

REGULATION ON
CONDITIONS AND MANNER OF CLINICAL TESTING OF MEDICINAL PRODUCTS,
PROCEDURE AND CONTENTS OF DOCUMENTATION FOR AUTHORISING CLINICAL
TRIALS OF MEDICINAL PRODUCTS
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I INTRODUCTORY PROVISIONS

Article 1

This Regulation determines the conditions and manner of clinical testing of medicinal products, as well as the procedure and content of documentation for authorising clinical trials of medicinal products, for medicinal products for human use.

Article 2

The terms used in this Regulation shall, within the meaning of this Regulation, have the following meanings:

1) **clinical trials of medicinal products** are studies performed on human subjects with the aim of determining or verifying the clinical, pharmacological and pharmacodynamic effect of one or more medicinal products being studied, identifying all adverse reactions to one of more medicinal products being studied, with the aim of studying the resorption, distribution, metabolism and excretion of one or more medicinal products, determining the safety of a medicinal product and its efficiency.

Clinical trials of medicinal products also encompass post-marketing interventional trials of medicinal products, as well as post-marketing non-interventional trials of medicinal products;

2) **post-marketing interventional trials of medicinal products** are studies in which medicinal products are administered in accordance with the conditions laid down in the marketing authorisation for the medicinal product, and which requires additional diagnostic procedures, as well as monitoring procedures defined by the protocol on the clinical testing of the medicinal product;

3) **post-marketing non-interventional trials of medicinal products** (pharmacoepidemiological trials) are studies in which the medicinal product is administered in accordance with the conditions laid down in the marketing authorisation for the medicinal product in which the selection of patients is not determined in advance by the protocol of clinical testing but is part of the ongoing practice of normal manner of treatment, wherein the dispensation of the medicinal product is clearly distinct from the decision to involve the patient in the study. No additional diagnostic procedures or monitoring procedures are applied, and the results obtained are analysed using epidemiological methods.

4) **medicinal products under clinical trial** are the pharmaceutical forms of the active substances being studied or a placebo with which the substance being studied is compared, as well as medicinal products which have marketing authorisations where their form or packaging has been altered, or where they are used in a manner other than that approved by the authorisation, where a medicinal product is tested for use in a new indication or where a medicinal product is used in order to obtain new information about the approved use of the medicinal product;

5) **Good Clinical Practice (GCP)** in clinical trials is a system of directives for ensuring good quality of planning and implementing clinical trials for the purpose of obtaining valid clinical conclusions while appropriately protecting the trial subjects;

6) **trial subjects** are persons participating in clinical trials of medicinal products irrespective of whether they are users of the medicinal products which are being clinically tested or participating

for the purpose of controlling the application of the medicinal product, or using the medicinal product with which the medicinal product being clinically tested is being compared;

7) **voluntary consents of trial subjects** are written declarations of the trial subjects, properly dated and signed, to participate in a given clinical trial of a medicinal product, provided by persons able to give such consent, or, where such persons are not capable of giving such consent, provided by their legal representatives, in accordance with the law, and which are given voluntarily after being fully informed about the nature, significance, consequences and risk to health;

8) **safety of trial subjects** is the physical and mental integrity, i.e., safety, of trial subjects participating in clinical trials of medicinal products;

9) **identification codes of trial subjects** are unique designations given by investigators to every trial subject in lieu of their names in order to protect their identities when reporting adverse reactions to a medicinal product or other data in clinical trials of medicinal products;

10) **investigators in clinical trials** are medical doctors or qualified dentists directly involved in and responsible for the treatment and care for patients or participants in the trials and responsible for the conduct of the clinical trials; where clinical trials are conducted by a team of investigators, the investigator responsible for the performance of the clinical trial is the principal investigator;

11) **the investigator's brochure** is a document which contains analytical, pharmacological - toxicological and clinical data about the medicinal product being studied which are important for studying the effect of the medicinal product on humans;

12) **clinical trial documentation** is the complete record in any form (including handwritten, electronic, magnetic and optical inscriptions, as well as optical and x-ray photographs, electrocardiograms and other records) used to describe and record data, of the conduct and results of the trial, all activities conducted, and factors which affect the clinical trial of a medicinal product;

13) **the ethnics committee** is an expert body formed in the health-care institution in accordance with the law regulating health care;

14) **decisions of the ethics committee** are decisions issued by the ethics committee that clinical trials of medicinal products may be conducted in the place of study, within the limitations defined by the ethics committee and the directives of Good Clinical Practice in clinical trials, in accordance with the law and this Regulation;

15) **the clinical trial protocol** (hereinafter: protocol) is a document containing the objectives, plan and methodology of the trial, manner of processing data and organising the clinical trial of the medicinal product in accordance with the directives of Good Clinical Practice in clinical trials;

16) **revisions of the protocol** are a document on the alterations of and amendments to the protocol or a formal explanation of the protocol;

17) **the sponsor of a clinical trial** of a medicinal product is an individual or a legal person who assumes the responsibility for initiating, conducting and funding the clinical trial;

18) **the clinical trial report** is a document on the full investigation of the therapeutic, prophylactic or diagnostic efficacy of the medicinal product being studied in which are given integrated clinically and statistically significant data, findings and analyses of the results obtained (a report on the course, results and conclusions of the trial in accordance with the directives of Good Clinical Practice in clinical trials);

19) **report on the course of a clinical trial** of a medicinal product is a report on the results of the clinical trial containing an estimate based on analyses conducted for a given time interval during the clinical trial;

20) **source documentation** are original documents, data and dossiers (for example case histories, clinical and administrative documents, laboratory findings, memorandums, journals of trial subjects or test lists of trial subjects, records on medicinal products dispensed, automatic records, copies or transcripts certified after checking their validity, negatives of photographs, microfilms or magnetic records, x-ray photographs, records kept in pharmacies, laboratories and medical technical services involved in the clinical trials of the medicinal product);

21) **source data** are all original medical data from the source documentation and certified copies of original clinical and laboratory findings or other results of activities conducted during a clinical trial of a medicinal product which are necessary for assessing the results of the study. Source data are located in the source documentation (in the form of originals or certified copies);

22) **the reference medicinal product** is an investigated medicinal product or a medicinal product from the market which represents active control or a placebo, with which is compared the medicinal product on clinical trial;

23) **quality control** designates the operating techniques and activities undertaken to ensure control of the quality of work in the procedure of conducting clinical trials;

24) **control of implementation of directives of Good Clinical Practice** in clinical trials is a procedure whereby the Serbian Agency for Medicinal Products and Medical Devices (hereinafter: the Agency) controls whether a given clinical trial is conducted in accordance with the trial protocol and the directives of Good Clinical Practice in clinical trials, at the site of the performance of clinical trial of a medicinal product, at the site of the applicant for clinical trial, at the site of any other legal or physical person to whom the applicant has contractually transferred authority or part of authority in the clinical study of the medicinal product, or at other relevant places, if so required;

25) **the site of the clinical trial of a medicinal product** is one or more health-care institutions in which trial subjects are undergoing medical treatment where clinical trials are being conducted;

26) **monitors** are specially-qualified persons who monitor the performance of clinical trials of medicinal products for the needs of the sponsor and guarantee that the course, documentation and reports on the clinical trials of medicinal products are in compliance with the protocol, standard operating procedures, the directives of Good Clinical Practice in clinical trials and regulations in force;

27) **standard operating procedures (SOP)** are detailed written instructions for achieving uniformity of all procedures in the performance of clinical trials of medicinal products;

28) **monitors' reports** are written reports submitted by the monitor to the applicant for clinical trials of medicinal products after each visit to the site of the trial, as well as reports on all other data in connection with the clinical trial of the medicinal product, in accordance with the standard operating procedures (SOP) of the applicant for clinical trials of medicinal products;

29) **auditors** are specially-qualified persons independently assessing on behalf of the applicant conformity of all activities related to the clinical trial of a medicinal product with the protocol, standard operating procedures (SOP) of the sponsor, directives of Good Clinical Practice in clinical trials, the law and this Regulation;

30) **the audit report** is a written report of the auditor on the results of the audit performed;

31) **ensuring the quality of clinical trials of medicinal products** is a set of planned and systematic activities established to ensure the performance of clinical trials, as well as recording, storage and analysis of data in accordance with the directives of Good Clinical Practice in clinical trials, the law and this Regulation;

32) **basic documentation** are the documents which individually and together make possible evaluation of the conduct of clinical trials and the good quality of data obtained;

33) **observance of the adopted clinical trial plan** is observance of all requirements laid down by the clinical trial protocol, directives of Good Clinical Practice in clinical trials and regulations in force;

34) **pre-clinical trials** of medicinal products are trials which are not conducted on humans;

35) **trial lists** are printed, optical or electronic documents for each trial subject intended for recording all data required by the protocol for the purpose of reporting to the applicant;

36) **adverse reactions** are all harmful and unintended reactions to medicinal products which appear during application of normal doses of the product in humans (for the purpose of treatment, prevention of disease, diagnosing, recuperation, improvement or alteration of physiological function), or the application of any dose of the medicinal product during clinical study;

37) **serious adverse reactions** are all harmful and unintended reactions to medicinal products which result in death, disability, inpatient hospitalisation or prolongation of existing hospitalisation, congenital anomalies or birth defects, are life-threatening, or require interventions aimed at preventing the aforementioned consequences;

38) **unexpected adverse reactions** are reactions to the medicinal product whose nature, severity or outcome are not known or consistent with the summary of product characteristics or investigator's brochure and cannot be expected on the basis of the known pharmacological characteristics of the medicinal product;

39) **undesirable events** are unwanted occurrences during use of a medicinal product for which a causal link with the administration of the medicinal product does not need to be proved. Unwanted occurrences are all unintended and undesirable signs, (for example abnormal laboratory findings), symptoms or illnesses occurring at the same time as the medicinal product is used;

40) **serious undesirable events** are all undesirable events which result in death, disability, inpatient hospitalisation or prolongation of existing hospitalisation, congenital anomalies, birth defects or threat to life, or require interventions aimed at preventing the aforementioned consequences;

41) **multi-centric clinical trials** are clinical trials of medicinal products performed according to a single protocol at more than one trial site and by more than one investigator, irrespective of whether the clinical trial sites are in one country or more countries;

42) **contracting research organisations** are legal or physical persons which conclude contracts with the applicant for clinical testing of medicinal products on the basis of which they take over from the applicant for clinical trials all powers in the clinical trials of medicinal products or part of the authority for clinical trials of medicinal products, and are responsible for all powers transferred in the conduct of clinical trials of medicinal products;

43) **blind clinical trials of medicinal products** is a procedure whereby one or more parties in the trials is not aware which trial subject belongs to which therapy group.

