MINISTRY OF HEALTH

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Pursuant to Article 8, paragraph 3, Article 13, and Article 18, paragraph 1 of the Act on Medicinal Products (Official Gazette 76/2013 and 90/2014), the Minister of Health hereby adopts the following

ORDINANCE

ON CLINICAL TRIALS ON MEDICINAL PRODUCTS AND ON GOOD CLINICAL PRACTICE

Article 1

(1) This Ordinance regulates the procedure and conditions for the conduct of clinical, non-profit, and non-interventional trials on medicinal products, and Good Clinical Practice in the conduct of clinical trials on medicinal products.

(2) Compliance with the requirements of Good Clinical Practice provides assurance that the rights, safety and wellbeing of trial subjects are protected, and that the results of the clinical trials are credible.

Article 2

This Ordinance transposes into the legal order of the Republic of Croatia:

– Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1. 5. 2001). [1]

Article 3

(1) The following terms shall have the following meaning in this Ordinance:

Good Clinical Practice is a set of internationally recognised ethical and scientific requirements which must be observed for designing, conducting, recording and reporting clinical trials.

Investigational medicinal product dossier (hereinafter: IMPD) means a document that includes data relating to the quality of the investigational medicinal product, the production and control of the investigational medicinal product, data from non-clinical and clinical trials, and data on the application of the investigational medicinal product for human use.

Informed consent means consent, which must be written, signed by the subject, and dated, to take part in a clinical trial, taken freely further to duly received and appropriately documented information of its nature and significance, and implications and risks. Where the person is not

capable of giving consent or where the person is under age, the consent is signed by his or her legal representative or guardian. If the person concerned is illiterate or is unable to write, oral consent in the presence of at least one witness who is not a member of the investigating team may be given.

Inspection is the inspection by a competent authority of the conducting of a clinical trial, a review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at the site of other legal persons which the competent authority sees fit to inspect.

Subject is an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or as a control.

Investigator is a doctor of medicine or a person with adequate professional qualifications for clinical trials due to his or her scientific background and experience in patient care. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and is called the principal investigator.

Trial site is the healthcare institution in which a clinical trial is conducted.

Investigational medicinal product is the pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including medicinal products already with marketing authorisation but used in a way different from the authorised form, or different in terms of formulation or packaging, or used for an unauthorised indication, or used to gain further information about the authorised form of the medicinal product.

Clinical trial is any investigation on human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. This includes clinical trials conducted on either one site or multiple sites, whether in one or more than one Member State of the European Union.

Monitor is a person who performs monitoring during a clinical trial and ensures that it is conducted, documented and recorded in accordance with the protocol, standard operating procedures, Good Clinical Practice, and special legislation.

Non-interventional clinical trial is any study where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice, and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients but epidemiological methods are used for the analysis of collected data.

Non-profit clinical trial is a clinical trial conducted by the investigator without the participation of the pharmaceutical industry.

Sponsor of a clinical/non-interventional clinical trial is a natural or legal person who takes responsibility for the initiation of a clinical/non-interventional clinical trial, the management of a clinical/non-interventional clinical trial and/or the financing of a clinical/non-interventional clinical trial.

Protocol is a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial, where the term includes the protocol, successive versions of the protocol and protocol amendments.

Paediatric Investigation Plan (PIP) means a study or development programme to ensure the collection of data essential to establish conditions in which a medicinal product may be authorised for the treatment of the paediatric population.

Representative of the sponsor of a clinical/non-interventional clinical trial is a natural or legal person established in the European Union authorised by the sponsor of a clinical/non-interventional trial established outside the European Union.

Applicant for a clinical/non-profit clinical trial (hereinafter: applicant) is the sponsor of a clinical trial established in the European Union or its authorised representative established in the European Union if the sponsor is established outside the European Union.

Applicant for a non-interventional clinical trial is the holder of the marketing authorisation in the Republic of Croatia, the holder of an authorisation for a medicinal product authorised in a centralised procedure, or the representative of the holder of the marketing authorisation.

Central Ethics Committee is an independent body consisting of healthcare professionals and other members of the nonmedical profession whose responsibility is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators, the legal person in which the trial is conducted, the equipment, and on the methods and documents to be used to inform trial subjects and obtain their informed consent. The Central Ethics Committee is appointed by the Minister of Health (hereinafter: Minister).

Investigator's Brochure is a compilation of the clinical and non-clinical data on the investigational medicinal product which are relevant to the clinical trial concerned.

Request for the conduct of a clinical/non-profit clinical trial is a request submitted by the applicant to the Ministry of Health (hereinafter: Ministry) that includes all documents necessary for the issuing of an approval for the conduct of a clinical trial.

Request for the conduct of a non-interventional clinical trial is a request submitted by the applicant to the Agency for Medicinal Products and Medical Devices of Croatia (hereinafter: Agency) that includes all documents necessary for the issuing of an approval for the conduct of a non-interventional clinical trial.

Substantial amendments to a clinical trial are those that can substantially affect the following:

– the safety of clinical trial subjects, the physical or spiritual integrity of clinical trial subjects;

– the scientific value (usefulness) of the study.

Article 4

A clinical trial may be conducted in any legal person that satisfies the following requirements:

– the employment of experts whose knowledge and experience ensure that the clinical trial will be conducted in accordance with the protocol;

– equipment is available that enables the conduct of the clinical trial according to the protocol, or that a system is in place for using equipment and/or procedures foreseen in the protocol;

–a system exists for filing documents arising from the clinical trial in conformity with this Ordinance.

Article 5

Clinical trials shall be conducted by investigators who:

– hold an undergraduate and graduate university degree or integrated undergraduate and graduate university degree in healthcare, and relevant training if foreseen by the protocol;

– have documented training in Good Clinical Practice;

– simultaneously conduct no more than five clinical trials in the phase of actively enrolling subjects.

Article 6

(1) The monitor of a clinical trial is a person appointed by the applicant who:

– has completed a professional study or undergraduate university study or undergraduate and graduate university study or integrated undergraduate and graduate university study;

– has documented training in Good Clinical Practice;

– is a citizen of the Republic of Croatia or an alien having a permit or approval to work in accordance with special legislation concerning aliens, and evidence on knowledge of the Croatian language.

(2) The eligibility of the monitor is reviewed by the Ministry.

(3) The register of monitors is maintained by the Ministry.

Article 7

(1) Clinical trials of medicinal products, including non-profit clinical trials, in the Republic of Croatia may not commence without a favourable opinion of the Central Ethics Committee and the authorisation of the Ministry, unless in the event referred to in Article 14, paragraph 9 of this Ordinance.

(2) An applicant to whom the Ministry has issued an approval to conduct a clinical trial further to a positive opinion of the Central Ethics Committee, and who requests consent to conduct a clinical trial in additional legal persons, shall obtain the consent of the Central Ethics Committee for each legal person to be included in the clinical trial, and shall obtain the approval of the Ministry.

