

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance)

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APPLICATION DOSSIER FOR THE INITIAL APPLICATION

- A. INTRODUCTION AND GENERAL PRINCIPLES
 - 1. The sponsor shall, where appropriate, refer to any previous applications...
 - 2. Where a clinical trial has more than one sponsor, detailed...
 - 3. The application shall be signed by the sponsor or a...
 - 4. The application dossier for an application limited to Part I...
 - 5. Without prejudice to Article 26, the application dossier for an...
- B. COVER LETTER
 - 6. The cover letter shall specify the EU trial number and...
 - 7. However, in the cover letter it is not necessary to...
 - 8. The cover letter shall indicate where the information listed in...
 - 9. The cover letter shall indicate if the clinical trial is...
 - 10. The cover letter shall indicate if the methodology of the...
 - 11. The cover letter shall indicate the location in the application...
 - 12. In the case of a resubmission, the cover letter shall...
- C. EU APPLICATION FORM
 - 13. The EU application form, duly completed.
- D. PROTOCOL
 - 14. The protocol shall describe the objective, design, methodology, statistical considerations,...
 - 15. The protocol shall be identified by:
 - 16. The protocol shall, when possible, be written in an easily...

17. The protocol shall at least include:
 18. If a clinical trial is conducted with an active substance...
 19. With regard to the notification of adverse events, the protocol...
 20. The protocol shall describe the procedures for:
 21. In case the sponsor intends to submit a single safety...
 22. Issues regarding labelling and the unblinding of investigational medicinal products...
 23. The protocol shall be accompanied by the Charter of the...
 24. The protocol shall be accompanied by a synopsis of the...
- E. INVESTIGATOR'S BROCHURE (IB)
25. An IB, which has been prepared in accordance with the...
 26. The purpose of the IB is to provide the investigators...
 27. The information in the IB shall be presented in a...
 28. If the investigational medicinal product is authorised, and is used...
 29. For a multinational clinical trial where the medicinal product to...
 30. If the IB is not an SmPC, it shall contain...
- F. DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR...
31. As regards documentation relating to GMP compliance, the following shall...
 32. No documentation needs to be submitted where the investigational medicinal...
 33. If the investigational medicinal product is not authorised, and does...
 34. In all other cases, a copy of the authorisation referred...
 35. For processes related to investigational medicinal products set out in...
- G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)
36. The IMPD shall give information on the quality of any...
 - 1.1. Data relating to the investigational medicinal product
 - Introduction
 37. Regarding data, the IMPD may be replaced by other documentation...
 38. Each section of the IMPD shall be prefaced with a...
 39. The information in the IMPD shall be concise. The IMPD...
 - Quality data
 40. Quality data shall be submitted in a logical structure such...
 - Non-clinical pharmacology and toxicology data
 41. The IMPD shall also contain summaries of non-clinical pharmacology and...
 42. Non-clinical pharmacology and toxicology data shall be submitted in a...
 43. The IMPD shall provide a critical analysis of the data,...
 44. The IMPD shall contain a statement of the good laboratory...
 45. The test material used in toxicity studies shall be representative...
 - Data from previous clinical trials and human experience
 46. Data from previous clinical trials and human experience shall be...
 47. This section shall provide summaries of all available data from...
 - Overall risk and benefit assessment
 48. This section shall provide a brief integrated summary that critically...

49. Where appropriate, safety margins shall be discussed in terms of...
- 1.2. Simplified IMPD by referring to other documentation
 50. The applicant may refer to other documentation submitted alone or...
Possibility of referring to the IB
 51. The applicant may either provide a stand-alone IMPD or cross-refer...
Possibility of referring to the SmPC
 52. The applicant may submit the version of the SmPC valid...
 53. If the investigational medicinal product is defined in the protocol...
- 1.3. IMPD in cases of placebo
 54. If the investigational medicinal product is a placebo, the information...
- H. AUXILIARY MEDICINAL PRODUCT DOSSIER
 55. Without prejudice to Article 65, the documentation requirements set out...
- I. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)
 56. If available, a copy of the summary of scientific advice...
 57. If the clinical trial is part of an agreed PIP,...
- J. CONTENT OF THE LABELLING OF THE INVESTIGATIONAL MEDICINAL PRODUCTS
 58. A description of the content of the labelling of the...
- K. RECRUITMENT ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)
 59. Unless described in the protocol, a separate document shall describe...
 60. Where the recruitment of subjects is done through advertisement, copies...
- L. SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE (INFORMATION...)
 61. All information given to the subjects (or, where applicable, to...
 62. A description of procedures relating to informed consent for all...
 63. In the cases set out in paragraph 62, the information...
- M. SUITABILITY OF THE INVESTIGATOR (INFORMATION PER MEMBER STATE CONCERNED)
 64. A list of the planned clinical trial sites, the name...
 65. Description of the qualification of the investigators in a current...
 66. Any conditions, such as economic interests and institutional affiliations, that...
- N. SUITABILITY OF THE FACILITIES (INFORMATION PER MEMBER STATE CONCERNED)
 67. A duly justified written statement on the suitability of the...
- O. PROOF OF INSURANCE COVER OR INDEMNIFICATION (INFORMATION PER MEMBER STATE...)
 68. Proof of insurance, a guarantee, or a similar arrangement shall...
- P. FINANCIAL AND OTHER ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)
 69. A brief description of the financing of the clinical trial....