A single-blind approach means that one trial subject or more trial subjects are not aware to which therapy group they belong, while a double-blind approach means that, as a rule, the trial subject of trial subjects, the investigator or investigators, the monitor, or monitors in some cases, as well as the data analyst, are not aware of which trial subject belongs to which therapy group.

II CLINICAL TRIALS OF MEDICINAL PRODUCTS

1. Joint Provisions

Article 3

Application for clinical trials, conduct of clinical trials and reporting on clinical trials are performed in accordance with directives of Good Clinical Practice in clinical trials (GCP).

Clinical trials of medicinal products also include clinical studies of bioavailability and bioequivalence.

Article 4

In the performance of clinical trials of medicinal products, the rights, safety and interests of trial subjects must have precedence over the rights, safety and interests of science and society as a whole.

Clinical trials of medicinal products must be planned and conducted in such a manner as to ensure the lowest possible degree of pain, discomfort, fear and all other foreseeable risks to the health of trial subjects (the risk threshold and degree of pain are specially defined and constantly supervised).

Article 5

Documentation in connection with clinical trials of medicinal products is kept by the Agency in accordance with its Act on professional secrets.

Article 6

The provisions of this Regulation shall not apply to non-interventional clinical trials of medicinal products, unless otherwise specified by this Regulation.

2. Obligations of the Manufacturers of Medicinal Products Subject to Clinical Trials

Article 7

Manufacturers of medicinal products which are in the clinical trial stage must hold manufacturing authorisations issued by the competent authority on the basis of regulations in force in the country where the medicinal product on clinical trial is manufactured.

The manufacturer of the medicinal product referred to in § 1 of this Article must also hold a Good Manufacturing Practice certificate (GMP certificate).

Article 8

All batches of the medicinal product under clinical trial must be produced in accordance with the directives of Good Manufacturing Practice.

Article 9

The manufacture of medicinal products referred to in Article 7 of this Regulation must have a person responsible for production and a person responsible for the control of quality of each batch of the medicinal product under clinical trial.

3. Protection of Trial Subjects in Clinical Trials of Medicinal Products

Article 10

In choosing the target group of trial subjects shall be taken into account the degree of risk for individual groups of trial subjects.

No persons who are not able to decide by themselves on participation in clinical trials shall be included in such trials if the trials can be conducted on persons who are able to decide by themselves on participation in the clinical trials of the medicinal product.

Certain age groups (children, elderly persons etc.) shall only be included in special clinical trials of medicinal products, in accordance with the law and this Regulation.

Article 11

Before the start of clinical trials of medicinal products the principal investigator or member of the investigating team has an obligation to inform trial subjects verbally and in writing of the following:

- 1) the aim and procedure of the clinical trials of the medicinal product;
- 2) the expected positive and negative effects of the clinical trials of the medicinal product;
- 3) possible discomfort, consequences and risks of the clinical trials of the medicinal product;
- 4) other opportunities for medical treatment without the use of the medicinal product which is on clinical trial;
- 5) the manner of ensuring confidentiality of personal data during the clinical trials of the medicinal product;
- 6) the option of trial subjects to suspend or abandon the clinical trials of the medicinal product, at any time, or to revoke their written consent for participation in clinical trials of the medicinal product.

Article 12

Before the start of the clinical trials of the medicinal product trial subjects must sign declarations that they have been informed about the data referred to in Article 11 of this Regulation, and issue written consent to participate in the clinical trials of the medicinal product, in the presence of witnesses.

Article 13

In the procedure of clinical trials of medicinal products the principal investigator, or a member of the investigating team, has an obligation to secure the right of trial subjects to physical and mental integrity, as well as to privacy and protection of data accessible only to authorised persons.

During the course of the clinical trials of medicinal products the principal investigator, or a member of the investigating team, have an obligation to inform trial subjects about all information of importance to them in connection with the planning and conduct of the clinical trials.

Article 14

Where adverse reactions or serious adverse reactions occur during the course of clinical trials of medicinal products, the trial subject is entitled to necessary health care during and after the conclusion of the clinical trial of the medicinal product.

Article 15

Trial subjects are entitled to revoke the written consent referred to in Article 12 of this Regulation. Trial subjects may revoke the written consent referred to in Article 12 at any time and without explanation.

In the case referred to in § 1 of this Article, trial subjects may not suffer any adverse consequences on account of their decision to pull out of or abandon clinical trials of the medicinal product.

Article 16

Trial subjects are entitled to compensation of expenses incurred in connection with their participation in clinical trials of medicinal products, which shall be borne by the applicant for clinical trials of the medicinal product.

Protection of Juvenile Trial Subjects in Clinical Trials of Medicinal Products

Article 17

Where necessary, and subject to special precautions, clinical trials of medicinal products may also be conducted on persons aged below 18 who suffer from the disease or the condition intended to be treated by the medicinal product under clinical trial.

Clinical trials of medicinal products in which juvenile trial subjects participate are conducted under conditions prescribed by the law and this Regulation.

Apart from the conditions referred to in §§ 1 and 2 of this Article, clinical trials of medicinal products on juvenile trial subjects may be conducted provided that:

- 1) their parents, or guardians, have issued written consent (the written consent must represent the assumed desire of the juvenile person and may be revoked at any moment, without any damage to the juvenile person);
- 2) the juvenile person has received information, in accordance with his or her ability to comprehend, from a person experienced in working with juveniles, about the course of the clinical trials, the risks and benefits to the health of trial subjects;
- 3) the written consent has been issued without inducement to take part in clinical trials of medicinal products by offer or provision of any material or other benefit;
- 4) the ethics committee has ruled that clinical trials of medicinal products on juvenile trial subjects will result in direct benefit to certain groups of patients, and that such trials are significant for the assay of data acquired from clinical trials on persons able to issue written consent by themselves;
- 5) the positive decision on implementation of clinical trials of the medicinal product in the health-care institution was issued by the ethics committee on the basis of an opinion rendered by a qualified paediatrician, with particular emphasis on the clinical, ethical and psycho-social problems in the implementation of the clinical trials of the medicinal product.

Article 18

In the course of the conduct of the clinical trials of the medicinal product, juvenile trial subjects capable of forming an opinion and assessing information received about their participation in the clinical trials of the medicinal product may decide at any moment to withdraw from or abandon the clinical trials of the medicinal product, of which they shall inform the principal investigator or a member of the investigating team.

Protection of Adults Not Capable of Granting Written Consent During the Clinical Trials of Medicinal Products

Article 19

Clinical trials of medicinal products on adult trial subjects who are not capable of issuing written consent (due to state of unconsciousness, limited physical or mental capacity etc.), or on adult trial subjects who had not refused consent to participate in clinical trials of medicinal products before the onset of their incapacity, are conducted in accordance with conditions prescribed by law and this Regulation.

Besides the conditions referred to in § 1 of this Article, clinical trials of medicinal products may also be conducted provided that:

- 1) the legal representative of the adult trial subject not capable of issuing written consent has given written consent (the written consent must represent an assumed desire of the trial subject and may be revoked at any moment without damage to the trial subject);

- 2) the adult trial subject not capable of issuing written consent has received information in accordance with his or her comprehension ability, from a person experienced in working with such persons, which concern the course of the clinical trials, the risks and benefits to the health of trial subjects;
- 3) the written consent has been issued without inducement to take part in clinical trials of the medicinal product by offer or provision of any material or other benefit;
- 4) it has been assessed that clinical trials of the medicinal product on that person would result in direct benefits to a group of patients whose illness or condition corresponds to the illness or condition of the trial subject;
- 5) the positive decision on implementation of clinical trials of the medicinal product in the health-care institution was issued by the ethics committee on the basis of an opinion rendered by a physician specialising in the illness or condition of the trial subject, or for the population of patients whom the clinical trials of the medicinal product concern, with particular emphasis on the clinical, ethical and psycho-social problems in the implementation of the clinical trials of the medicinal product.

Article 20

During the conduct of the clinical trials of the medicinal product, adult persons not capable of issuing written consent, but who are capable of forming an opinion and assessing information received about their participation in the clinical trials of the medicinal product, may decide at any moment to withdraw from or abandon the clinical trials of the medicinal product, of which they shall inform the principal investigator or a member of the investigating team.

4. Applicants for Clinical Trials of Medicinal Products

Article 21

Applicants for the clinical trials of medicinal products (hereinafter: applicants) may be the manufacturer of the medicinal product, the sponsor of the trial, as well as the investigator in the conduct of the clinical trials, and are responsible for the conduct of the clinical trials.