Article 8

The Central Ethics Committee is competent to issue an opinion in the procedure of approval and in the procedure of issuing an opinion on substantial amendments to clinical, non-interventional and non-profit trials in the Republic of Croatia.

Article 9

(1) The Central Ethics Committee is an independent body consisting of health professionals and members of the nonmedical profession organised in conformity with the requirements of Good Clinical Practice; it has nineteen members.

(2) The president, deputy president and members of the Central Ethics Committee are appointed by the Minister.

(3) Administrative activities for the operation of the Central Ethics Committee are conducted by the Agency.

Article 10

The manner of work of the Central Ethics Committee is regulated by its standing orders.

Article 11

In the procedure of adopting an opinion on the acceptability of implementation of a clinical trial, the Central Ethics Committee shall consider, in particular:

– the relevance of the protocol;

– the justifiability of the foreseeable hazards and risks in relation to the anticipated benefits for the subjects;

– the suitability of the investigator and of the facilities;

– the adequacy of the arrangements for the recruitment of subjects in the clinical trial;

– the adequacy of data stated in the Investigator's Brochure;

– the completeness, adequacy and comprehensibility of all information given to subjects, and of the procedures to be followed for the purpose of obtaining informed consent, and the justification for the research on persons incapable of giving consent independently;

– the existence of the protection of the privacy of subjects and the protection of data on the subject;

– the acceptability of compensation to investigators and trial subjects;

– the acceptability of the financial plan of the trial;

– the existence of insurance in the event of injury, death, or the treatment of the subject attributable to the clinical trial;

– the existence of insurance to cover the liability of the investigator or sponsor;

– the acceptability of substantive amendments to the clinical trial (if any).

Article 12

(1) The Central Ethics Committee shall have a maximum of 30 days from the date of receipt of a valid request prescribed in this Ordinance to give its written opinion concerning the acceptability of the proposed clinical trial.

(2) The valid request within the meaning of this Ordinance means the submission of a complete set of documents prescribed in Article 16 of this Ordinance.

(3) The Central Ethics Committee shall notify the applicant within 5 days of the receipt of the request, in writing (by electronic means or telefax), if it establishes that the set of documents submitted is not complete. If notification is not given, the request is deemed to have been duly submitted.

(4) Notwithstanding paragraph 1 of this Article, the Central Ethics Committee shall issue a written opinion on the acceptability of the proposed clinical trial of finished medicinal products intended for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms, within 90 days of the day of receipt of a duly submitted request prescribed in this Ordinance.

(5) The deadline referred to in paragraph 1 of this Article may be extended by a further period of 90 days where consultations with experts or committees are necessary.

(6) In the case of xenogenic cell therapy, there shall be no time limit for the issuing of an opinion on the acceptability of implementing the clinical trial.

(7) In the procedure of issuing an opinion on the acceptability of implementing the proposed clinical trial, the Central Ethics Committee may send a single request for documentation to be supplemented or for the delivery of further data supplementary to those already supplied by the applicant. The period laid down in paragraphs 1, 4 and 5 shall be suspended until the requested documentation is received.

Article 13

The Central Ethics Committee shall deliver the opinion referred to in Article 8 of this Ordinance to the applicant and the Ministry in written form.

Article 14

(1) The authorisation to conduct clinical trials, including non-profit clinical trials, is issued by the Ministry.

(2) The applicant, after a positive opinion of the Central Ethics Committee is obtained, shall submit a request to the Ministry for the implementation of a clinical trial in the Republic of Croatia.

(3) The Ministry shall either authorise or refuse to authorise a clinical trial within 30 days of the day of receipt of a duly submitted request.

(4) A duly submitted request within the meaning of this Ordinance means the submission of a complete set of documents prescribed in Article 16 of this Ordinance.

(5) The Ministry shall notify the applicant within 5 days of the receipt of the request, in writing (by electronic means or telefax), if it establishes that the set of documents submitted is not complete. If no notification is given, the request is deemed to have been duly submitted.

(6) The applicant may supplement the request, and the period referred to in paragraph 3 of this Article begins on the day of receipt of a duly submitted request.

(7) Within the period referred to in paragraph 3 of this Article, the applicant may amend its request before the issuing of a decision of the Ministry.

(8) The period referred to in paragraph 3 of this Article may be extended in the case of a clinical trial intended for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms, and xenogenic cell therapy.

(9) If the Ministry does not authorise or refuses to authorise a clinical trial within the period referred to in paragraphs 3 and 8 of this Article, the authorisation shall be deemed issued, unless a written approval of the Ministry is required before the commencement of a clinical trial in the case of clinical trials intended for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms, and xenogenic cell therapy.

(10) The Ministry shall refuse to authorise a clinical trial for gene therapy if there is risk of changes in the reproductive cell genome of the subject.

(11) The Ministry shall notify the applicant about defects in the request referred to in paragraph 2 of this Article and request the documentation to be supplemented. The applicant may make a single amendment to the request referred to in paragraph 2 of this Article.

(12) If the applicant does not submit supplementary documents or a written explanation stating the period of delivery of supplementary documents (by electronic means or telefax) within 5 days of the receipt of the conclusion, the Ministry shall issue a decision rejecting the request.

(13) The applicant shall notify the Ministry of the intention to withdraw a request that was submitted for the authorisation of a clinical/non-profit trial as soon as possible following the issuing of a decision. The notification submitted by electronic means or telefax must be delivered to the Ministry within the shortest term possible, in writing, with a brief description of the grounds for withdrawing the request.

(14) Where the applicant intends to re-submit a request for authorisation that was withdrawn, the applicant shall state on the request to the Ministry and on the EudraCT Clinical Trial Request Form (hereinafter: EudraCT Form) that the request is being re-submitted in accordance with the Communication from the Commission 2010/C 82/01 — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1).

Article 15

(1) The authorisation to conduct a clinical trial, including a non-profit clinical trial, is issued or denied by the Ministry in a decision against which no appeal is allowed, but an administrative dispute may be initiated.

(2) The Ministry shall deliver the authorisation to conduct a clinical trial to the applicant, the Central Ethics Committee, the Agency, the Croatian Institute for Health Insurance, and the pharmaceutical inspection of the Ministry.

