the respective classification and its reference number	yes ☐ no ☐
D.3.11.4 This is a combination which includes a medical device but does not involve an Advanced Therapy form?	yes ☐ no ☐
D.3.11.5 Radiopharmaceutical medicinal product?	yes ☐ no ☐
D.3.11.6 Immunological medicinal product (such as vaccine, allergen, immune serum)?	
D.3.11.7 Plasma-derived medicinal product?	yes ☐ no ☐
D.3.11.8 Extractive medicinal product?	
D.3.11.9 Recombinant medicinal product?	yes ☐ no ☐
D.3.11.10 Medicinal product containing genetically modified organisms (GMO)?	yes ☐ no ☐
D.3.11.10.1 The authorisation for contained GMO use or release has been granted	yes ☐ no ☐
D.3.11.10.2 It is pending	yes ☐ no ☐
D.3.11.11 Herbal medicinal product?	yes ☐ no ☐
D.3.11.12 Homeopathic medicinal product?	yes ☐ no ☐
D.3.11.13 Another type of medicinal product?	yes ☐ no ☐
If yes, specify:	yes ☐ no ☐
D.3. 12. Mode of action (*text*[63])	yes ☐ no ☐
D.3. 13. This is an IMP to be used in a first-in-human clinical trial	yes ☐ no ☐
D.3.13.1 If yes, the risk factors have been identified in accordance with the guidance FIH[64]:	yes ☐ no ☐
	yes ☐ no ☐

D.4. SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATIONS)

D.4.1 Origin of cells

[59] Also fill in section D.4 – Cell therapy, in accordance with Annex 1, part IV of amended Directive 2001/83/EC transposed through Minister of Public Health Order No. 615/01.06.2010

[60] Also fill in section D.5 – Gene therapy, in accordance with Annex 1, part IV of amended Directive 2001/83/EC, transposed through Minister of Public Health Order No. 615/01.06.2010

[61] Also fill in section D.6 – Tissue engineering medicinal product, as defined in Art. 2(1)(b) of Regulation 1394/2007/EC

[62] Also fill in section D.7

[63] The mode of action involves a brief presentation of the chemical, biochemical, immunological or biological means employed by the IMP in view of achieving the pharmaceutical action.

[64] Guideline on "Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products" (EMEA/CHMP/SWP/28367/2007, 19 July 2007)

D.4.1.1 Autologous	yes ☐	no ☐
D.4.1.2 Allogeneic	yes ☐	no ☐
D.4.1.3 Xenogeneic		
D.4.1.3.1 If yes, specify species of origin:	yes ☐	no ☐
D.4.2.Type of cells		
D.4.2.1 Stem cells	yes ☐	no ☐
D.4.2.2 Differentiated cells	yes ☐	no ☐
D.4.2.2.1 If yes, specify the type (e.g. keratinocytes, fibroblasts, chondrocytes, …)		
D.4.2.3 Others D.4.2.3.1 If others, specify:	yes ☐	no ☐

D.5. GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS		
D.5.1 Gene(s) of interest		
D.5.2 *In vivo* gene therapy	yes ☐	no ☐
D.5.3 *Ex vivo* gene therapy	yes ☐	no ☐
D.5.4 Type of gene transfer product		
D.5.4.1 Nucleic acid (e.g. plasmid)	yes ☐	no ☐
If yes, specify if:		
D.5.4.1.1 Naked	yes ☐	no ☐
D.5.4.1.2 Complexes	yes ☐	no ☐
D.5.4.2 Viral vector:	yes ☐	no ☐
D.5.4.2.1 If yes, specify the type: adenovirus, retrovirus, AAV,…:	yes ☐	no ☐
D.5.4.3 Others	yes ☐	no ☐
D.5.4.3.1 If others, specify:		
D.5.5 Genetically modified somatic cells:	yes ☐	no ☐
If yes, specify the cell origin:		
D.5.5.1 Autologous	yes ☐	no ☐
D.5.5.2 Allogeneic	yes ☐	no ☐
D.5.5.3 Xenogeneic	yes ☐	no ☐
D.5.5.3.1 If yes, specify species of origin:		
D.5.5.4 Other types of cells (haematopoietic stem cells, …)		

D.6 TISSUE ENGINEERED MEDICINAL PRODUCT

The indication which determines at this is a tissue engineered product as opposed to a Cell Therapy product is given in section E.1.1