Applicants conduct the following activities:

- 1) prepare full documentation required for obtaining authorisation for clinical trials of medicinal products, or required for applying for post-marketing interventional clinical trials of medicinal products, as well as documentation needed for revising protocols or authorisations for the clinical trials of medicinal products;
- 2) designate the principal investigator, who signs a declaration of consent with the proposed protocol, and conclude with the principal investigator a contract on the performance of activities on the clinical trials of the medicinal product, in accordance with the law and this Regulation;
- 3) designate the site of the clinical trials of the medicinal product (one of more institutions) where the clinical trials of the medicinal product will be conducted, as well as the main location of clinical trials of the medicinal product, on the basis of a contract with the health-care institution on the use of premises, equipment and personnel of that institution for conducting the clinical trials of the medicinal product;
- 4) before the start of the clinical trials of the medicinal product take out insurance for the trial subjects, in accordance with the law, for any possible damage to the health of those persons caused by the clinical trials of the medicinal product;
- 5) provide a sufficient amount of pre-clinical and clinical data about the medicinal product on trial and make them available to the principal investigator;
- 6) inform the principal investigator, the Agency and the ethics committee of the health-care institution about new relevant data concerning the medicinal product subject to the clinical trial;
- 7) provide data about the quality of the medicinal product on clinical trial, as well as data on earlier pre-clinical and clinical trials of that medicinal product;
- 8) notify the Agency and the ethics committee of the health-care institution about all serious adverse reactions to the medicinal product under clinical trial and serious undesirable events in clinical trials, in accordance with the secondary legislation regulating the manner of reporting, collecting and monitoring adverse reactions to medicinal products;

- 9) provide for trial subjects full health care for the treatment of certain illnesses or conditions which are the consequence of the clinical trials of the medicinal product;
- 10) provides a monitor and auditor in the clinical trials of the medicinal product;
- 11) provides timely notification to the Agency and the principal investigator about changes and amendments to the protocol, in accordance with the law and this Regulation.

Article 22

Besides the conditions referred to in Article 21 of this Regulation, applicants have an obligation to provide a sufficient quantity of the medicinal product which is subject to clinical trials.

The medicinal product referred to in § 1 of this Article must be labelled and carry at the least the following data on its outer packaging:

- 1) the name of the medicinal product, proprietary name, INN or generic name or other identifying marking;
- 2) name of the manufacturer;
- 3) expiry date;
- 4) batch number;
- 5) other requisite markings depending on the type of medicinal product on clinical trials.

The outer packaging of the medicinal product referred to in § 1 of this Article must be labelled: "For Clinical Trials".

Where blind clinical trials of the medicinal product referred to in § 1 of this Article are being conducted, the medicinal product must also be labelled with a special code.

5. Contracting Research Organisation

Article 23

Applicants for the clinical trials of medicinal products may contractually transfer some or all of their powers in clinical trials of medicinal products to a contracting research organisation, which performs contractual obligations on behalf of the applicant.

The contracting research organisation founded as a legal person, which does not have its seat in the Republic of Serbia, may perform part of the contractual obligations taken over from the applicant through its licensed agent in the Republic of Serbia with whom it will sign a temporary service contract, in accordance to the law regulating labour.

Article 24

Within the scope of the powers taken over in clinical trials the contracting research organisation must conduct all the activities that would have been conducted by the applicant for clinical trials of medicinal products if it had not transferred some or all of its powers in clinical trials to the contracting research organisation.

The licensed agent of the contracting research organisation in the Republic of Serbia performs only those activities which it has been authorised to perform under the contract with the contracting research organisation.

The contracting research organisation, and the licensed agent of the contracting research organisation in the Republic of Serbia, exercise all or some of the transferred powers in clinical trials in accordance with the law, this Regulation, and directives of Good Clinical Practice in clinical trials.

Article 25

The contracting research organisation has an obligation to submit to the Agency proof of registration with the competent authority in the Republic of Serbia, or corresponding proof of performance of activities according to the regulations of the country where it has its seat.

The contracting research organisation has an obligation to submit to the Agency a certified copy of the contract from which will be established the scope of the powers transferred from the applicant for clinical trials to the contracting research organisation.

The licensed agent of the contracting research organisation in the Republic of Serbia has an obligation to submit to the Agency a certified copy of the contract from which will be established the scope of the powers it exercises in the name and on behalf of the contracting research organisation.

The contracting research organisation, and its licensed agent in the Republic of Serbia, are responsible for the transferred powers in clinical trials, but the transfer of some or all of the powers to the contracting research organisation, and its licensed agent in the Republic of Serbia, does not relieve the applicant for the clinical trials of the final responsibility for the conduct of the clinical trials.

6. Principal Investigator and Investigating Team in Clinical Trials of Medicinal Products

Article 26

The principal investigator in clinical trials of medicinal products is a person with a university degree in medicine or stomatology with specialisation in the area in which the medicinal product under study is primarily in use, a person holding a scientific teaching post in medicine or stomatology, and, depending on the type of medicinal product under clinical trial – also a person who is employed in the health-care institution and is directly responsible for the treatment of the trial subject.

The principal investigator in clinical trials of medicinal products must also possess additional knowledge in the area of Good Clinical Practice in clinical trials.

Article 27

Before commencing clinical trials of medicinal products, the principal investigator:

- 1) submits to the applicant his biography and documentation proving his qualifications and training for the post of principal investigator;
- 2) signs a declaration that he has been informed about the characteristics of the medicinal product under clinical trial and the objective of the clinical trial of the medicinal product which will be conducted according to the protocol attached and in accordance with regulations in force;
- 3) signs with the applicant for clinical trials of the medicinal product a contract on the performance of activities on clinical trials of the medicinal product, in accordance with the law;
- 4) submits to the applicant a list of members of the investigating team.

Article 28

In the procedure of nominating the investigating team referred to in Article 27 § 1.4 of this Regulation, the principal investigator informs the members of the investigating team about the protocol, pre-clinical and clinical data about the medicinal product and test lists, and informs them regularly about important changes and amendments to the protocol and problems in the conduct of clinical trials of the medicinal product.

The members of the investigating team have an obligation to inform the principal investigator about adverse reactions to the medicinal product under clinical trial, or undesirable events and measures needed to protect the health of trial subjects.

Article 29

The principal investigator and the investigating team conduct the following activities in the course of clinical trials of the medicinal product:

- 1) determine the sufficient number of trial subjects according to the criteria set by the protocol for including and excluding trial subjects;

- 2) provide verbal and written explanations to trial subjects, in a manner comprehensible to them, of data about the medicinal product under clinical trial, the aim and plan of conduct of the clinical trial, the dangers and benefits to the trial subjects, the manner of selection of trial subjects, the approximate number of trial subjects, and other possible forms of treatment, and also about their advantages and negative sides;
- 3) obtain the voluntary written consent of trial subjects for participation in the clinical trials of the medicinal product;
- 4) provide to trial subjects appropriate health care for the duration of the clinical trials and after the conclusion of the clinical trials if medical treatment continues or if the illness or condition is a consequence of the clinical trials of the medicinal product;
- 5) ensure that the data about the clinical trials of the medicinal product are accurate, comprehensive, legible and properly updated, and maintain the confidentiality of the data accessible to the supervision of the applicant and the Agency;
- 6) maintain the confidentiality of the trial subjects' codes and of the medicinal product under study, which they may divulge on their own initiative only in emergencies linked with the protection of the health of trial subjects.

Article 30

During the course of the clinical trials of the medicinal product, the principal investigator has the following obligations:

- 1) to determine the dates of commencing and terminating the clinical trials of the medicinal product in agreement with the applicant for the clinical trials, and to inform the applicant for the clinical trials about suspension of clinical trials of the product;
- 2) to safeguard the medicinal product under trial in an appropriate manner, to record the dispensation and consumption of samples of the medicinal product under trial, and to safeguard in the prescribed manner unused samples of the medicinal product and to dispose of them in agreement with the applicant for clinical trials;
- 3) in the event of a direct threat to a trial subject, to inform the applicant for clinical trials about the suspension of clinical trials of the medicinal product;
- 4) to prepare a report on the completed clinical trials, and if needed also at the request of the Agency, to submit reports on the course of the clinical trials of the medicinal product.

If needed, the principal investigator is also obliged to recommend revisions of the trial protocol, and in case proposed alterations are approved, the principal investigator is obliged to ensure that all trial subjects are informed about the approved change and amendment to the protocol and that treatment is continued in accordance with the revision of the trial protocol.

Article 31

In clinical trials of medicinal products conducted in health-care institutions which provide secondary or tertiary health care, the investigating team must contain a medical doctor specialising in clinical pharmacology, in the case where the first and second phases of clinical trials of the medicinal product are being implemented, as well as in the case of multi-centric international clinical trials of the medicinal product.

In certain parts of the clinical trials of medicinal products, besides doctors of medicine and stomatology, the investigating team shall also include experts with other appropriate qualifications (graduate pharmacists, specialists in medical biochemistry or specialists in clinical biochemistry, nurses, medical technicians etc.).

Article 32

The principal investigator, members of the investigating team, as well as the persons referred to in Article 31 § 2 of this Regulation, sign temporary service contracts with the applicant for the clinical trials of the medicinal product in accordance with the law regulating labour, which must besides other elements prescribed by law contain the amount of the compensation for the performance of activities in clinical trials of the medicinal product.

7. Site of Clinical Trials of Medicinal Products

Article 33

Clinical trials of medicinal products, as well as of post-marketing interventional clinical trials of medicinal products and post-marketing non-interventional clinical trials of medicinal products, are conducted in health-care institutions holding licences for performing health-care activities issued by the ministry in charge of health, in accordance with legislation regulating health care.