- 70. Information on financial transactions and compensation paid to subjects and...
- 71. Description of any other agreement between the sponsor and the...
- Q. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)...
- 72. Proof of payment shall be submitted, if applicable.
- R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION...
- 73. A statement by the sponsor or his or her representative...

ANNEX II

APPLICATION DOSSIER FOR SUBSTANTIAL MODIFICATION

- A. INTRODUCTION AND GENERAL PRINCIPLES
 - 1. Where a substantial modification concerns more than one clinical trial...
 - 2. The application shall be signed by the sponsor or a...
- B. COVER LETTER
 - 3. A cover letter with the following information:
- C. MODIFICATION APPLICATION FORM
 - 4. The modification application form, duly completed.
- D. DESCRIPTION OF THE MODIFICATION
 - 5. The modification shall be presented and described as follows:
 - 6. The new version of the document shall be identified by...
- E. SUPPORTING INFORMATION
 - 7. Where applicable, additional supporting information shall at least include:
- F. UPDATE OF EU APPLICATION FORM
 - 8. If a substantial modification involves changes to entries on the...
- G. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)...
- 9. Proof of payment shall be submitted, if applicable.

ANNEX III

SAFETY REPORTING

- 1. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE...
 - 1. The investigator does not need to actively monitor subjects for...
- 2. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) BY THE...
 - 2.1. Adverse Events and Causality
 - 2. Medication errors, pregnancies and uses outside what is foreseen in...
 - 3. In determining whether an adverse event is an adverse reaction,...
 - 4. In the absence of information on causality provided by the...

- 2.2. Expectedness, unexpectedness and the RSI
 5. In determining whether an adverse event is unexpected, consideration shall...
 6. The expectedness of an adverse reaction shall be set out...
 7. The RSI shall be contained in the SmPC or the...
 8. The RSI may change during the conduct of a clinical...
 9. If information on expectedness has been provided by the reporting...
- 2.3. Information for the reporting of SUSARs
 10. The information shall at least include:
 11. In addition, in order to properly process the report electronically,...
- 2.4. Follow-up reports of SUSARs
 12. If the initial report of a SUSAR referred to in...
 13. The clock for initial reporting (day 0 = Di 0)...
 14. If significant new information on an already reported case is...
 15. If the initial report of a SUSAR referred to in...
 16. In cases where a SUSAR turns out to be fatal...
- 2.5. Unblinding treatment allocation
 17. The investigator shall only unblind the treatment allocation of a...
 18. When reporting a SUSAR to the Agency, the sponsor shall...
 19. If an event is potentially a SUSAR the blind shall...
 20. Unblinded information shall be accessible only to persons who need...
 21. However, for clinical trials carried out in high morbidity or...
 22. If following unblinding, an event turns out to be a...
3. ANNUAL SAFETY REPORTING BY THE SPONSOR
 23. The report shall contain, in an appendix, the RSI in...
 24. The RSI in effect at the start of the reporting...
 25. If there are significant changes to the RSI during the...

ANNEX IV

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

The summary of the results of the clinical trial shall...

- A. CLINICAL TRIAL INFORMATION:
- B. SUBJECT DISPOSITION:
- C. BASELINE CHARACTERISTICS:
- D. END POINTS:
- E. ADVERSE EVENTS:
- F. ADDITIONAL INFORMATION:

ANNEX V

CONTENT OF THE SUMMARY OF THE RESULTS
OF THE CLINICAL TRIAL FOR LAYPERSONS

The summary of the results of the clinical trial for...
Clinical trial identification (including title of the trial, protocol
number,...

ANNEX VI

LABELLING OF INVESTIGATIONAL MEDICINAL
PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

- A. UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS
- A.1. General rules
1. The following particulars shall appear on the immediate and the...
 2. Symbols or pictograms may be included to clarify certain information...
 3. The address and telephone number of the main contact shall...
- A.2. Limited labelling of immediate packaging
- A.2.1. Immediate and outer packaging provided together
4. When the product is provided to the subject or the...
- A.2.2. Small immediate packaging
5. If the immediate packaging takes the form of blister packs...
- B. UNAUTHORISED AUXILIARY MEDICINAL PRODUCTS
6. The following particulars shall appear on the immediate and the...
- C. ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS
7. In accordance with Article 67(2), the following particulars shall appear...
- D. REPLACING OF INFORMATION
8. The particulars listed in sections A, B and C, other...
 9. The particulars referred to in the following points shall not...

ANNEX VII

CORRELATION TABLE

- (1) [OJ C 44, 15.2.2013, p. 99.](#)
- (2) Position of the European Parliament of 3 April 2014 (not yet published in the Official Journal) and decision of the Council of 14 April 2014.
- (3) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use ([OJ L 121, 1.5.2001, p. 34.](#))
- (4) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products ([OJ L 18, 22.1.2000, p. 1.](#))
- (5) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use ([OJ L 311, 28.11.2001, p. 67.](#))
- (6) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency ([OJ L 136, 30.4.2004, p. 1.](#))
- (7) Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers ([OJ L 55, 28.2.2011, p. 13.](#))
- (8) Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data ([OJ L 281, 23.11.1995, p. 31.](#))
- (9) Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data ([OJ L 8, 12.1.2001, p. 1.](#))
- (10) [OJ C 253, 3.9.2013, p. 10.](#)