D.6.1 Origin of cells		
D.6.1.1 Autologous	yes ☐	no ☐
D.6.1.2 Allogeneic	yes ☐	no ☐
D.6.1.3 Xenogeneic	yes ☐	no ☐
D.6.1.3.1 If yes, specify species of origin:		
D.6.2. Type of cells		
D.6.2.1 Stem cells	yes ☐	no ☐
D.6.2.2 Differentiated cells	yes ☐	no ☐
D.6.2.2.1 if yes, specify the type (e.g. keratinocytes, fibroblasts, chondrocytes, …)		
D.6.2.3 Others		
D.6.2.3.1 If others, specify:	yes ☐	no ☐

D.7 MEDICINAL PRODUCTS CONTAINING DEVICES (MEDICAL DEVICES, SCAFFOLDS ETC.)
D.7.1 Brief description of the device
D.7.2 Name of the device

D.7.3 It is implantable	yes ☐	no ☐

D.7.4 The product contains:

D.7.4.1 A medical device	yes ☐	no ☐
D.7.4.1.1 The medical device has a CE mark	yes ☐	no ☐
D.7.4.1.1.1 The notified body is:		
D.7.4.2 Biomaterial	yes ☐	no ☐
D.7.4.3 Scaffold	yes ☐	no ☐
D.7.4.4 Matrix	yes ☐	no ☐
D.7.4.5 Other	yes ☐	no ☐
D.7.4.5.1 If yes, please specify:		

D.8. INFORMATION ON PLACEBO (if relevant) (repeat as necessary)

D.8.1 Placebo is to be used: yes ☐ no ☐

D.8.2 Placebo no. (...)

D.8.3 Pharmaceutical form:

D.8.4 Route of administration:

D.8.5 This a placebo for the following IMP. The IMP number is to be specified in section D 1.1 (...)

D.8.5.1 Composition, apart from the active substance(s) :

D.8.5.2 It is otherwise identical to the IMP yes ☐ no ☐

D.8.5.2.1 If not, specify major ingredients:

D.9 SITE(S) WHERE THE QUALIFIED PERSON CERTIFIES THE BATCH RELEASE[65]

*This section is dedicated to finished IMPs**,** i.e. medicinal products randomised, packaged, labelled and released for use in the clinical trial. If there is more than one site or more than one IMP is certified, use extra pages and give each IMP its number from section D.1.1 or D.8.2. In the case of multiple sites, indicate the product certified by each site.*

D.9.1 Do **not** fill in section D.9.2 for an IMP which:

Has an MA in the EU **and**
Is sourced from the EU market **and**
Is used in the trial without modification (i.e. not over encapsulated) **and**
Packaging and labelling for local use are carried out in accordance with Art. 24 of Order of the Minister of Public Health No. 903/2006 (transposing Art. 9.2 of Directive 2005/28/EC).

If all requirements are met, check box ☐ and list the number(s) for each IMP, including placebo in sections D.1.1 and D.8.2 to which this applies. (....)

D.9.2 Who is responsible within the Community for the certification of the finished IMP?

This site is responsible for the certification of (list the number(s) of each IMP, including placebo from sections D.1.1 and D.8.2): **(..);**

Please tick the appropriate box……..

D.9.2.1 Manufacturer ☐

D.9.2.2 Importer ☐

D.9.2.3 Name of the organisation:

D.9.2.4 Address

D.9.2.4.1 Street:
D.9.2.4.2 City:
D.9.2.4.3 Post code:
D.9.2.4.4 Country:

D.9.2.5 Please give the marketing authorisation number:

D.9.2.5.1 If no authorisation, give the reasons:

[65] In accordance with the provisions of Art. 38, Annex 13 to Eudralex – Volume 4

*Where the IMP does not have an MA within the EU, but is supplied in bulk **and** the final packaging and labelling for local use are carried out according to Art. 24 of Order of the Minister of Public Health No. 903/2006, transposing Art. 9.2 of Directive 2005/28/EC, then specify the site where the IMP was finally certified for release by the Qualified Person for use in the clinical trial, section D.9.2*

E. GENERAL INFORMATION ON THE TRIAL

This section should be used to provide information on the aims, scope and design of the clinical trial. When the protocol includes a sub-study in a MS concerned, section E.2.3 must be filled in providing information about the sub-study. To identify it, check the sub-study box in the "Objective of the trial" question below.