The clinical trials of medicinal products referred to in § 1 of this Article may be conducted in one or more health-care institutions nominated by the applicant for the clinical trials of the medicinal product. If the clinical trials of the medicinal product are performed in several health-care institutions on the territory of the Republic of Serbia, the applicant for the clinical trials determines the principal site of the clinical trials of the medicinal product.

Article 34

The applicant for the clinical trials of the medicinal product concludes a contract with the health-care institution on the conduct of the clinical trials of the medicinal product.

The contract referred to in § 1 of this Article regulates the following: conditions and manner of conducting the specified clinical trials of the medicinal product in the health-care institution, the amount and manner of payment of the compensation the applicant for the clinical trials of the medicinal product pays to the health-care institution for the use of that health-care institution's capacities for the conduct of the clinical trials, the number of health-care professionals and other persons participating in the conduct of the clinical trials of the medicinal product who are employees of the health-care institution, and other questions of importance for regulating their mutual relations.

The health-care institution referred to in § 1 of this Article must provide the necessary conditions for the work of the investigators, or of the principal investigator, and the unobstructed work of the monitor, auditor and the Agency's official in charge of controlling the conduct of the clinical trials in accordance with the law, this Regulation the directives of Good Clinical Practice in clinical trials.

8. Ethics Committee in the Health-Care Institution in Which the Clinical Trials of Medicinal Products are Conducted

Article 35

The ethics committee is formed in the health-care institution in accordance with the law regulating health care.

In the health-care institution in which clinical trials of medicinal products are conducted a certain number of the members of the ethics committee must be persons possessing appropriate qualifications and experience in assessing scientific and medical aspects and ethical principles for clinical trials of medicinal products.

For the purpose of preventing conflicts of interest, only those members of the ethics committee who are not investigators in a given clinical trial and in no way connected to the applicant may vote and issue opinions on questions in connection with the clinical trial of the medicinal product.

U health-care institutions in which clinical trials of medicinal products are conducted, the composition of the ethics committee, its tasks, operating and other documents must be in compliance with the directives of Good Clinical Practice in clinical trials.

Article 36

Clinical trials of medicinal products may begin if the ethics committee issues a positive decision on implementation of the clinical trials of the medicinal product before the start of the clinical trials of the medicinal product.

Before the issuance of the positive decision referred to in § 1 of this Article, the ethics committee reviews the following:

- 1) the significance and plan of the clinical trials of the medicinal product;
- 2) justification for the clinical trial of the medicinal product – evaluation of the anticipated benefits and risks to the health of trial subjects;
- 3) the protocol;
- 4) the qualifications of the principal investigator and the investigating team;
- 5) the investigator's brochure;
- 6) the capacity of the health-care institution for the conduct of the clinical trial of the medicinal product;
- 7) whether the form with the information provided to trial subjects for the purpose of obtaining their written consent is adequate and complete;
- 8) whether conduct of the clinical trial of the medicinal product on trial subjects unable to issue written consent is justified;
- 9) whether it is justified to conduct the clinical trial of the medicinal product on healthy women in their periods of fertility, on pregnant women, lactating women, elderly persons and patients with serious illnesses or conditions, as well as on certain age groups of trial subjects (children, elderly persons etc.), and whether clinical trial of the medicinal product can be conducted on other persons;
- 10) proof of insurance provided to trial subjects by the applicant in the event of damage to the health of trial subjects caused by the clinical trial of the medicinal product (injury or death of trial subjects);
- 11) the financial resources which the applicant for the clinical trials is providing for the conduct of the clinical trial of the medicinal product for the needs of the principal investigator and members of the investigating team;
- 12) other questions of significance for the issuance of a positive decision on the conduct of a clinical trial of a medicinal product.

Where the ethics committee does not issue a positive decision on the conduct of a clinical trial of a medicinal product, the Agency will not issue authorisation for the clinical trials of the medicinal product.

Article 37

In multi-centric clinical trials which are being conducted in the Republic of Serbia the ethics committee in the health-care institution which is the principal site of the clinical trial of the medicinal product in the Republic of Serbia provides expert assistance to other ethics committees in health-care institutions where the clinical trials of the medicinal product are being conducted.

In multi-centric clinical trials which are conducted in the Republic of Serbia, the ethics committee in the health-care institution which is the principal site of the clinical trial of the medicinal product in the Republic of Serbia may recommend to the applicant for the clinical trial of the medicinal product, or to the principal investigator, that the conduct of the clinical trial in a certain health-care institution in which the clinical trial of the medicinal product is being conducted be suspended, if there are justified grounds for doing so.

Article 38

The applicant for the clinical trial of a medicinal product, of the principal investigator, has an obligation to notify the ethics committee of the health-care institution about the conduct of a post-marketing non-interventional clinical trial of a medicinal product on trial subjects who exercise their health-care rights in that health-care institution, or in the institution where the principal investigator is employed.

The ethics committee of the health-care institution referred to in § 1 of this Article has an obligation to notify the Agency about the conduct of the post-marketing non-interventional clinical trial.

Article 39

In multi-centric clinical trials which are conducted in the Republic of Serbia in several health-care institutions, all ethics committees of the health-care institutions where the concrete clinical trials of the medicinal product are being conducted must together issue a joint decision referred to in Article 36 § 1 of this Regulation, which is signed by the presidents of those ethics committees.

In multi-centric clinical trials which are conducted in several countries, positive decisions on conducting multi-centric clinical trials of medicinal products must be issued by every one of those countries, or the competent ethics committee in each of those countries.

Article 40

The work of ethics committees in health-care institutions in the conduct of clinical trials of medicinal products is coordinated by the Ethics Committee of Serbia, which is formed in accordance with the law regulating health care.

The Ethics Committee of Serbia, in accordance with the law regulating health care, monitors the conduct of clinical trials of medicinal products in health-care institutions on the territory of the Republic of Serbia, and renders decisions and opinions on controversial issues which are of significance for the conduct of clinical trials of medicinal products in health-care institutions in the Republic of Serbia.

The Agency has an obligation to notify the Ethics Committee of Serbia about the conduct of clinical trials of medicinal products for which it has issued clinical trials authorisations.

The Agency may, before authorising clinical trials of medicinal products, seek the opinion of the Ethics Committee of Serbia on applications for conducting clinical trials of medicinal products, and on all controversial issues which may arise in the conduct of clinical trials of medicinal products.

9. Procedure of and Documentation for Authorising Clinical Trials

Article 41

Applicants for clinical trials of medicinal products who do not hold marketing authorisations before starting the clinical trials submit to the Agency requests to authorise the clinical trials.

The request for authorising clinical trials contains the following:

- 1) covering letter of the applicant;
- 2) a duly filled in standard form of the request for authorising clinical trials of the medicinal product – application for clinical trial;
- 3) data on the applicant for the clinical trial of the medicinal product;
- 4) proof that the contracting research organisation is registered with the competent authority in the Republic of Serbia in the Register of Legal Persons, or Register of Entrepreneurs, or proof of performance of the activity issued according to the regulations of the country in which the contracting research organisation has its seat;
- 5) a certified copy of the contract on transferring powers to the contracting research organisation, or the licensed agent of the contracting research organisation in the clinical trials of the medicinal product;
- 6) the protocol of the clinical trials of the medicinal product;
- 7) information about adverse reactions to the medicinal product;
- 8) the investigator's brochure;
- 9) a sample test list (CRF);

- 10) the positive opinion of the appropriate ethics committee, or joint opinion of ethics committees in multi-centric clinical trials of the medicinal product;
- 11) the written consent of the health-care institution in which the clinical trial of the medicinal product will be conducted;
- 12) documentation about the medicinal product which is being studied, the GMP certificate, the analysis certificate, the product's labelling in Serbian and its original language, for the medicinal product being studied, and also for the reference medicinal product;
- 13) a written declaration of the principal investigator that he is informed about the characteristics of the medicinal product under clinical trial and the objective of the clinical trial, and that the trial will be conducted in accordance with regulations in force and the principles of Good Clinical Practice in clinical trials;
- 14) a short biography and references of the principal investigator;
- 15) proof of insurance provided to trial subjects by the applicant in the event of damage to the health of trial subjects caused by the clinical trial of the medicinal product (injury or death of trial subjects);
- 16) the standard form of information for trial subjects and for the written consent signed by the trial subjects, in the Serbian language,
- 17) other information for the trial subjects (patient's journal, instructions etc., in the Serbian language);
- 18) a list of countries where the medicinal product has marketing authorisation;
- 19) a list of countries where clinical trial of the same medicinal product has been approved;
- 20) a list of centres in which the clinical trials of the medicinal product are being conducted, if the trial is multi-centric;
- 21) additional information relating to the protection of the health of trial subjects, at the request of the Agency;
- 22) proof of payment to the Agency of the requisite fees for the issuance of authorisation for clinical trial of medicinal products.

The standard form of the request to authorise clinical trials of a medicinal product – notification of clinical trial – is attached to this Regulation and is its constituent part (Form No.1).

Article 42

The covering letter referred to in Article 41 § 2.1 of this Regulation contains the following:

- 1) the logo, name and address of the applicant;
- 2) the subject matter or a brief summary of the request for authorisation of the clinical trial;
- 3) a summary of the protocol in the Serbian language;
- 4) the name of the clinical trial;
- 5) the name of the medicinal product subject to clinical trial;
- 6) the pharmaceutical form and strength of the medicinal product;
- 7) the name of the manufacturer;
- 8) the date and signature of the responsible person for clinical trial of the medicinal product.