Article 16

(1) In the procedure of submitting a request to the Ministry for the authorisation of a clinical trial of a medicinal product, including a non-profit trial, and obtaining an opinion of the Central Ethics Committee, it is necessary to submit the following documents:

1. a request in the Croatian language signed by the responsible person of the applicant. The request must include the following information: protocol identifying code, the EudraCT number, the title of the trial, the phase of the trial, the name and address of the sponsor, the name and address of the applicant, and the list of the main investigators and facilities in which the clinical trial is to be carried out, as well as a brief explanation of the grounds for submitting the request;

2. the Investigator’s Brochure for an investigational medicinal product without a marketing authorisation, issued within a period of one year;

3. a summary of product characteristics for investigational medicinal products having a valid marketing authorisation;

4. the curriculum vitae of the investigator, showing that he/she meets the benchmarks referred to in Article 5 of this Ordinance;

5. the curriculum vitae of the monitor, showing that he/she meets the benchmarks referred to in Article 6 of this Ordinance;

6. a list of states in which it is planned to conduct the clinical trial concerned and in which, at the moment of submission of the request for the issuing of authorisation, the trial has been authorised or has not been accepted, including the grounds for such non-acceptance;

7. the protocol and any amendments signed by the principal investigator;

8. a copy of the case report form of the subjects in electronic form;

9. the informed consent form in the Croatian language and in Latin script, and the original text;

10. a summary scientific opinion of the European Medicines Agency in connection with the application of the investigational medicinal product (if available);

11. a copy of the decision of the European Medicines Agency concerning the paediatric investigation plan and an opinion of the paediatric committee if the clinical trial is carried out according to the paediatric investigation plan of a medicinal product (PIP);

12. an example of the method of marking the investigational medicinal product;

13. the financial plan of the trial;

14. proof of insurance of subjects against possible adverse effects of the clinical trial;

15. written authorisation to the legal person submitting the request to the Minister for the authorisation of a clinical trial when the request is not submitted by the sponsor;

16. proof of payment of the costs in the procedure of the issuing of an authorisation to conduct a clinical trial.

(2) The applicant shall deliver to the Central Ethics Committee, in addition to the documentation referred to in paragraph 1 of this Article, the following:

– the completed form from Schedule IV and Schedule V that accompany this Ordinance and which form an integral part hereof.

(3) The applicant shall deliver to the Ministry, in addition to the documents referred to in paragraph 1 of this Article, the following:

– the completed form from Schedule III that accompanies this Ordinance and which forms an integral part hereof;

– the IMPD;

– the CTA form in the English language;

– proof of payment of the administrative fees.

Article 17

(1) In the procedure of authorising a clinical trial involving children or the treatment of psychiatric patients, the Central Ethics Committee may seek the assistance of experts and may consult committees for paediatrics and psychiatry of the Ministry in accordance with point 3.2.6 of Schedule I to this Ordinance.

(2) The Central Ethics Committee must conduct the counselling referred to in paragraph 1 of this Article within the periods stated in Article 12, paragraph 1 of this Ordinance.

Article 18

(1) The CTA form referred to in Article 16, paragraph 3, subparagraph 3 of this Ordinance must be delivered to the Ministry in .xml and .pdf formats on a CD-ROM and in a .pdf format in printed form, dated and signed by the responsible person of the applicant.

(2) The CTA form must be delivered to the Ministry at the time of submitting the request for conducting a clinical trial and at the time of submitting a request for substantial amendments to the trial.

(3) After the CTA form is completed, the validity of the data must be verified, and a "Validation Report" document must be delivered to the Ministry in a .pdf format on a CD-ROM, confirming the validity of the completed form.

(4) Each CD-ROM delivered must be marked with its EudraCT number, the date of submission of the form, the name of the sponsor and the applicant, and a brief description of the content.

(5) Other than the CTA form, the applicant shall deliver to the Ministry completed printed forms notifying the Ministry of substantial amendment and of the end of the trial.

(6) The forms referred to in paragraphs 1 and 5 of this Article are available and published on the website of the European Commission (*EudraLex – Volume 10 Clinical trials guidelines*).

Article 19

(1) The contract between the applicant and the legal person (hereinafter: Contract) in which the trial is to be conducted must stipulate the following:

– the total costs of implementing the clinical trial;

– the costs borne by the applicant, including the costs of medical and other services provided by the legal person in which the trial is conducted;

– the amount of compensation to legal persons, investigators and subjects;

– the obligations of the applicant to bear the costs of all diagnostic procedures and examinations foreseen in the protocol.

(2) In the procedure of obtaining an opinion of the Central Ethics Committee, the applicant shall deliver to the Central Ethics Committee a financial plan of the trial for each legal person in which it is planned to conduct the clinical trial, with a description of the financial aspects of the clinical trial, including the elements referred to in paragraph 1, subparagraphs 1 to 4 of this Article.

(3) In the procedure of approving a clinical trial, the applicant shall deliver to the Ministry a financial plan of the trial for each legal person in which it is planned to conduct the clinical trial, approved by the Central Ethics Committee (hereinafter: approved financial plan) and, by the end of the period stipulated in Article 14, paragraph 3 of this Ordinance, at least one

signed Contract; if the applicant fails to do so, the Ministry shall issue a decision not to accept the request.

(4) If in its review of the approved financial plan and the signed contract the Ministry establishes that there were substantial amendments to the financial aspects of the clinical trial and/or to the minimum requirements for contracts prescribed by the Minister, it may request the applicant within 5 days, in writing (by electronic means or telefax), to deliver an amended contract in conformity with the instruction of the Ministry and/or to obtain from the Central Ethics Committee an additional opinion on the acceptability of the financial plan. If this is not done, the approved financial plan and the signed contract are deemed valid.

(5) The period referred to in paragraph 4 of this Article also applies in the event of the submission of an additional opinion of the Central Ethics Committee on the acceptability of the financial plan and/or an amended contract in accordance with the instruction of the Ministry.

(6) Substantial amendments to the approved financial plan, within the meaning of this Ordinance, are all amendments that may have an impact on the safety of the subjects or on the final outcome of the clinical trial.

(7) Following the expiration of the period stated in Article 14, paragraph 3 of this Ordinance, the applicant may deliver to the Ministry other Contracts that were signed but not initially submitted. Following receipt of the signed Contracts, the Ministry shall issue decisions on the implementation of the clinical trial to such legal persons.

Article 20

(1) The applicant who has received authorisation of the Ministry for the implementation of the clinical trial shall submit a report to the Ministry and the Central Ethics Committee once a year, by 31 January for the previous year, concerning the implementation of the clinical trial in authorised trial sites, the total number of subjects in the screening process, and the total number of subjects involved in the trial.

(2) The applicant shall notify the Central Ethics Committee and the Ministry of all amendments to the clinical trial.

(3) Substantial amendments are subject to the procedure of obtaining an opinion of the Central Ethics Committee and an authorisation of the Ministry.

(4) Minor administrative amendments are not subject to the procedure of obtaining an opinion of the Central Ethics Committee and an authorisation of the Ministry, but the Central Ethics Committee and the Ministry must be duly notified.

(5) The applicant must enclose a certificate concerning the costs of the procedure paid in conformity with the decision of the competent authority with the request for the approval of substantial amendments to the clinical trial.