E.1 MEDICAL CONDITION OR DISEASE UNDER INVESTIGATION

E.1.1 The medical condition(s) to be investigated shall be specified (free text):

E.1.1.1 Medical condition in easily understandable language

E.1.1.2 Therapeutic area

E.1.2 MedDRA version, level, term and classification code[67] (repeat as necessary):

E.1.3 Is any of the conditions under study a rare disease[68]? yes ☐ no ☐

E.2 TRIAL OBJECTIVES

E.2.1 Main objective:

E.2.2 Secondary objectives:

E.2.3 Is there a sub-study as well? yes ☐ no ☐

E.2.3.1 If yes, mention the full title, date and version of each sub-study and their objectives:

E.3 **MAIN INCLUSION CRITERIA** ***(list the most important)***

E.4 **MAIN EXCLUSION CRITERIA** ***(list the most important)***

E.5 END POINT(S)

E.5.1 Primary End Point (repeat, as necessary)[69]

E.5.1.1 Time point(s) of evaluation of this end point

E.5.2 Second End Point (repeat, as necessary)

E.5.2.1 Time point(s) of evaluation of this end point

E.6 SCOPE OF THE TRIAL – check all the boxes, where applicable		
E.6.1 Diagnosis	yes ☐	no ☐
E.6.2 Prophylaxis	yes ☐	no ☐
E.6.3 Therapy	yes ☐	no ☐
E.6.4 Safety	yes ☐	no ☐
E.6.5 Efficacy	yes ☐	no ☐
E.6.6 Pharmacokinetic	yes ☐	no ☐
E.6.7 Pharmacodynamic	yes ☐	no ☐
E.6.8 Bioequivalence	yes ☐	no ☐
E.6.9 Dose Response	yes ☐	no ☐
E.6.10 Pharmacokinetic	yes ☐	no ☐
E.6.11 Pharmacogenomis	yes ☐	no ☐
E.6.12 Pharmacoeconomic	yes ☐	no ☐
E.6.13 Other	yes ☐	no ☐
E.6.13.1 If other, please specify:		
E.7 TRIAL TYPE[66]		
E.7.1 Human pharmacology (Phase I)		
E.7.1.1 First administration to humans	yes ☐	no ☐
E.7.1.2 Bioequivalence study	yes ☐	no ☐
E.7.1.3 Others:		
E.7.1.3.1 If others, please specify		
E.7.2 Therapeutic exploratory agent (Phase II)	yes ☐	no ☐
E.7.3 Therapeutic confirmatory (Phase III)	yes ☐	no ☐
E.7.4 Therapeutic use (Phase IV)	yes ☐	no ☐

E.8 DESIGN OF THE TRIAL

E.8.1 Controlled:	yes ☐	no ☐
If yes, please specify:		
E.8.1.1 Randomised	yes ☐	no ☐
E.8.1.2 Open:	yes ☐	no ☐
E.8.1.3 Single blinded:	yes ☐	no ☐
E.8.1.4 Double blinded	yes ☐	no ☐
E.8.1.5 Parallel group:	yes ☐	no ☐
E.8.1.6 Cross over:	yes ☐	no ☐
E.8.1.7 Other:	yes ☐	no ☐
E.8.1.7.1 If yes, please specify:		
E.8.2 If controlled, please specify the comparator:		
E.8.2.1 Other medicinal product(s)	yes ☐	no ☐
E.8.2.2 Placebo	yes ☐	no ☐
E.8.2.3 Other	yes ☐	no ☐
E.8.2.3.1 If yes, please specify:		
E.8.2.4 Number of treatment arms in the trial		
E.8.3 Single trial site in Romania (see also section G):		
E.8.4 Multiple trial sites in Romania (see also section G):	yes ☐	no ☐
E.8.4.1 Number of trial sites anticipated in Romania		
E.8.5 Multiple EU Membre States:	yes ☐	no ☐
E.8.5.1 Number of trial sites anticipated in the EEA		
E.8.6 Trial involving sites outside the EEA:		
E.8.6.1 Trial being conducted both within and outside the EEA:	yes ☐	no ☐
E.8.6.2 Trial being conducted completely outside of the EEA:	yes ☐	no ☐
E.8.6.3 If the answer to E.8.6.1 or E.8.6.2 is yes, please specify the regions in trial sites are planned (repeat, as necessary)	yes ☐	no ☐
E.8.6.4 If the answer to E.8.6.1 or E.8.6.2 is yes, please specify the number of sites anticipated outside the EEA E.8.7 Trial having an independent data monitoring committee	yes ☐	no ☐
E.8.8 Definition of the end of trial; if it is the last visit of the last subject, please enter "LVLS". It this is not LVLS, please provide the following:		
E.8.9 Initial estimate of the duration of the trial[67] (years, months, days)		
E.8.9.1 In Romania	years months	days
E.8.9.2 In all countries concerned	years months	days
E.8.10 date proposed for start of recruitment		
E.8.10.1 In Romania		