Article 43

The protocol of the clinical trial of the medicinal product referred to in Article 41 § 2. 6 of this Regulation contains the following:

- 1) general information;
- 2) basic information;
- 3) the aims and purpose of the clinical trial of the medicinal product;
- 4) the plan of the clinical trial of the medicinal product;
- 5) the selection of trial subjects;
- 6) data about the medical treatment of trial subjects;
- 7) an estimate of efficacy;
- 8) an estimate of safety;
- 9) statistical data;
- 10) data on direct access to source data or information;
- 11) data on controlling and ensuring quality;

- 12) ethical aspects of the clinical trial of the medicinal product;
- 13) data about the management of data and keeping of documentation;
- 14) data on the funding of the clinical trial of the medicinal product and insurance of trial subjects;
- 15) the manner of publication of results in the clinical trial of the medicinal product;
- 16) other attachments.

The structure and contents of the protocol of the clinical trials are annexed to this Regulation and are its constituent part (Annex No. 1).

Article 44

The investigator's brochure referred to in Article 41 § 2.8 of this Regulation contains the following:

- 1) cover page;
- 2) declaration on confidentiality of data;
- 3) contents;
- 4) summary;
- 5) introduction;
- 6) physical, chemical and pharmaceutical characteristics of the pharmaceutical form of the medicinal product;
- 7) data on pre-clinical studies of the medicinal product;
- 8) data on the effect of the medicinal product being studied on humans;
- 9) conclusion.

The structure and contents of the investigator's brochure are annexed to this Regulation and are its constituent part (Annex No. 2).

Besides the data referred to in § 1 of this Regulation, the investigator's brochure referred to in Article 41 § 2.8 of this Regulation also contains information about the quality, safety and efficacy of the medicinal product, and an estimate of the risk-to-benefit ratio of the medicinal product under study.

The documentation referred to in § 3 of this Article concerns the medicinal product under clinical trial and the reference medicinal product.

10. Issuance of Authorisation for Clinical Trial of a Medicinal product

Article 45

The Agency assesses the completeness of the application to authorise clinical trial of the medicinal product within 30 days of the date of submission of the request.

If the request referred to in § 1 of this Article is not complete, the Agency informs the applicant in writing to complete the request with requisite data in a specified time limit.

The time limit for the issuance of an authorisation for clinical trial of a medicinal product stops running on the date when the Agency asks the applicant to provide additional data and resumes running on the date when the applicant submits the requested data.

If the applicant does not submit the requested additional data within the specified time period, the Agency rejects the request for authorising clinical trial of a medicinal product as incomplete.

Where the request for authorising clinical trial of a medicinal product is complete begins to run the 60-day time limit for issuing authorisation for clinical trial of the medicinal product.

Article 46

Where the conditions prescribed by law and this Regulation are satisfied, the Agency issues authorisation for clinical trial of the medicinal product.

11. Revisions of Protocols and Authorisations for Clinical Trials of Medicinal products

Article 47

Applicants for clinical trials monitor scientific and technical development of the profession, the results of pharmacovigilance and other relevant data, and accordingly propose to the Agency revisions of protocols and/or authorisations for clinical trials of medicinal products.

Article 48

Complete requests for authorisation of revisions of the protocol, and/or authorisation for clinical trial of a medicinal product contain the following:

- 1) a covering letter of the applicant or contracting research organisation, or licensed agent of the contracting research organisation;
- 2) a duly filled in standard form for revisions of the protocol, and/or authorisation of clinical trial of the medicinal product;
- 3) documentation concerning the revision of the protocol, and/or authorisation for clinical trial of the medicinal product;
- 4) proof of payment of the requisite fees to the Agency.

The standard form of the request for authorising revisions of the protocol – authorisation of clinical trials is attached to this Regulation and is its constituent part (Form No. 2).

Article 49

The covering letter referred to in Article 48 § 1.1 of this Regulation contains the following:

- 1) the logo, name and address of the applicant;
- 2) the subject matter: brief explanation of the revisions;
- 3) the name of the clinical trial of the medicinal product;
- 4) the name of the medicinal product under clinical trial;
- 5) the pharmaceutical form, strength and packaging of the medicinal product;
- 6) the name of the manufacture of the medicinal product;
- 7) the date an signature of the responsible person for the clinical trial of the medicinal product.

Article 50

The Agency assesses the completeness of the request to authorise revisions of the protocol, and/or authorisation for clinical trial, within 30 days of the date of receiving the request.

If the request referred to in § 1 of this Article is not complete, the Agency informs the applicant in writing to amend the request with additional data.

The time limit for revising the protocol, and/or authorisation for clinical trial of a medicinal product, stops running from the date when the Agency requests the applicant to supplement data and resumes running from the date when the applicant submits the requested additional data.

If the applicant fails to submit the requested data in the specified time period, the request for revising the protocol, and/or the authorisation for clinical trial of the medicinal product, is rejected as incomplete.

Where the request is complete begins to run the 60-day time limit for revising the protocol, and/or the authorisation for clinical trial of the medicinal product.

12. Notification of the Agency of Post-Marketing Interventional Clinical Trials of Medicinal Products

Article 51

Applicants for clinical trials of medicinal products have an obligation, before commencing post-marketing interventional clinical trials of medicinal products, to notify the Agency about the

conduct of clinical trials of medicinal products which have marketing authorisations, if the trials are being conducted according to the approved summary product characteristics.

The notification referred to in § 1 of this Article contains the data referred to in Article 41 § 2.8 of this Regulation.

Instead of the investigator's brochure referred to in Article 41 § 2.8 of this Regulation, the applicant may also submit the approved summary product characteristics.

Article 52

Provisions of Articles 41 through 44 of this Regulation shall also apply to the content of documentation for post-marketing interventional clinical trials of medicinal products.

Article 53

The Agency assesses notifications of post-marketing interventional clinical trials of medicinal products within 15 days of the date of submission of the request.

If the notification referred to in § 1 of this Article is not complete, the Agency informs the applicant in writing to amend the notification with additional data in a specified time limit.

If the applicant fails to submit the requested additional data in the specified time limit, the Agency rejects the notification of post-marketing interventional clinical trial of the medicinal product as incomplete.

When the notification of post-marketing interventional clinical trial of a medicinal product is complete begins to run the 30-day time limit for confirming reception of the notification for post-marketing interventional clinical trial of the medicinal product.

If the Agency does not confirm reception of the notification within 30 days of receiving the notification, the applicant for post-marketing interventional clinical trial of the medicinal product may commence the conduct of the clinical trial of the medicinal product.

13. Reporting on the Conduct of the Clinical Trials of Medicinal Products

Article 54

Applicants for clinical trials of medicinal products have an obligation to inform the Agency about the conduct of clinical trials of medicinal products once every three months, and in the case of discontinuing the clinical trials, to inform the Agency thereof within 15 days of the discontinuation date.

Applicants for clinical trials of medicinal products have an obligation to inform the Agency about discontinuation of clinical trials of medicinal products (termination of the clinical trials in the Republic of Serbia, termination of the trials in all other countries where clinical trials are being conducted, premature termination of the clinical trials, or suspension of the clinical trials), within 15 days of the discontinuation date of the clinical trial (notification about the discontinuation of the clinical trials).

The standard form of the notification about discontinuation of the clinical trials is attached to this Regulation and is its constituent part (Form No. 3).

Article 55

Applicants for clinical trials of medicinal products prepare final reports on the results of the clinical trials of medicinal products which they submit to the Agency within one year after the conclusion of the clinical trial of the medicinal product.

The report referred to in § 1 of this Article must contain the positive and negative results of the clinical trial of the medicinal product, on the basis of which shall be rendered an objective assessment of the clinical trial of the medicinal product, i.e., of the benefits and risks of the medicinal product studied, and its safety and efficacy.

The structure and contents of the report on completed clinical trials of a medicinal product are attached to this Regulation and are its constituent part (Annex No. 3).

Article 56

The applicant keeps documentation about clinical trials of a medicinal product for the duration of the period in which that medicinal product is deemed a new medicinal product, or a medicinal product with a new manner of administration or new indications, which implies a period of five years from the day of issuance of the first marketing authorisation, or of the revision of the marketing authorisation.

14. *Monitoring of Adverse Reactions to the Medicinal Product*

Article 57

Monitoring of adverse reactions to medicinal products on clinical trial is conducted in accordance with secondary legislation regulating the manner of reporting, collecting and monitoring adverse reactions to medicinal products.

15. *Control of the Conduct of Clinical Trials of Medicinal Products*

Article 58

The Agency performs control of the conduct of clinical trials of medicinal products in the health-care institutions in which the clinical trials are being conducted, in accordance with the Law on Medicinal Products and Medical Devices, regulations adopted for the implementation of that law, and in accordance with the directives of Good Clinical Practice in clinical trials.

The Agency performs control of the conduct of clinical trials of medicinal products with the applicant, contracting research organisation, licensed agent of the contracting research organisation, in respect of the part of the activities performed by the contracting research organisation, or licensed agent of the contracting research organisation, in accordance with the Law on Medicinal Products and Medical Devices, regulations adopted for the implementation of that law, and in accordance with the directives of Good Clinical Practice in clinical trials.

Control of the conduct of clinical trials of medicinal products is performed by an authorised official of the Agency.

Article 59

Before starting control of clinical trials of medicinal products, the Agency is obliged to inform the applicant and the principal investigator, as well as the contracting research organisation, or the licensed agent of the contracting research organisation, about the performance of control of the clinical trial of the medicinal product.

The Agency submits to the applicant a report on the control it has performed of the clinical trial of the medicinal product.