Article 21

Clinical trials in the Republic of Croatia are conducted in accordance with the standard set out in the Note for Guidance of the European Medicines Agency and its Committee for Proprietary Medicinal Products: "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95). The text of the Note for Guidance in its translation into the Croatian language is enclosed in Schedule I of this Ordinance and forms an integral part hereof.

Article 22

Along with the Note for Guidance referred to in Article 21 of this Ordinance, clinical trials of minors are conducted in accordance with the standard set out in the Note for Guidance of the European Medicines Agency and its Committee for Proprietary Medicinal Products: "Clinical Investigation of Medicinal Products in the Paediatric Population" (CPMP/ICH/2711/99). The text of the Note for Guidance in its translation to the Croatian language is enclosed in Schedule I of this Ordinance and forms an integral part hereof.

Article 23

(1) The personal integrity and wellbeing of subjects shall be ensured in the implementation of clinical trials in accordance with the Declaration of Helsinki.

(2) All clinical trials authorised in the Republic of Croatia are published at the website of the Ministry and on the website of the European Medicines Agency in the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

(3) The Ministry maintains a register of all clinical trials authorised in the Republic of Croatia.

Article 24

(1) The pharmaceutical inspection of the Ministry shall conduct inspections of clinical trials.

(2) The pharmaceutical inspector of the Ministry shall conduct inspections of clinical trials at the trial site, in the facilities of the sponsor and/or the contract institution or in other legal persons in which the competent authority holds that it is necessary to conduct supervision.

(3) The pharmaceutical inspection shall perform regular and extraordinary inspections of clinical trials on medicinal products:

– regular inspections are conducted in conformity with the annual plan of inspections;

– extraordinary inspections of clinical trials on medicinal products are conducted in the event of incidents.

(4) Inspections of clinical trials on medicinal products may also be requested and coordinated by the European Medicines Agency.

(5) Inspections of clinical trials of medicinal products may be conducted:

– before, during or after the clinical trial;

– as part of the procedure of obtaining the marketing authorisation;

– as a repeated inspection after the marketing authorisation is obtained.

(6) Inspections of clinical trials are conducted in accordance with the guidelines and guidance published on the website of the European Commission: *EudraLex – Volume 10 Clinical trials guidelines*.

Article 25

In the event of an event affecting the safety of trial subjects, the investigator and the sponsor of a clinical trial shall take emergency measures to protect trial subjects without any delay and, after having taken such measures, they shall notify the Central Ethics Committee, the Agency and the Ministry without delay of the measures taken and amendments to the protocol.

Article 26

(1) The investigator and health professionals taking part in a clinical trial who learn about an adverse event that occurred during the clinical trial shall notify the applicant of such an event in accordance with special legislation, other than those not subject to such notification further to the protocol and the Investigator's Brochure.

(2) The Agency shall maintain a record on Development Safety Update Reports (DSUR), Suspected Unexpected Serious Adverse Reactions (SUSAR) that have occurred in clinical trials in the Republic of Croatia, and other safety issues, and notify the Central Ethics Committee and the Ministry accordingly.

Article 27

If a clinical trial ends earlier than foreseen in the protocol or if it is temporarily suspended, the applicant shall notify the Central Ethics Committee that issued its favourable opinion and the Ministry within 15 days and state a detailed explanation of the causes.

Article 28

(1) The applicant shall deliver a notice to the Central Ethics Committee and the Ministry of the end of a clinical trial within 90 days of the day of end of such a clinical trial.

(2) The day of the last examination/procedure on the last subject involved in the clinical trial shall be regarded as the end of the clinical trial referred to in paragraph 1 of this Article.

Article 29

Following the end of a clinical trial, the applicant shall deliver to the Central Ethics Committee and the Ministry a summary final report within one year of the end of the clinical trial.

Article 30

(1) The sponsor may enable trial subjects to take part in expanded access programmes after the end of their participation in the clinical trial (hereinafter: programme).

(2) In the event referred to in paragraph 1 of this Article, the applicant shall notify the Central Ethics Committee about the planned programme and request authorisation from the Ministry.

(3) The applicant shall state the grounds for the initiation and the duration of the programme, the number of positions for investigators and the number of trial subjects at the trial site to take part in the programme, and the dose(s) and use(s) of the medicinal product. With the request, the applicant shall enclose statements provided by the principal investigators confirming their participation in the programme and accepting further monitoring of the safety of application of the medicinal product, and that the relationship of the risks and benefits justifies the use of the medicinal product in the dose(s) and in the way foreseen in the proposed programme.

(4) The applicant shall notify the Central Ethics Committee and the Ministry at least once a year about the implementation of the programme with an emphasis on the safe application of the medicinal product.

(5) The applicant shall notify the Central Ethics Committee and the Ministry of the completion of the programme within 90 days of the day of completion of the programme.

Article 31

(1) In the procedure of submitting a request to the Agency for the authorisation of a non-interventional clinical trial and obtaining an opinion of the Central Ethics Committee, the applicant shall deliver the following documentation:

– a request in the Croatian language signed by the responsible person of the applicant; the request should include the name and address of the sponsor, the name and address of the applicant, and the signature of the principal investigators and facilities in which the non-interventional trial is to be conducted;

– the protocol stating the code of the protocol, its version, and the date of the version of the protocol;

– the case report form of trial subjects;

– a decision on the marketing authorisation, if applicable;

– the approved summary of product characteristics for an approved product and package insert in the Croatian language;

– the informed consent for the subject in the Croatian language, stating the version of the informed consent and the date of the version;

– a copy of the informed consent for the subject in the English language, if applicable;

– the financial plan of the trial;

– proof of payment of the costs in the procedure of obtaining an opinion of the Central Ethics Committee and obtaining an approval for the implementation of the non-interventional trial.

(2) The applicant shall deliver the following to the Central Ethics Committee, in addition to the documents referred to in paragraph 1 of this Article:

– the completed form referred to in Schedule VI that accompanies this Ordinance and which forms an integral part hereof.

(3) The applicant shall deliver the following to the Agency, in addition to the documents referred to in paragraph 1 of this Article:

– the completed form from Schedule VII that accompanies this Ordinance and which forms an integral part hereof;

– the opinion of the Central Ethics Committee about the non-interventional trial;

– proof of payment of the administrative fees.

(4) The Central Ethics Committee shall issue a written opinion about the acceptability or non-acceptability of the proposed non-interventional trial within 30 days of the day of receipt of a valid request.

(5) A valid request within the meaning of this Ordinance means the submission of a complete set of documents stipulated in paragraph 1 of this Article.

(6) The Central Ethics Committee shall notify the applicant within 5 days of receipt of the request, in writing (by electronic means or telefax), if the submitted documents are not complete. If this is not done, the submitted request is deemed valid.