[67] From the first inclusion to the last visit of the last subject

E.8.10.2 In any country

F. TRIAL SUBJECTS (POPULATION OF TRIAL SUBJECTS)

F.1 AGE RANGE		
F.1.1 Under 18 years old	yes ☐	no ☐
If yes, specify the estimated number of subjects planned in each age range for the entire trial:		
	Approximate number of patients[68]	
F.1.1.1 In utero	( ) yes ☐	no ☐
F.1.1.2 Preterm newborn infants (up to 37 gestational weeks)	( ) yes ☐	no ☐
F.1.1.3 New-borns (0-27 days)	( ) yes ☐	no ☐
F.1.1.4 Infants and toddlers (28 days-23 months)	( ) yes ☐	no ☐
F.1.1.5 Children (2-11 years old)	( ) yes ☐	no ☐
F.1.1.6 Adolescents (12-17 years old)	( ) yes ☐	no ☐
F.1.2 Adults (18-65 years old)	( ) yes ☐	no ☐
F.1.3 Elderly (over 65 years old)	( ) yes ☐	no ☐

F.2 GENDER
F.2.1 Female ☐
F.2.2 Male ☐

F.3 TRIAL SUBJECTS		
F.3.1 Healthy volunteers	yes ☐	no ☐
F.3.2 Patients	yes ☐	no ☐
F.3.3 Specific vulnerable populations	yes ☐	no ☐
F.3.3.1 Women of childbearing potential	yes ☐	no ☐
F.3.3.2 Women of childbearing potential using contraceptives	yes ☐	no ☐
F.3.3.3 Pregnant women	yes ☐	no ☐
F.3.3.4 Nursing women	yes ☐	no ☐
F.3.3.5 Emergency situation	yes ☐	no ☐
F.3.3.6 Subjects incapable of giving consent personally	yes ☐	no ☐
F.3.3.6.1 If yes, please specify	yes ☐	no ☐
F.3.3.7. Others:	yes ☐	no ☐
F.3.3.7.1 If yes, specify:	yes ☐	no ☐

[68] These numbers are initial estimates. Applicants are not required to update this information nor do they constitute an authorisation or restriction on the inclusion of these numbers of patients in the trial. The numbers of subjects whose inclusion is authorised are those set out in the authorised version of the protocol, or subsequent authorised amendments

F.4 PLANNED NUMBER OF SUBJECTS TO BE INCLUDED:

F.4.1 In Romania:	( )
F.4.2 For multinational trials:	
F.4.2.1 In the EEA:	( )
F.4.2.2 In the whole clinical trial:	( )

F.5 PLANS FOR TREATMENT OR CARE AFTER A SUBJECT HAS ENDED HIS/HER PARTICIPATION IN THE TRIAL

Please specify *(text*):

G. PROPOSED CLINICAL TRIAL SITE(S)/INVESTIGATORS IN ROMANIA

G1. Co-ordinating investigator *(for multicentre trial)* and/or principal investigator *(for single centre trial)*

G.1.1 First name

G.1.2 Middle name:

G.1.3 Surname:

G.1.4 Qualification (MD….)

G.1.5 Address

G.1.5.1 Name of the institution

G.1.5.2 Department of the institution

G.1.5.3 Street

G.1.5.4 City

G.1.5.5 Post code

G.1.5.6 Country

G.1.6 Telephone number:

G.1.7 Fax number:

G.1.8 E-mail:

G2. PRINCIPAL INVESTIGATORS *(for multicentre trials; where necessary, use additional forms)*

G.2.1 First name:

G.2.2 Middle name, if required:

G.2.3 Surname:

G.2.4 Qualification (MD….)

G.2.5 Address

G.2.5.1 Street

G.2.5.2 City

G.2.5.3 Post code

G.2.5.4 Country

G.2.6 Telephone number

G.2.7 Fax number

G.2.8 E-mail

G3. CENTRAL TECHNICAL FACILITY TO BE USED IN THE CONDUCT OF THE TRIAL

Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised (repeat as needed for multiple participant organisations)

G.3.1 Organisation:
G.3.2 Department:
G.3.3 Name of contact person:
G.3.3.1 First name
G.3.3.2 Middle name
G.3.3.3 Surname
G.3.4 Address
G.3.4.1 Street
G.3.4.2 City
G.3.4.3 Post code
G.3.4.4 Country
G.3.5 Telephone number
G.3.6 Fax number
G.3.7 E-mail
G.3.8 Duties subcontracted:

G4. NETWORKS TO BE INVOLVED IN THE TRIAL

(e.g. Paediatric networks involved in the trial)

G.4.1 Organisation:

G.4.2 Name of the contact person:

G.4.2.1 First name:

G.4.2.2 Middle name:

G.4.2.3 Surname:

G.4.3 Address:

G.4.3.1 Street:

G.4.3.2 City:

G.4.3.3 Post code:

G.4.3.4 Country:

G.4.4 Telephone number:

G.4.5 Fax number:

G.4.6 E-mail:

G.4.7 Activities carried out by the network:

G5. ORGANISATIONS TO WHOM THE SPONSOR HAS TRANSFERRED PART OF THE TRIAL RELATED DUTIES AND FUNCTIONS (repeat as needed for multiple organisations)

G.5.1 **Has the sponsor transferred any major or all the sponsor's trial related duties and functions to another organisation or third party?** yes ☐ no ☐

Repeat as needed for multiple organisations:

G.5.1.1 Organisation:

G.5.1.2 Department:

G.5.1.3 Name of the contact person::

G.5.1.3.1 First name:

G.5.1.3.2 Middle name:

G.5.1.3.3 Surname:

G.5.1.4 Address:

G.5.1.4.1 Street:

G.5.1.4.2 City:

G.5.1.4.3 Post code:

G.5.1.4.4 Country:

G.5.1.5 Telephone number:

G.5.1.6 Fax number:

G.5.1.7 E-mail:

G.5.1.8 All sponsor's duties:	yes ☐	no ☐
G.5.1.6 Monitoring:	yes ☐	no ☐
G.5.1.7 Regulatory (e.g. preparation of applications to be submitted to the CA and the EC)	yes ☐	no ☐
G.5.1.8 Investigator recruitment	yes ☐	no ☐
G.5.1.9 Treatment randomisation – IVRS [69]	yes ☐	no ☐
G.5.1.10 Data management	yes ☐	no ☐
G.5.1.11 Electronic capture of data	yes ☐	no ☐
G.5.1.12 SUSAR reporting	yes ☐	no ☐
G.5.1.13 Quality assurance auditing	yes ☐	no ☐
G.5.1.14 Statistical analysis	yes ☐	no ☐
G.5.1.15 Medical writing	yes ☐	no ☐
G.5.1.16 Other duties sub-contracted:	yes ☐	no ☐

G.5.1.16.1 if yes, specify:

[69] Interactive Voice Response System: commonly used for the randomisation of treatment and controlling the shipment of stock of product

H. COMPETENT AUTHORITY/ETHICS COMMITTEE CONCERNED BY THIS REQUEST

H.1 TYPE OF APPLICATION

If this application is addressed to the NAMMD, please tick the Ethics Committee box and give information on the Ethics Committee and vice versa

H.1.1 NAMMD ☐

H.1.2 Ethics Committee ☐

H.2 INFORMATION ON THE NAMMD/EC

H.2.1 Name:

H.2.2 Address:

H.2.2.1 Street:

H.2.2.2 City:

H.2.2.3 Post code:

H.2.2.4 Country:

H.2.2.3 Date of submission:

H.3 AUTHORISATION/OPINION

H.3.1 To be requested ☐

H.3.2 Pending ☐

H.3.3 Given ☐

If 'Given', specify:

H.3.3.1 Date of authorisation/opinion:

H.3.3.2 Authorisation accepted/opinion favourable ☐

H.3.3.3 Authorisation not accepted/opinion not favourable ☐

If the authorisation is not accepted/opinion is not favourable, give:
H.3.3.3.1 The reasons:

H.3.3.3.2 The eventual anticipated date of resubmission:

I. SIGNATURE AND PRINT NAME OF THE APPLICANT IN ROMANIA

I.1 I hereby confirm that/confirm on behalf of the sponsor (*delete which is not applicable*) that

- The above information given on this application is correct;
- The attached documents accurately describe the information available
- The trial will be conducted according to the protocol
- The clinical trial will be conducted and SUSARs and result-related information will be reported in accordance with regulations in force

I.2 APPLICANT OF THE REQUEST FOR THE NAMMD (in accordance with the declaration in section C.1):
I.2.1 Date:
I.2.2 Signature[70]:
I.2.3 Print name:
I.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (in accordance with the declaration in section C.2):
I.3.1 Date:
I.3.2 Signature[71]:
I.3.3 Print name:

ANNEX 2
to guideline

FORM FOR NOTIFICATION TO THE NAMMD AND THE EC OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

(in accordance with section III.7.b a of the *Detailed guidance for the request to the competent authority for authorisation of a clinical trial with a medicinal product for human use, the notification of substantial amendments and declaration of end of a clinical trial*[72])

To be filled in by the NAMMD/EC:

Date of receipt:	**Grounds for non-acceptance/negative opinion:** **Date:**	☐
Date of start of procedure:	***Authorisation/Positive opinion*** **Date:**	☐
NAMMD registration number of the trial: **Ethics Committee registration number of the trial :**	***Application for amendment withdrawal*** **Date:**	☐

To be filled in by the applicant:
This form is meant to be used both for a request to the NAMMD for authorisation of a substantial amendment and to the Ethics Committee for its opinion on a substantial amendment. The relevant purpose is to be indicated in section A.