Article 60

In the procedure of controlling the conduct of clinical trials of medicinal products at the site where the control referred to in Article 58 §§ 1 and 2 of this Regulation is performed, the Agency may order in writing that certain irregularities in the conduct of the clinical trials are rectified, within a specified period of time.

If the irregularities are not rectified within the specified time period, the Agency may, following the control, suspend or ban the clinical trial of the medicinal product, if it determines that the clinical trial of the medicinal product is not being conducted in accordance with the Law on Medicinal Products and Medical Devices, regulations adopted for the implementation of that law and the directives of Good Clinical Practice in clinical trials, or the notification of an interventional clinical trial of the medical product.

The Agency may suspend or ban a clinical trial of a medicinal product for which it has issued authorisation for conducting a clinical trial of the product in the Republic of Serbia, if it would be in the interest of protecting the health of trial subjects, or in the best interest of science and society as a whole.

If in the opinion of the Agency an already initiated clinical trial of a medicinal product does not need to be stopped urgently for the purpose of protecting the health of trial subjects, the Agency will first request from the applicant or the principal investigator information about the conduct of the clinical trial.

The applicant or the principal investigator have an obligation to submit the requisite data to the Agency within 15 days of the date when the information was requested, following which the Agency notifies the applicant, the principal investigator and the ethics committee of the health-care institution about its decision.

III CONCLUDING PROVISION

Article 61

This Regulation shall enter into force on the eighth day from the date of its publication in the *Official Gazette of the Republic of Serbia*.

Form No. 1

Prim. prev. SLIKE FORMULARA U FAJLU SU PRESEČENE NA POLA I VIDLJIVA IM JE SAMO LEVA POLOVINA
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Request to Authorise Clinical Trials of a Medicinal Product – Notification of Clinical Trial

Instructions for the applicant submitting a Request to Authorise Clinical Trials of a Medicinal Product – Notification of Clinical Trial

A request to authorise a clinical trial is submitted for every clinical trial of a medicinal product which does not have authorisation to be placed on the market in the Republic of Serbia (clinical trial: phases I-III and study of bioequivalence); notification of a clinical trial is submitted in the case when the study concerns a medicinal product with marketing authorisation in the Republic of Serbia, when the medicinal product is being used in accordance with the marketing authorisation, for example in accordance with the approved summary product characteristics. The application must be typewritten or printed from a computer. If there is a shortage of space for data in any part of the form, additional pages may be used and become an integral part of the form, and must be labelled as such.

References to documentation are not advised.

1) Specify all forms of the medicinal product and all strengths of the medicinal product which is being studied which will be used in the clinical trial in the Republic of Serbia. The strength is the quantity of active substance by individual dosage unit, by unit of volume or by unit of weight and that is specified in the case that the medicinal product contains a single active substance. Where

the active substance is in the form of a salt, hydrate etc., it must be specified whether the strength relates to the entire molecule of the substance or only its active part.

2) Specify whether the medicinal product has an authorisation to be placed on the market in the Republic of Serbia.

3) If there is more than one form or strength of the medicinal product used in the clinical trial, specify data for each form and strength.

4) In the case of medicinal products which do not have marketing authorisations, specify the proposed shelf life.

5) In case there is more than one form of the medicinal product or more than one manner of administering the medicinal product, specify all necessary data.

6) If the active substance is in the form of a salt, hydrate etc., it must be specified whether the quantity relates to the entire molecule of the substance or only its active part.

7) If the medicinal product contains more than one active substance, specify all active substances on an additional page with all the data as for the first active substance.

8) Narcotic and psychotropic substances are substances listed in the Law on the Production and Circulation of Narcotic Drugs and the Decision on the Determination of a List of Narcotic Drugs.

9) Specify the medicinal products which will be used in trials in the Republic of Serbia and which are explicitly designated in the trial protocol, for example reference medicinal products or medicinal products separately proposed for basic or auxiliary treatment. If there is more than one such medicinal product, an additional page may be used and becomes an integral part of the request.

10) Specify all forms of the medicinal product and all strengths of the medicinal product which will be used in trials in the Republic of Serbia.

11) If the trial cannot be classified into just one of the phases, state that there are more possibilities or specify them.

12) Trials are classified in phase IV if the medicinal product is used in accordance with the approved summary product characteristics. Trials in which new indications, new manners of administration and new fixed combinations are being studied, trials with considerably higher dosages than previously approved and trials conducted on groups of patients which were not approved in advance are not deemed phase IV trials.

13) Several types of trials may be marked.

14) In the case of large-scale trials, specify the approximate number of trial subjects.

15) Specify all institutions where the trials are being conducted in the Republic of Serbia. If there is insufficient space, use an additional page, which becomes an integral part of the request.

16) If there are more investigators, specify the principal investigator responsible for the conduct of the trial.

17) The institution which performs laboratory research is deemed a part of the institution in which the study of the medicinal product is being conducted if it is located within the same health-care institution and is located on the same address. All biochemical and haematological studies, and determination of the level of the medicinal product in plasma or concentration of the medicinal product in urine, faeces etc.

18) Specify if the same clinical trial, or study of the same medicinal product or same active substance, was approved.

19) Mark those parts of the documentation which are being submitted together with the request.

20) Pursuant to regulations, applicants shall cover all costs of the evaluation of the request to authorise the clinical trials or costs of the notification of clinical trial before submitting the request. The amount payable and the payment procedure are specified in the Agency's guide or information leaflet.

Form No. 2

Request for Authorising Revisions of the Protocol – Authorisation of the Clinical Trial

Prim. prev.

SLIKE FORMULARA U FAJLU SU PRESEČENE NA POLA
I VIDLJIVA IM JE SAMO LEVA POLOVINA

Form No. 3

Notification of Discontinuation of the Clinical Trial

Prim. prev.
SLIKE FORMULARA U FAJLU SU PRESEČENE NA POLA
I VIDLJIVA IM JE SAMO LEVA POLOVINA

Annex No. 1

STRUCTURE AND CONTENT OF THE CLINICAL TRIAL PROTOCOL

Protocols of clinical trials should contain the information specified below. However, information linked to the site of the clinical trial may be specified on separate protocol pages or in a separate contract, while some of the information listed below may be part of other documents connected to the protocol, such as the investigator's brochure.

1. *General information*

1.1. The name of the protocol, the protocol identification number and the date. All revisions must also be labelled with the number of the revision and the date.

1.2. The name and address of the applicant and the monitor (if the address of the latter differs from that of the applicant).

1.3. The names and functions of persons authorised to sign the protocol and revisions of the protocol in the name of the applicant.

1.4. The name, function and contact details (address and telephone number) of the investigator charged by the applicant with conducting the trial.

1.5. The names and functions of investigators in charge of conducting the trial and the addresses and telephone number of the trial sites.

1.6. The name, function and contact details (address and telephone number) of the appropriately qualified external consultant in charge of making important medical (or stomatological) decisions at the trial site (if that person is not the investigator).

1.7. The name and address of the laboratories and other medical and/or technical services and/or institutions involved in the trial.

2. *Basic information*

2.1. Name and description of the medicinal product or products being studied.

2.2. A summary of potentially significant results of pre-clinical trials, as well as of the results of other clinical trials of importance for planning the trial.

2.3. A description and explanation of the manner of administration, dosages, regime and duration of therapy.

2.5. A declaration that the trial will be conducted in compliance with the protocol, directives of Good Clinical Practice and regulations in force.

2.6. A description of the population structure involved in the trial.

2.7. References and data of importance for the trial which support the rationale of the trial.

3. *Aims and purpose of the trial*

Detailed description of the aims and purpose of the trial.

4. *Plan of the trial*

The scientific integrity of the trial and the credibility of the data obtained in the trial depend greatly on the plan of the trial. The description of the trial plan encompasses:

4.1. A detailed description of all primary results and secondary results, if any, which should be measured during the trial.

4.2. A description of the type of trial (e.g., double blind, with placebo control, randomised) and a schematic diagram of the trial plan, procedures and phases.

4.3. A description of steps taken to reduce or eliminate bias, including:

a) randomisation,

b) encoding.

4.4. A description of the investigated therapy, doses and dosage regime of the medicinal product on trial. Include descriptions of the doses, packagings and labelling of the medicinal product on trial.

4.5. The expected duration of participation of the trial subjects and descriptions and durations of all individual phases of the trial, including the monitoring period, if any.

4.6. A description of operative procedures for suspending or terminating trials for trial subjects, parts of the trial or the entire trial.

4.7. Procedures for keeping documentation on the use of the medicinal product on trial, including placebos and reference medicinal products, if any.

4.8. Maintenance of randomisation codes and procedures for deciphering the codes.

4.9. Identification of the data which should be entered directly into the test lists (for example without prior handwritten or electronic recording of data) and which will be regarded as source data.

5. Selection and inclusion of trial subjects

5.1. Criteria for inclusion of trial subjects.

5.2. Criteria for non-inclusion of trial subjects.

5.3. Criteria for withdrawing trial subjects (termination of the therapy with the medicinal product on trial, or termination of the treatment which is on trial) and specific procedures:

a) how and when to withdraw trial subjects from the trial or therapy with the medicinal product on trial;

b) types of necessary data about withdrawn trial subjects and time-limit for their collection;

c) whether and how to replace trial subjects;

d) the monitoring period for trial subjects removed from therapy with the medicinal product on trial or from the treatment.

6. Treatment of trial subjects

6.1. The therapy which will be applied, including the names of all medicinal products, doses, dosage regimes, manner of administration and duration of treatment, including the period of monitoring of trial subjects, for each medicinal product being studied, for each therapy group and for every part of the trial.