(7) The Central Ethics Committee shall notify the Agency and the Ministry, in writing, of the opinion provided on the acceptability of conducting a non-interventional trial.

(8) Following the receipt of a valid request, the Agency shall either authorise or deny authorisation for implementing a non-interventional trial within 30 days.

(9) A valid request within the meaning of this Ordinance means the submission of a complete set of documents stipulated in paragraph 1 of this Article.

(10) The Agency shall notify the applicant within 5 days of the receipt of the request, in writing (by electronic means or telefax), if it establishes that the submitted documents are not complete. If it does not do so, the submitted request is deemed valid.

(11) If the Agency does not give authorisation or does not deny authorisation within the term referred to in paragraph 8 of this Article, the authorisation shall be deemed granted and the trial may begin.

(12) The Agency shall deliver the decision on the implementation of a non-interventional trial to the applicant, the Ministry, and the Croatian Health Insurance Institute.

(13) Regarding paragraph 11 of this Article, the applicant shall deliver to the Ministry and the Croatian Health Insurance Institute a notification on the expiration of the deadline referred to in paragraph 8 of this Article and, in place of the authorisation of the Agency, enclose a favourable opinion of the Central Ethics Committee and proof of a valid request received by the Agency.

(14) The Agency shall maintain a record of all authorised non-interventional trials.

(15) All non-interventional trials authorised in the Republic of Croatia shall be published on the website of the Agency.

Article 32

(1) In the case of a non-interventional trial concerning the safety of application of a medicinal product after the marketing authorisation was obtained, with respect to which the Agency does not issue authorisations to conduct clinical trials, the applicant shall deliver to the Agency for review the following:

– the written consent of the Pharmacovigilance Risk Assessment Committee (hereinafter: PRAC) on the implementation of a non-interventional trial;

– the protocol of the non-interventional trial accepted by the PRAC;

– the case report form of trial subjects;

– the informed consent for the subject in the Croatian language;

– the original informed consent for the subject in the English language, if applicable;

– the list of principal investigators and institutions in which the non-interventional trial is to be conducted;

– the planned beginning and end of the non-interventional trial.

(2) The trial referred to in paragraph 1 of this Article may begin in the Republic of Croatia further to a written consent of the PRAC after the marketing authorisation holder delivers the accepted protocol to the Agency.

Article 33

All clinical trials authorised before the entry into force of this Ordinance shall proceed in accordance with the legislation valid at the time of their beginning.

Article 34

On the entry into force of this Ordinance, the Ordinance on clinical trials and Good Clinical Practice (Official Gazette 14/2010 and 127/2010) shall cease to have effect.

Article 35

This Ordinance shall enter into force on the eighth day following the day of its publication in the Official Gazette.

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Zagreb, 20 February 2015

Minister
Siniša Varga,
m.p.

ANNEX I

GOOD CLINICAL PRACTICE

GUIDELINE FOR GOOD CLINICAL PRACTICE

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human trial subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH Guideline for Good Clinical Practice is to provide a unified standard for the European Union (EU), Japan and the United States of America to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current Good Clinical Practices of the European Union, Japan, and the United States of America, as well as those of Australia, Canada, the Nordic countries and the World Health Organisation (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and wellbeing of trial subjects.

1. GLOSSARY

1.1. Adverse Drug Reaction

In the pre-approval clinical experience with a new medicinal product/medical device or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product/medical device related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product/medical device” means that a causal relationship between a medicinal product/medical device and an adverse drug reaction is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products/medical devices: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2. Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product/medical device, whether or not caused by such medicinal (investigational) product/medical device (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3. Amendment (to the protocol)

See Protocol Amendment.

1.4. Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational medicinal products/medical devices.

1.5. Approval (in relation to Institutional Review Boards)

The affirmative decision of the Institutional Review Board that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the Institutional Review Board, the institution, Good Clinical Practice, and the applicable regulatory requirements.

1.6. Audit

A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures, Good Clinical Practice, and the applicable regulatory requirement(s).

1.7. Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8. Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9. Audit Trail

Documentation that allows reconstruction of the course of events.

1.10. Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-

blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11. Case Report Form

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12. Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13. Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14. Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15. Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice requirements, and the applicable regulatory requirements.

1.16. Confidentiality

Prevention of disclosure, to other than authorised individuals, of a sponsor's proprietary information or of a subject's identity.

1.17. Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18. Coordinating Committee

A committee that a sponsor may organise to coordinate the conduct of a multicentre trial.

1.19. Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20. Contract Research Organisation

A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions

1.21. Direct Access

Permission to examine, analyse, verify, and reproduce any data and reports that are important to the evaluation of a clinical trial. Any party (e.g., domestic or foreign regulatory authorities, the sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subjects' identities and the sponsor’s proprietary information.

1.22. Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23. Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24. Good Clinical Practice

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25. Independent Data-Monitoring Committee (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26. Impartial Witness

A person who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the

subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27. Independent Ethics Committee

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility is to ensure the protection of the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing a favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting the informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with Good Clinical Practice as described in this guideline.

1.28. Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29. Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation’s facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30. Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31. Institutional Review Board

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and wellbeing of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32. Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33. Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34. Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35. Investigator/Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36. Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

1.37. Legally Acceptable Representative

An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38. Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, Good Clinical Practice, and the applicable regulatory requirement(s).

1.39. Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's standard operating procedures.

1.40. Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

1.41. Nonclinical Study

Biomedical studies not performed on human subjects.

1.42. Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee.

1.43. Original Medical Record

See Source Documents.

1.44. Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH Guideline the term "protocol" refers to protocol and protocol amendments.

1.45. Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46. Quality Assurance

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice and the applicable regulatory requirement(s).

1.47. Quality Control

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48. Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49. Regulatory Authorities

Bodies having the power to adopt applicable regulatory requirement(s). In this guideline the expression "Regulatory Authorities" includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50. Serious Adverse Event or Serious Adverse Drug Reaction

Any untoward medical occurrence that at any dose:

- results in death;

- is life threatening;

- requires inpatient hospitalisation or prolongation of existing hospitalisation;

- results in persistent or significant disability/incapacity;

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51. Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source data are contained in source documents (original records or certified copies).

1.52. Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53. Sponsor

An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54. Sponsor – Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency).

The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55. Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56. Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57. Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58. Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

1.59. Trial Site

The location(s) where trial-related activities are actually conducted.

1.60. Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61. Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in the case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention or prison. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62. Wellbeing (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

2. THE PRINCIPLES OF ICH GOOD CLINICAL PRACTICE

2.1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and the applicable regulatory requirement(s).

2.2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and wellbeing of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6. A trial should be conducted in compliance with the protocol that has received prior institutional review board/independent ethics committee approval/favourable opinion.

2.7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice. They should be used in accordance with the approved protocol.