[70] The application to the NAMMD only is to be signed by the applicant
[71] The application to the Ethics Committee is to be signed by the applicant
[72] OJ, C82, 30.3.2010, p. 1; hereinafter "Detailed guideline CT-1"

A. TYPE OF NOTIFICATION

A.1 Name of the Member State where the notification of the substantial amendment is being submitted:	
A.2 Notification for authorisation to the NAMMD:	☐
A.3 Notification for an opinion to the Ethics Committee:	☐

B. DATA CONCERNING TRIAL IDENTIFICATION (*in case the amendment concerns several trials, this section of this form is to be repeated, as necessary)*

B.1. Does the substantial amendment concern several trials for the same IMP?[73] yes ☐ no ☐
B.1.1 If yes, repeat this section, as necessary.

B.2 EudraCT number:
B.3 Full title of the trial:
B.4 Sponsor's protocol code number, version and date:

C. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1 Sponsor
C.1.1 Organisation:
C.1.2 Name of the contact person:
C.1.3 Address:
C.1.4 Telephone number:
C.1.5 Fax number:
C.1.6 E-mail**:**

C.2 Legal representative[74] of the sponsor in the European Union for this trial (if different from the sponsor)
C.2.1 Organisation
C.2.2 Name of the contact person
C.2.3 Address
C.2.4 Telephone number
C.2.5 Fax number
C.2.6 E-mail

D. APPLICANT IDENTIFICATION (please tick the appropriate box)

D.1 Request for the NAMMD	
D.1.1 Sponsor	☐
D.1.2 Legal representative of the sponsor	☐
D.1.3 Person or organisation authorised by the sponsor to make the application.	☐
D.1.4 Fill in below:	
D.1.4.1 Organisation:	
D.1.4.2 Name of the contact person:	
D.1.4.3 Address:	
D.1.4.4 Telephone number:	
D.1.4.5 Fax number:	
D.1.4.6 E-mail:	

[73] In accordance with Section III.7. of the detailed guideline CT-1

[74] In accordance with Art. 67 of Minister of Public Health Order No. 904/2006, transposing Art. 19 of Directive 2001/20/EC

D.1 Request for the Ethics Committee	
D.2.1 Sponsor	☐
D.2.2 Legal representative of the sponsor	☐
D.2.3 Person or organisation authorised by the sponsor to make the application	☐
D.2.4 Investigator in charge for the application, if required [75]	
- Co-ordinating investigator (for multicentre trial)	☐
- Principal investigator (for single centre trial):	☐
D.2.5 Fill in below:	
D.2.5.1 Organisation:	
D.2.5.2 Name of the contact person:	
D.2.5.3 Address:	
D.2.5.4 Telephone number:	
D.2.5.5 Fax number:	
D.2.5.6 E-mail:	

E. IDENTIFICATION DATA OF THE SUBSTANTIAL AMENDMENT

E.1 Sponsor's substantial amendment code number, version and date for the clinical trial concerned:		
E.2. Type of substantial amendment		
E.2.1 Amendment to information in the application form	***yes*** ☐	***no*** ☐
E.2.2 Amendment to the protocol	yes ☐	no ☐
E.2.3 Amendment to other documents attached to initial application form	yes ☐	no ☐
E.2.3.1 If yes, please specify:		
E.2.4 Amendment to other information/documents:	yes ☐	no ☐
E.2.4.1 *If yes, please specify:*		
***E.2.5 This amendment concerns mainly urgent safety measures already implemented*[76]**	yes ☐	no ☐
	yes ☐	no ☐
E.2.6 This amendment is to notify a temporary halt of the trial[77]	yes ☐	no ☐
E.2.7 This amendment is to request the restart of the trial [78]		

E.3 Grounds for the substantial amendment:

[75] In accordance with national legislation
[76] In accordance with section III.9 of the detailed guideline CT-1
[77] In accordance with section III.10 of the detailed guideline CT-1
[78] In accordance with section III.10 of the detailed guideline CT-1