6.2. Permissible use of medicinal products, or therapy (including urgent therapy) which is permissible before and/or during the trial.

6.3. Procedures for monitoring the compliance of trial subjects.

7. Assessment of efficacy

7.1. Determination of efficacy parameters.

7.2. Methods and timeframe for assessing, recording and analysing efficacy parameters.

8. Assessment of safety

8.1. Determination of safety parameters.

8.2. Methods and timeframe for assessing, recording and analysing safety parameters.

8.3. Procedures for encouraging reporting on undesirable events and associated illnesses, as well as procedures for recording them and reporting them.

8.4. Manner and duration of monitoring of trial subject following undesirable events.

9. Statistical data

9.1. A description of the statistical methods which will be used, including time planned for processing data during the trial.

9.2. The number of trial subjects planned for inclusion in the trial. For multi-centric trials should be specified the number of trial subjects planned for inclusion in the trial at each site where the trial will be conducted. The reason for carefully choosing the size of the sample or number of trial subjects includes the influence on the significance of the trial and clinical justification.

9.3. The degree of significance which will be used.

9.4. The criteria for concluding the trial.

9.5. The procedure for explaining deficiencies, unused data and false data.

9.6. Procedures for reporting any deviation from the original statistical plan (all deviations from the original statistical plan should be described and explained in the protocol, and in the final report).

10. *Direct access to source data/documentation*

The applicant should ensure that it is specified in the protocol or other written document that investigators/institutions will allow direct access to source data/documentation for the purpose of monitorings of the trial, audits, evaluation by the ethics committee of the institution and control by the Agency.

11. *Control of quality and ensuing quality*

12. *Ethical aspects of the trial*

Description of the ethical aspects connected to the clinical trial.

13. *Data management and keeping of documentation*

14. *Finance and insurance*

The manner of funding and insurance provisions should be given only if they are not specified in a separate agreement.

15. *Publication policy*

The understanding about the publication of the results of the trial should be cited only if the matter is not covered by a separate agreement.

16. *Attachments*

Annex No. 2

THE STRUCTURE AND CONTENTS OF THE INVESTIGATOR'S BROCHURE

The investigator's brochure (hereinafter: the brochure) is a compilation of clinical and pre-clinical data about the medicinal product or products on trial and which are of significance for clinical trials on human subjects.

The investigator's brochure should contain a cover page and a provision on the confidentiality of data.

The cover page should specify the name of the applicant, the identification of the medicinal product on trial (identification number, chemical name, INN or generic name, proprietary name, if any), and the date of issue of the brochure. The number of the brochure in effect until then is specified, as is the date and number of issue of the brochure being replaced.

The applicant may if desired include a notice for the investigator instructing him to treat the brochure as a confidential document, and to only use it as a source of information for the investigating team and make it available only to the ethics committee and the Agency.

The brochure should include the following chapters, documented with available data from literature:

1. *Contents*

2. *Summary*

A brief summary should be given (two pages at most, if possible) of available significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic and clinical characteristics of the medicinal product on trial.

3. *Introduction*

A brief introductory chapter should contain the chemical name (INN or generic name, proprietary name, if any) of the medicinal product or products on trial, all active substances, pharmacological group and classification in the group, the rationale for conducting the trial and the anticipated prophylactic, therapeutic or diagnostic efficacy. The introductory chapter should establish the principles according to which will be assayed the results of the study of the medicinal product on trial.

4. *Physical, chemical, pharmaceutical characteristics and formulation*

The active substance of the medicinal product on trial (including chemical and/or structural formula) and a brief summary of the physical, chemical and pharmaceutical characteristics should be specified.

In order to provide for implementation of appropriate safety measures during the clinical trial, the formulation of the medicinal product which will be used should be explained, including all excipients, if clinically significant. There should be instructions for storing and handling certain pharmaceutical form of the medicinal product.

All structural similarities with other known medicinal products should be specified.

5. Pre-clinical studies

Here should be listed summaries of results of all significant pre-clinical pharmacological, toxicological, pharmacokinetic studies of the medicinal product on trial. The summary should specify the methodology used, the results and consideration of significant findings about the medicinal product on trial and possible adverse and unexpected reactions to the medicinal product in humans.

If they are known and available, this information should also include the following:

- Types of test animals on which the pre-clinical studies were conducted;
- Number and sex of animals in each group;
- Dosage units (e.g., mg/kg);
- Dosage regimes;
- Manner of administration;
- Duration of administration, or use of the medicinal product;
- Information about systemic distribution;
- Duration of the monitoring period after therapy;
- The results, including the following aspects:
 - the nature and frequency of pharmacological or toxicological reactions,
 - the degree or intensity of pharmacological or toxicological reactions,
 - the reaction withdrawal period,
 - the duration of reactions,
 - the relationship between the dose and the reaction.

Good legibility requires that the data are presented in tabular form.

In the chapters which follow should be reviewed the most important findings from pre-clinical studies, including reactions recorded to the doses applied, possible extrapolation to humans and all other aspects which will be studied on humans. If possible, findings of efficient and non-toxic doses in the same animal species should be compared (therapeutic index). The significance of these data in planning doses in humans should be emphasised. Wherever possible, comparisons should be made on the basis of the blood or tissue levels of the medicinal product, not on the basis of dosage units (e.g., mg/kg).

5.1. Pre-clinical pharmacology

A summary of the pharmacological characteristics of the medicinal product on trial, as well as the characteristics of metabolites discovered after animal studies, if any were found, should be specified. The summary should also contain studies on the basis of which can be estimated the potential therapeutic effects (e.g., the manner in which the medicinal product acts, bonds with receptors and selectivity of binding) as well as those on the basis of which can be estimated safety (e.g., special studies for assessing pharmacological effect outside those looking at the achievement of therapeutic efficacy).

5.2. Pharmacokinetics and metabolism of the product in animals

A summary of pharmacokinetics and biological transformation and disposition of the medicinal product on trial in all species tested should be given. In reviewing results should be taken into consideration resorption and local and systemic bioavailability of the medicinal product on trial and its metabolites, as well as their link with the pharmacological and toxicological data obtained from animal tests.

5.3. Toxicology

In the summary should be described the toxic effects of the medicinal product from significant studies conducted on different animal species, with the following elements:

- individual doses;
- repeated doses;
- carcinogenic potential;
- special studies, for example generation of irritation and allergizing potential;
- reproductive toxicology;
- mutagenic potential.

6. Effects of the product on trial on humans

Known reactions to the medicinal product, including information about pharmacokinetics, metabolism, pharmacodynamics, dosages and efficacy, safety and other pharmacological effects should be specified in detail. Wherever possible give a summary of each of the clinical trials, as well as information about the results of administration of the medicinal product different from that anticipated in the clinical trials, for example experiences from the markets of a country where the medicinal product is already on sale.

6.1. Pharmacokinetics and metabolism of the medicinal product in humans

If data on the pharmacokinetics of the medicinal product on trial are available, a summary should be given, including the following:

- pharmacokinetics (including, if possible, metabolism, resorption, bonding with plasma proteins, distribution and elimination);
- bioavailability of the medicinal product on trial (absolute and/or relative, if possible) for various pharmaceutical forms;
- specific population groups (e.g., sex, age, damage to the function of certain organs);
- interactions (e.g., interaction between medical products and the effects of food);
- other pharmacokinetic data (e.g., results of studies conducted in different population groups during the clinical trials).

6.2. Safety and efficacy

A summary of data on the safety, pharmacodynamic properties, efficacy (and metabolism, if possible) of the medicinal products on trial should be given, as well as information about dependence of reactions on dosage, obtained in prior human trials (healthy volunteers and/or patients). The significance of all these data should be analysed.

After numerous clinical trials have been completed, a clear presentation of data from several studies can be achieved by using the summary on safety and efficacy by indication. A summary tabular overview of adverse reactions to the medicinal product from all clinical trials (including those for all indications studied) can be very significant.

Important differences exhibited in connection with the cause and incidence of adverse reactions to the medicinal product in various indications or sub-groups should be reviewed.

The investigator's brochure should provide a list of all potential differences and adverse reactions to the medicinal product which may be anticipated on the basis of earlier experiences with the medicinal product on trial and other medicinal products in the same ATC group. Precautions and special measures which need to be taken as part of the use of the medicinal product being studied should be specified.

6.3. Market experience

The countries where the medicinal product on trial has been granted marketing authorisation should be listed, as well as those where marketing authorisation was denied, where the product was recalled from sale, and those where the authorisation was revoked. All significant data received from the market should be explained (e.g., formulations, dosages, manner of administration, adverse reactions to the medicinal product).

7. Summary of data and investigator's instructions

A comprehensive analysis of pre-clinical and clinical data and information from various sources about the medicinal product on trial should be given, if possible. In this way is provided for the investigator the most informative possible presentation of available data, with an estimate of the influence of the data on future clinical trials.

If available, published data on medicinal product in the same ATC group should be reviewed. This may assist the investigator to predict adverse reactions to the medicinal product or other problems in the clinical trial.

The data in this chapter must be used to clearly present possible risks and adverse reactions to the medicinal product, as well as special tests, observations and precautions which may be necessary during the clinical trials. The data should be based on existing physical, chemical, pharmaceutical, pharmacological, toxicological and clinical particulars of the medicinal product on trial. Instructions should be provided to the investigator how to recognise and treat possible overdoses and adverse reactions to the medicinal product, on the basis of earlier experiences in humans and the pharmacology of the medicinal product on trial.