2.13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1. Responsibilities

3.1.1. An institutional review board/independent ethics committee (hereinafter: Committee) should safeguard the rights, safety, and wellbeing of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects

3.1.2. The Committee should obtain the following documents: trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for

use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the Committees may regard as essential to fulfil their responsibilities. The Committee should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the date of the opinion, the trial, and the documents reviewed:

- approval/favourable opinion;

- modifications required prior to its approval/favourable opinion;

- disapproval / negative opinion; and

- termination/suspension of any prior approval/favourable opinion.

3.1.3. The Committee should consider the qualifications of the investigator for the proposed trial, as documented by a curriculum vitae and/or by any other relevant documentation the Committee requests.

3.1.4. The Committee should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5. The Committee may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the Committee, the additional information would add meaningfully to the protection of the rights, safety and/or wellbeing of the subjects.

3.1.6. When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the Committee should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7. Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (i.e. in emergency situations, see 4.8.15), the Committee should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.8. The Committee should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9. The Committee should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2. Composition, Functions and Operations

3.2.1. The Committee should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the Committee should include:

(a) At least five members;

(b) At least one member whose primary area of interest is in a non-scientific area;

(c) At least one member who is independent of the institution/trial site.

Only those Committee members who are independent of the investigator and the sponsor of the trial should vote/provide an opinion on a trial-related matter. A list of Committee members and their qualifications should be maintained.

3.2.2. The Committee should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with Good Clinical Practice and with the applicable regulatory requirement(s).

3.2.3. The Committee should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4. Only members who participate in the Committee review and discussion should vote/provide their opinion and/or advice.

3.2.5. The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the Committee or in the vote/opinion of the Committee.

3.2.6. The Committee may invite non-members with expertise in special areas for assistance.

3.3. Procedures

The Committee should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2. Scheduling, notifying its members of, and conducting its meetings.

3.3.3. Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5. Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the Committee.

3.3.6. Specifying that no subject should be admitted to a trial before the Committee issues its written approval/favourable opinion of the trial.

3.3.7. Specifying that no deviations from, or changes of, the protocol should be initiated without prior written Committee approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8. Specifying that the investigator should promptly report to the Committee:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

(c) All adverse drug reactions that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9. Ensuring that the Committee promptly notifies in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

3.4. Records

The Committee should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The Committee may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1. Investigator's Qualifications and Agreements

4.1.1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the Committee, and/or the regulatory authority(ies).

4.1.2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3. The investigator should be aware of, and should comply with, Good Clinical Practice and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2. Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3. Medical Care of Trial Subjects

4.3.1. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical decisions.

4.3.2. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4. Communication with the Committee

4.4.1. Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the Committee for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2. As part of the investigator's/institution's written application to the Committee, the investigator/institution should provide the Committee with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the Committee.

4.4.3. During the trial the investigator/institution should provide to the Committee all documents subject to review.

4.5. Compliance with Protocol

4.5.1. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the Committee. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the Committee of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in telephone number(s)).

4.5.3. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior approval/favourable opinion of the Committee. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the Committee for review and approval/favourable opinion,

(b) to the sponsor for agreement,

(c) to the regulatory authority(ies), if required.

4.6. Investigational Product(s)

4.6.1. Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4. The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7. Randomisation Procedures and Unblinding

The investigator should follow the trial's randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8. Informed Consent of Trial Subjects

4.8.1. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the Committee's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the Committee's approval/favourable opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's

legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the Committee.

4.8.6. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8. Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion with the subject/legally acceptable representative.

4.8.9. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject’s legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject’s participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative.

4.8.10. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research;

(b) The purpose of the trial;

(c) The trial treatment(s) and the probability for random assignment to each treatment;

(d) The trial procedures to be followed, including all invasive procedures;

(e) The subject's responsibilities;

(f) Those aspects of the trial that are experimental;

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant;

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this;

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks;

(j) The compensation and/or treatment available to the subject in the event of trial-related injury;

(k) The anticipated prorated payment, if any, to the subject for participating in the trial;

(l) The anticipated expenses, if any, to the subject for participating in the trial;

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled;

(n) That the monitor(s), the auditor(s), the Committee, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access;

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential;

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial;

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury;

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated;

(s) The expected duration of the subject's participation in the trial;

(t) The approximate number of subjects involved in the trial.

4.8.11. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject’s participation in

the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13. Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low;

(c) The negative impact on the subject's wellbeing is minimised and low;

(d) The trial is not prohibited by law;

(e) The approval/favourable opinion of the Committee is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended

Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with the documented approval/favourable opinion by the Committee, to protect the rights, safety and wellbeing of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9. Records and Reports

4.9.1. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor on the case report forms and in other required reports.

4.9.2. Data reported on the case report form, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3. Any change or correction to a case report form should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections on case report forms made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7. Upon the request of the monitor, auditor, the Committee, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10. Progress Reports

4.10.1. The investigator should submit written summaries of the trial status to the Committee annually, or more frequently, if requested by the Committee.

4.10.2. The investigator should promptly provide written reports to the sponsor, the Committee (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11. Safety Reporting

4.11.1. All serious adverse events should be reported immediately to the sponsor except for those serious adverse events that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, identification numbers (e.g., citizen’s identification numbers), and/or

addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the Committee.

4.11.2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3. For reported deaths, the investigator should supply the sponsor and the Committee with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12. Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the Committee, and should provide the sponsor and the Committee with a detailed written explanation of the termination or suspension.

4.12.2. If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the Committee and provide the Committee with a detailed written explanation of the termination or suspension.

4.12.3. If the Committee terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13. Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the Committee with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

5.1. Quality Assurance and Quality Control

5.1.1. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirement(s).

5.1.2. The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4. Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2. Contract Research Organisation (CRO)

5.2.1. A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a contract research organisation, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The contract research organisation should implement quality assurance and quality control.

5.2.2. Any trial-related duty and function that is transferred to and assumed by a contract research organisation should be specified in writing.

5.2.3. Any trial-related duties and functions not specifically transferred to and assumed by a contract research organisation are retained by the sponsor.

5.2.4. All references to a sponsor in this guideline also apply to a contract research organisation to the extent that a contract research organisation has assumed the trial-related duties and functions of a sponsor.

5.3. Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4. Trial Design

5.4.1. The sponsor should utilise qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and case report forms and planning the analyses to analysing and preparing interim and final clinical trial reports.

5.4.2. For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5. Trial Management, Data Handling, and Record Keeping

5.5.1. The sponsor should utilise appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2. The sponsor may consider establishing an independent data-monitoring committee to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The independent data-monitoring committee should have written operating procedures and maintain written records of all its meetings.