E.3.1 Changes in safety or integrity of trial subjects	yes ☐	
E.3.2 Changes in interpretation of scientific documents/value of the trial	yes ☐	**no ☐**
E.3.3 Changes in IMP quality	yes ☐	**no ☐**
E.3.4 Changes in the management or conduct of the trial	yes ☐	**no ☐**
E.3.5 Change/Addition of principal investigator(s)/coordinating investigator(s)	yes ☐	**no ☐**
E.3.6 Change/Addition of investigational site(s)		
E.3.7 Other change		**no ☐**
E.3.7.1 *If yes, please specify*		
E.3.8 Other case	yes ☐	**no ☐**
E.3.8.1 If yes, please specify		**no ☐**

E.4 Information on temporary halt of the trial[79]		
E.4.1 Date of temporary halt (DD/MM/YYYY)		
E.4.2 Recruitment has been stopped	yes ☐	no ☐
E.4.3 Treatment has been stopped	yes ☐	no ☐
E.4.4 Number of patients still receiving treatment at the time of the temporary halt in Romania		
E.4.5 Brief description (text) - Justification of temporary halt of the trial - Proposed management of patients still receiving treatment at the time of the trial temporary halt (text) - Consequences of the temporary halt for the assessment of the outcomes and for overall risk-benefit assessment of the investigational medicinal product (text).		

F. DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[80] (*text*):

New and previous wording in "track changes" modus	**New wording**	**Comments/Explanations/Grounds for substantial amendment**

[79] In accordance with section III.10 of the detailed guideline CT-1

[80] In accordance with section III.7.c of the detailed guideline CT-1. The sponsor may submit the required documentation on a separate sheet

G. CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN ROMANIA

G.1 Type of change
G.1.1 Addition of a new investigation site
G.1.1.1 Principal investigator (fill in below:)
G.1.1.1.1 First name
G.1.1.1.2 Middle name, if applicable
G.1.1.1.3 Name
G.1.1.1.4 Qualification (MD, ...)
G.1.1.1.5 Address
G.1.2 Removal of an existing trial site
G.1.2.1. Principal investigator (fill in below:)
G.1.2.1.1 First name
G.1.2.1.2 Middle name, if applicable
G.1.2.1.3 Name
G.1.2.1.4 Qualification (MD, ...)
G.1.2.1.5 Address
G.1.3 Change of coordinating investigator (please fill in below, on the new coordinating investigator)
G.1.3.1 First name
G.1.3.2 2 Middle name, if applicable
G.1.3.3 Name
G.1.3.4 Qualification (MD, ...)
G.1.3.5 Address
G.1.3.6 Name of the previous co-ordinating investigator
G.1.4 Change of the principal investigator at an existing investigation site (please fill in below on the principal investigator)
G.1.4.1 First name
G.1.4.2 2 Middle name, if applicable
G.1.4.3 Name
G.1.4.4 Qualification (MD, ...)
G.1.4.5 Address
G.1.4.6 Name of previous coordinating investigator

H. CHANGE OF INSTRUCTIONS TO THE NAMMD FOR FEEDBACK TO SPONSOR

H.1 Change of e-mail contact for feedback on the application*

H.2 Change to request to receive an .xml copy in format of data on the application for clinical trial authorisation (ACTA)		
H.2.1 Request for a .xml file copy of ACTA data saved in the EudraCT?	**yes** ☐	**no** ☐
H.2.1.1. If yes, specify the e-mail address(es) where this should be sent (up to 5 addresses)	**yes** ☐	**no** ☐
H.2.2 Request for transmission of this copy via password protected link(s) [81]? If no, the .xml file is to be transmitted via less secure e-mail link(s).	**yes** ☐	**no** ☐
H.2.3 Request for stop of messages to an e-mail address for which they had been previously requested?		
H.2.3.1 If yes, please provide the e-mail address(es) to which feedback should no longer be sent	**yes** ☐	**no** ☐
(*This issue only comes into effect from the time moment which the request is processed in the EudraCT)		

I. LIST OF DOCUMENTS APPENDED TO THE NOTIFICATION FORM (in accordance with subchapter III.7 of the detailed guideline CT-1)

Please submit only relevant documents and/or when applicable, make clear references to the ones already submitted. Make clear references to any changes on separate pages and submit old and new texts. Tick the appropriate box(es):

I.1 Cover letter	☐
I.2 Extract from the amended document in accordance with Section 3.7 of the detailed guideline CT-1 (if not included in Part F of this form)	
I.3 Entire new version of the document[82]	
I.4 Supporting information for the amendment	
I.5 Revised .xml document file and copy of the initial application form, with amended data highlighted	☐
I.6 Comments on any novel aspects of the amendment, if needed:	☐

J. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

J. 1 I hereby declare that/declare on behalf of the sponsor that (delete which is not applicable)

- **The hereby submitted information is correct;**
- **The trial will be conducted in accordance with the protocol, national regulations and Good Clinical Practice rules;**
- **I consider it reasonable for the proposed amendment to be undertaken;**

J.2 APPLICANT FOR THE REQUEST TO THE NAMMD (in accordance with Section D.1): ☐

[81] In this case, an EudraLink account (for further details, go to https://eudract.ema.europa.eu/)

[82] In accordance with section III.7.c of the detailed guideline CT-1

J.2.1 Signature[83]:
J.2.2 Print name:
J.2.3 Date:

J.3 APPLICANT FOR THE REQUEST TO THE ETHICS COMMITTEE (in accordance with Section C.2): ☐
J.3.1 Signature[84]:
J.3.2 Print name:
J3.3 Date:

ANNEX 3.
to guideline

FORM FOR NOTIFICATION OF THE END OF A CLINICAL TRIAL OF A MEDICINAL PRODUCT FOR HUMAN USE TO THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES (NAMMMD) AND THE ETHICS COMMITTEE (EC)

(**in accordance with section IV.2.1 of the** *Detailed guidance for the request to the competent authority for authorisation of a clinical trial with a medicinal product for human use, the notification of substantial amendments and declaration of end of a clinical trial*[85])

To be filled by the NAMMD/EC:

Date of receipt of the notification:	**NAMMD trial registration number:** **Ethics committee trial registration number:**

To be filled in by the applicant:

A. MEMBER STATE WHERE THE DECLARATION IS BEING SUBMITTED:

B. TRIAL IDENTIFICATION DATA

B.1 EudraCT number:	(..)
B.2 Protocol code given by the sponsor:	(..)
B.3 Complete name of the trial:	

C. APPLICANT IDENTIFICATION DATA (fill in the appropriate box)

C1. Declaration addressed to the NAMMD	☐

[83] The application submitted solely to the NAMMD should be signed by the applicant
[84] Application addressed to the Ethics Committee should be signed by the applicant to the EC
[86] OJ, C82, 30.3.2010, p. 1; hereinafter "Detailed guideline CT-1"

C.1.1 Sponsor C.1.2 Legal representative of the sponsor: C.1.3 Name of person/organisation authorised by the sponsor to make the application. C.1.4 In this case, fill in: C.1.4.1 Organisation: C.1.4.2 Name of the contact person: C.1.4.3 Address: C.1.4.4 Telephone number: C.1.4.5 Fax number: C.1.4.6 E-mail:	☐ ☐ ☐

C2. Application for the Ethics Committee	☐
C.2.1 Sponsor C.2.2 Legal representative of the sponsor: C.2.3 Person or organisation authorised by the sponsor to make the application. C.2.4 Investigator in charge of the application, if needed[86]: - Coordinator investigator (for multicentre trials) - Principal investigator (for single centre trials) C.2.5 In this case, fill in below: C.2.5.1 Organisation: C.2.5.2 Name of the contact person: C.2.5.3 Address : C.2.5.4 Telephone number: C.2.5.5 Fax number: C.2.5.6 E-mail:	 ☐ ☐ ☐ ☐ ☐

D. END OF TRIAL

D.1 Date of end of trial in all interested states
D.1.1 (DD/MM/YYYY)

D.2 This is an early termination of the trial[3]	yes ☐ no ☐
D.2.1 If yes, specify the date: D.2.2 Brief description in an Annex (*text*) D.2.2.1 Justification of early termination of the trial D.2.2.2 Number of patients still undergoing treatment at the time of the trial early termination in Romania and their proposed management D.2.2.3 Consequences of early termination for the evaluation of the results and for the overall risk/benefit assessment of the IMP	(DD/MM/YYYY)

E. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE:

[87] In accordance with national legislation
[88] In accordance with subchapter IV.2 of the detailed guideline CT-1

E.1 I hereby confirm that/on behalf of the sponsor confirm that (delete which is not applicable):

- The above information given in this declaration is correct
- that the clinical trial summary report will be submitted to the NAMMD, within the applicable deadlines, in accordance with NAMMD guidelines transposing the recommendations of the Ethics Committee.[87]

E.2 APPLICANT TO THE NAMMD (in accordance with section C1**):** ☐

E.2.1 Date:
E.2.2 Signature:
E.2.3 Print name:

E.3 APPLICANT TO THE ETHICS COMMITTEE (in accordance with section C2): ☐

E.3.1 Date:
E.3.2 Signature:
E.3.3 Print name:

[89] In accordance with subchapter IV.3 of the detailed guideline CT-1