Annex No. 3

STRUCTURE AND CONTENTS OF THE REPORT ON COMPLETED CLINICAL TRIALS

The report on completed clinical trials should contain the following elements:

1. *The cover page*

The cover page contains the following data:

- The title (of the trial);
- The name of the active substance of the medicinal product on trial;
- The indication which was studied;
- Where it cannot be concluded from the title, provide a brief description (1 to 2 sentences) of the trial method (randomised, cross-match, comparative, with placebo control, open, single blind, double blind), comparisons (placebo, active control, dose-effect dependence), duration of therapy, dosages and the population group of trial subjects;
- Name of the applicant
- Identification of the protocol (protocol number);
- The phase of the trial;
- The starting date of the trial (commencing with the first trial subject or on the basis of another definition which can be verified);
- The date of earlier cessation of the trial, if any;
- The date of concluding the trial (completion of data for the last trial subject);
- The name and function of the principal investigator or the coordinator of the trial, or the external consultant responsible for medical decisions appointed by the applicant;
- The name of the company or the sponsor, the name of the person with the sponsor responsible for the report (the name and contact details of the person charged by the company/sponsor with questions which may arise during evaluation of the report on the trial should be specified);
- Confirmation that the trial was conducted in accordance with the directives of Good Clinical Practice, including storage of the basic documentation;
- The date when the report was done (also listing all previous reports on the same trial with names and dates).

2. *Condensed contents (synopsis)*

It is necessary to include a brief summary (usually up to three pages) of the clinical trials. Besides the text and p-value, the synopsis should also contain numerical data and an illustrated presentation of the results.

3. *Contents of reports on individual completed clinical trials*

The contents should include:

- page-indexed chapters (page numbers), including summary tables, figures and graphs,
- a list of and number of pages in attachments, tables and every test list attached

4. *List of abbreviations and definitions*

It is necessary to provide a list of abbreviations, definitions of specific terms, and of the units of measurement used in the report.

5. *Ethics (the ethical section)*

5.1. The ethics committee of the institution

A positive opinion of the ethics committee of the institution from the conduct of the clinical trials should be provided, as should be a list of all ethics committees from which opinions were sought and the names of their presidents.

5.2. Declaration on ethical conduct of the trial

A declaration needs to be provided stating that the trial was conducted in accordance with the ethical principles based on the Helsinki Declaration on Biomedical Research on Humans.

5.3. Information for trial subjects and written consents

It should be described how and when written consent was obtained from the trial subject in connection with his or her inclusion in the clinical trial.

6. *Investigative and organisational provisions of the clinical trials*

Here should be given a description of the division of duties and activities of importance for proposing, conducting, controlling and assessing the trial. A list should be provided of investigators at each individual trial site, together with their biographies and qualifications data. A list of all associates who participated in the conduct of the clinical trial is also attached. Where large-scale clinical trials are concerned, only the most important information is provided.

7. *Introduction*

Here should be specified the phase of the clinical trial in relation to the overall development of the medicinal product, the basic characteristics of the clinical trial (reasons, aims, target population group, basic primary results), as well as regulations and recommendations of the competent authorities taken into consideration in preparing the plan of the clinical trial.

8. *The objective of the clinical trials*

The overall aims of the study should be specified.

9. *The plan of the trial*

9.1. The general plan - presentation of the trial

9.2. A discussion of the trial plan, including the selection of the control group

9.3. Selection of the population group for clinical trial

9.3.1. The criteria for including trial subjects in the clinical trial

9.3.2. The criteria for withdrawing trial subjects from the clinical trials

9.3.3. Trial subjects withdrawn from therapy or the clinical trial

9.4. Treatment

9.4.1. Treatment applied

9.4.2. The identity of the medicinal product or products on trial

9.4.3. The method of dividing trial subjects in treatment groups

9.4.4. selection of doses of the medicinal product on trial

9.4.5. Selection of the dosage regime for each trial subject

9.4.6. Encoding

9.4.7. Previous and accompanying therapy

9.4.8. Harmonisation of treatment

9.5. Parameters of efficacy and safety

9.5.1. Determination of efficacy and safety and schematic presentation of the plan

9.5.2. Adequacy of methods of measurement

9.5.3. Basic parameters of efficacy

9.5.4. Measurement of concentrations of the medicinal product

9.6. Ensuring good quality of the data

9.7. Statistical methods planned in the protocol and determining the size of the sample

9.7.1. The statistical and analytical plan

9.7.2. Determination of the size of the sample

9.8. Deviations from the trial or the planned analyses

10. *Trial subjects in the clinical trial*

10.1. Record of trial subjects

- 10.2. Deviations from the protocol
- 11. *Evaluations of efficacy*
 - 11.1. Analysis of overall data
 - 11.2. Demographic and other basic characteristics
 - 11.3. Determining uniformity of treatment
 - 11.4. Results of efficacy and tabular presentation of individual data on the trial subject
 - 11.4.1. Analysis of efficacy
 - 11.4.2. Statistical and analytical data
 - 11.4.2.1. Regulating covariants
 - 11.4.2.2. Action with excluded or lost data
 - 11.4.2.3. Prior analyses and monitoring of data
 - 11.4.2.4. Multi-centric trials
 - 11.4.2.5. Multiple comparisons/multicentricity
 - 11.4.2.6. Determination of "successfully subordinated" trial subjects
 - 11.4.2.7. Studies with active control intended for determining equivalence
 - 11.4.2.8. Assessment of sub-groups
 - 11.4.3. Tabular presentation of data on individual responses
 - 11.4.4. Doses of medicinal product, concentrations and efficacy, and their interdependence
 - 11.4.5. Interactions between two medicinal products and interactions of medicinal product and associated illnesses
 - 11.4.6. Graphical presentation of data on individual effect of the medicinal product on the trial subjects
 - 11.4.7. Conclusions on efficacy
- 12. *Evaluation of safety*
 - 12.1. Duration of the exposure of trial subjects
 - 12.2. Undesirable events
 - 12.2.1. Short summary of undesirable events
 - 12.2.2. Presentation of undesirable events (record of undesirable events)
 - 12.2.3. Analysis of undesirable events
 - 12.2.4. List of undesirable events in trial subjects
 - 12.3. Fatalities, other serious undesirable events and other significant undesirable events.
 - 12.3.1. List of fatalities, other serious undesirable events and other significant undesirable events.
 - 12.3.1.1. Fatalities
 - 12.3.1.2. Other serious undesirable events
 - 12.3.1.3. Other significant undesirable events
 - 12.3.2. Presentation of fatalities, other serious undesirable events and other significant undesirable events
 - 12.3.3. Analysis of and discussion about fatalities, other serious undesirable events and other significant undesirable events
 - 12.4. Clinical laboratory testing
 - 12.4.1. List of individual laboratory measurements for each trial subject (16.2.8) and of all unusual laboratory findings (14.3.4)
 - 12.4.2. Evaluation of all laboratory parameters
 - 12.4.2.1. Laboratory values
 - 12.4.2.2. Individual changes of laboratory values in trial subjects
 - 12.4.2.3. Clinically significant individual abnormalities
 - 12.5. Vital signs, physical (body) findings and other observations in respect of safety
 - 12.6. Conclusions about safety
- 13. *Discussion and overall conclusions*
- 14. Tables, figures and graphs linked with the trial, if not included in the text
 - 14.1. Demographic data
 - 14.2. Data on efficacy
 - 14.3. Data on safety
 - 14.3.1. Presentation of undesirable events
 - 14.3.2. List of fatalities, other serious and significant undesirable events

- 14.3.3. Presentation of fatalities, other serious undesirable events and some other significant undesirable events
- 14.3.4. List of unusual laboratory findings (for each trial subject)
- 15. *List of references*
- 16. *Attachments*
 - 16.1. Data about the trial
 - 16.1.1. The protocol, revisions of the protocol
 - 16.1.2. The standard form of the test list (single page)
 - 16.1.3. List of ethics committees (and names of the presidents, at the request of the Agency), presentation of the written information for trial subjects and the standard form of the written consent
 - 16.1.4. List and description of investigators and other important participants in the trial, including (one-page) biographies or appropriate list of training and experiences linked with the conduct of the clinical trial
 - 16.1.5. Signatures of the principal or coordinating investigator or external consultant of the sponsor, at the request of the Agency
 - 16.1.6. List of trial subjects receiving the studied active substance /medicinal product, or products, from a separate batch where several batches of the same product or products are used
 - 16.1.7. Schemes and codes in randomisation (identification of trial subjects and types of treatment)
 - 16.1.8. Certificate on audits performed (if any);
 - 16.1.9. Documentation on statistical methods
 - 16.1.10. Documentation o standardisation of inter-laboratory methods and procedures for ensuring good quality, if used
 - 16.1.11. Publications generated by the results of the clinical trials
 - 16.1.12. Important publications quoted in the report
 - 16.2. Data on trial subjects
 - 16.2.1. Trial subjects who disrupted the trial
 - 16.2.2. Deviations from the protocol
 - 16.2.3. Trial subjects excluded from the analysis of efficacy;
 - 16.2.4. Demographic data
 - 16.2.5. Compliance and/or data on concentration of the medicinal product (if available)
 - 16.2.6. Individual data on efficacy of the medicinal product in trial subjects
 - 16.2.7. List of undesirable events (for each trial subject)
 - 16.2.8. List of individual laboratory tests for each trial subject at the request of the Agency
 - 16.3. Test list standard form
 - 16.3.1. Test lists for fatalities, other serious undesirable events and withdrawal of trial subjects because of adverse reactions to the medicinal product on trial
 - 16.3.2. Other attached test lists
 - 16.4. List of individual data on trial subjects.