5.5.3. When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation);

(b) Maintains standard operating procedures for using these systems;

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail);

(d) Maintain a security system that prevents unauthorised access to the data;

(e) Maintain a list of the individuals who are authorised to make data changes (see 4.1.5 and 4.9.3);

(f) Maintain adequate backup of the data;

(g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.5.4. If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5. The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6. The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7. The sponsor should retain all sponsor-specific essential documents in conformity with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8. If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should

maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformity with the applicable regulatory requirement(s).

5.5.9. If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10. Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11. The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH country and until there are no pending or contemplated marketing applications in such countries or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12. The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed.

5.6. Investigator Selection

5.6.1. The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to be utilised in multicentre trials, their organisation and/or selection are the sponsor's responsibility.

5.6.2. Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3. The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with Good Clinical Practice, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the Committee (see 4.5.1);

(b) to comply with procedures for data recording/reporting;

(c) to permit monitoring, auditing and inspection (see 4.1.4); and

(d) to retain the trial-related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7. Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions

5.8. Compensation to Subjects and Investigators

5.8.1. If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2. The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3. When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9. Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10. Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11. Confirmation of Review by the Committee

5.11.1. The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution’s Committee;

(b) A statement obtained from the Committee that it is organised and operates according to Good Clinical Practice and the applicable laws and regulations.

(c) Documented Committee approval/favourable opinion and, if requested by the sponsor, a current copy of the protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the Committee may have requested.

5.11.2. If the Committee conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor

should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the Committee.

5.11.3. The sponsor should obtain from the investigator/institution documentation and dates of any re-approvals/re-evaluations of the Committee with a favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12. Information on Investigational Product(s)

5.12.1. When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2. The sponsor should update the Investigator's Brochure as significant new information becomes available.

5.13. Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1. The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable good manufacturing practice, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2. The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3. The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4. In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in the case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5. If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14. Supplying and Handling Investigational Product(s)

5.14.1. The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2. The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from the Committee and regulatory authority(ies)).

5.14.3. The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4. The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s);

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial);

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim);

(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5. The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use;

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15. Record Access

5.15.1. The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, review by the Committee, and regulatory inspection.

5.15.2. The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, review by the Committee, and regulatory inspection.

5.16. Safety Information

5.16.1. The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2. The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the Committee's approval/favourable opinion to continue the trial.

5.17. Adverse Drug Reaction Reporting

5.17.1. The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the Committees (where required), and to the regulatory authority(ies) of all adverse drug reactions that are both serious and unexpected.

5.17.2. Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3. The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18. Monitoring

5.18.1. Purpose

The purposes of trial monitoring are to verify that:

(a) The rights and wellbeing of human subjects are protected;

(b) The reported trial data are accurate, complete, and verifiable from source documents;

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with Good Clinical Practice, and with the applicable regulatory requirement(s).

5.18.2. Selection and Qualifications of Monitors

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor’s qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form, any other written information to be provided to subjects, the sponsor’s standard operating procedures, and the applicable regulatory requirement(s).

5.18.3. Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-

site monitoring, before, during, and after the trial. However in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with Good Clinical Practice. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4. Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator;

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period;

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial;

(ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s);

(iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s);

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately;

(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor;

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any;

(e) Verifying that written informed consent was obtained before each subject's participation in the trial;

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s);

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial;

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorised individuals;

(i) Verifying that the investigator enrols only eligible subjects;

(j) Reporting the subject recruitment rate;

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained;

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial;

(m) Checking the accuracy and completeness of the case report form entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the case report forms and are consistent with the source documents;

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects;

(iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the case report forms;

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the case report forms;

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the case report forms;

(n) Informing the investigator of any case report form entry error, omission, or illegibility.

The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorised to initial case report form changes for the investigator. This authorisation should be documented.

(o) Determining whether all adverse events are appropriately reported within the time periods required by the requirements of Good Clinical Practice, the protocol, the Committee, the sponsor, and the applicable regulatory requirement(s);

(p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial);

(q) Communicating deviations from the protocol, standard operating procedures, Good Clinical Practice, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5. Monitoring Procedures

The monitor(s) should follow the sponsor’s established written standard operating procedures as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6. Monitoring Report

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor has reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor’s designated representative.

5.19. Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1. Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, standard operating procedures, Good Clinical Practice, and the applicable regulatory requirements.

5.19.2. Selection and Qualification of Auditors

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor’s qualifications should be documented.

5.19.3. Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious Good Clinical Practice non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20. Noncompliance

5.20.1. Noncompliance with the protocol, standard operating procedures, Good Clinical Practice, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff, should lead to prompt action by the sponsor to secure compliance.

5.20.2. If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution’s participation in the trial. When an investigator's/institution’s participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21. Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The Committee should also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22. Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23. Multicentre Trials

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the Committee.

5.23.2 The case report forms are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental case report forms should also be provided that are designed to capture the additional data.

5.23.3. The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4. All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the case report forms.

5.23.5. Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1. General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (the qualified physician or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than the investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2. Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3. Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4. Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

6.4.1. A specific definition of the primary endpoints and the secondary endpoints to be measured during the trial.

6.4.2. A description of the type/design of trial to be conducted (e.g. double-blind, parallel design, placebo-controlled) and a schematic diagram of trial design, procedures and stages.

6.4.3. A description of the measures taken to minimise bias, including:

(a) Randomisation;

(b) Blinding.

6.4.4. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up (if required).

6.4.6. A description of the stopping rules or discontinuation criteria for individual subjects, parts of trial and entire trial.

6.4.7. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomisation codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the case report forms (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5. Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6. Treatment of Subjects

6.6.1. The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7. Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8. Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9. Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. The reason for the choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10. Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, review by the Committee, and regulatory inspection(s), providing direct access to source data/documents.

6.11. Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16. Supplements

(Note: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1. Introduction

The Investigator's Brochure is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The Investigator's Brochure also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an Investigator's Brochure, but the contents of the Investigator's Brochure should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an Investigator's Brochure and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive Investigator's Brochure may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an Investigator's Brochure specific to that new use should be prepared. The Investigator's Brochure should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Committee and/or regulatory authorities, before it is included in a revised Investigator's Brochure.

Generally, the sponsor is responsible for ensuring that an up-to-date Investigator's Brochure is made available to the investigator(s), and the investigators are responsible for providing the up-to-date Investigator's Brochure to the responsible Committee. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal Investigator's Brochure is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2. General Considerations

The IB should include:

7.2.1. Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example of the title page is given in Appendix 1.

7.2.2. Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the Investigator's Brochure as a confidential document for the sole information and use of the investigator's team and the Committee.

7.3. Contents of the Investigator's Brochure

The Investigator's Brochure should contain the following sections, each with literature references where appropriate:

7.3.1. Table of Contents

An example of the Table of Contents is given in Appendix 2

7.3.2. Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3. Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4. Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if

clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5. Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

• Species tested

• Number and sex of animals in each group

• Unit dose (e.g., milligram/kilogram (mg/kg))

• Dose interval

• Route of administration

• Duration of dosing

• Information on systemic distribution

• Duration of post-exposure follow-up

• Results, including the following aspects:

− Nature and frequency of pharmacological or toxic effects

− Severity or intensity of pharmacological or toxic effects

− Time to onset of effects

− Reversibility of effects

− Duration of effects

− Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

− Single dose

− Repeated dose

− Carcinogenicity

− Special studies (e.g. irritancy and sensitisation)

− Reproductive toxicity

− Genotoxicity (mutagenicity)

7.3.6. Effect in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from marketing experience.

(a) Pharmacokinetics and Product Metabolism in Humans

− A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

− Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

− Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

− Population subgroups (e.g., gender, age, and impaired organ function).

− Interactions (e.g., product-product interactions and effects of food).

− Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The Investigator’s Brochure should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The Investigator’s Brochure should identify countries where the investigational product has been approved or marketed. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The Investigator’s Brochure should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7. Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided

with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4. APPENDIX 1:

TITLE PAGE (*Example*)

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved), Trade Name(s) (if legally permissible and desired by the sponsor):

INVESTIGATOR'S BROCHURE

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date of Previous Edition:

7.5. APPENDIX 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (*Example*)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1. Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor.

These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences; 2) during the clinical conduct of the trial; and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution’s site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).

8.2. Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

Title of Document	Purpose	Located in Files of	
		Investigator/Institution	Sponsor
8.2.1. INVESTIGATOR’S BROCHURE	To document that relevant and current scientific information	X	X

	about the investigational product has been provided to the investigator		
8.2.2. SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM	To document investigator and sponsor agreement to the protocol/amendment(s) and the case report form	X	X
8.2.3. INFORMATION GIVEN TO TRIAL SUBJECT			
– INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
– ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4. FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5. INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6. SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:	To document agreements		
– investigator/institution and sponsor		X	X
– investigator/institution and contract research organisation		X	X

		(where required)	
– sponsor and contract research organisation			X
– investigator/institution and authority(ies) (where required)		X	X
8.2.7. DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
– protocol and any amendments			
– case report form(s)			
– informed consent form(s)			
– any other written information to be provided to the subject(s)			
– advertisement for subject recruitment (if used)			
– subject compensation (if any)			
– any other given approval			
8.2.8. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the institutional review board/independent ethics committee is constituted in agreement with Good Clinical Practice	X	X (where required)
8.2.9. REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)	To document appropriate authorisation/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10. CURRICULUM VITAE AND/OR OTHER RELEVANT	To document qualifications and	X	X

DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	eligibility to conduct trial and/or provide medical supervision of subjects		
8.2.11. NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
8.2.12. MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS	To document competence of facility to perform required test(s) , and support reliability of results	X (where required)	X
– certification, or			
– accreditation, or			
– established quality control and/or external quality assessment or			
– other validation (where required)			
8.2.13. SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14. INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15. SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S)	To document shipment dates, batch numbers	X	X

AND TRIAL-RELATED MATERIALS	and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability		
8.2.16. CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17. DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18. MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
8.2.19. PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20. TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3. During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

Title of Document	Purpose	Located in Files of	
		Investigator/Institution	Sponsor
8.3.1. INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	V
8.3.2. ANY REVISION TO:	To document revisions of these trial-related documents that take effect during trial	X	X
– protocol/amendment(s) and case report form(s)			
– informed consent form(s)			
– any other written information provided to subjects			
– advertisement for subject recruitment (if used)			
8.3.3. DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
– protocol amendment(s)			

– revision(s) of:			
– informed consent form(s)			
– any other written information to be provided to the subject			
– advertisement for subject recruitment (if used)			
– any other given approval			
– continuing review of trial (where required)			
8.3.4. REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:	To document compliance with applicable regulatory requirements	X (where required)	X
– protocol amendment(s) and other documents			
8.3.5. CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	(see 8.2.10)	X	X
8.3.6. UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7. UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
– certification, or			
– accreditation, or			
– established quality control and/or external quality assessment or			
– other validation (where required)			
8.3.8. DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	(see 8.2.15.)	X	X
8.3.9. CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	(see 8.2.16.)		X

8.3.10. MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		X
8.3.11. RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
– letters			
– meeting notes			
– notes of telephone calls			
8.3.12. SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with Good Clinical Practice and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13. SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of	X	

	subject		
8.3.14. SIGNED, DATED AND COMPLETED CASE REPORT FORMS	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15. DOCUMENTATION OF CORRECTIONS OF CASE REPORT FORMS	To document all changes/additions or corrections made to case report form(s) after initial data were recorded	X (copy)	X (original)
8.3.16. NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11 of the Guidance	X	X
8.3.17. NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and the Committee of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2 of the	X (where required)	X

	Guidance		
8.3.18. NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2 of the Guidance	X	X
8.3.19. INTERIM OR ANNUAL REPORTS TO THE COMMITTEE AND AUTHORITY(IES)	Interim or annual reports provided to the Committee in accordance with 4.10 and to authority(ies) in accordance with 5.17.3 of the Guidance	X	X (where required)
8.3.20. SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21. SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22. SUBJECT ENROLMENT LOG	To document chronological enrolment of subjects by trial number	X	
8.3.23. INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that	X	X

	investigational product(s) have been used according to the protocol		
8.3.24. SIGNATURE SHEET	To document signatures and initials of all persons authorised to make entries and/or corrections on case report forms	X	X
8.3.25. RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

8.4.1. INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2. DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3. COMPLETED SUBJECT IDENTIFICATION CODE LIST	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	

8.4.4. AUDIT CERTIFICATE (if available)	To document that audit was performed.		X
8.4.5. FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files.		X
8.4.6. TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred.		X
8.4.7. FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial.	X	
8.4.8. CLINICAL STUDY REPORT	To document results and interpretation of trial.	X (if applicable)	X

SCHEDULE II

European Medicines Agency

Committee for medicinal products for human use

London, 27 July 2000

CPMP/ICH/2711/99

ICH Topic E 11

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION

Step 4

GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION (CPMP/ICH/2711/99)

Entry into force: January 2001

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION

1. INTRODUCTION

1.1. Objectives of the guidance

The number of medicinal products currently labelled for paediatric use is limited. It is the goal of this guidance to encourage and facilitate timely paediatric medicinal product development internationally. The guidance provides an outline of critical issues in paediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the paediatric population.

1.2. Background

Other ICH documents with relevant information impacting on paediatric studies include:

E2: Clinical Safety Data Management

E3: Structure and Content of Clinical Study Reports

E4: Dose-Response Information to Support Drug Registration

E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

E6: Good Clinical Practice: Consolidated Guideline

E8: General Considerations for Clinical Trials

E9: Statistical Principles for Clinical Trials

E10: Choice of Control Group in Clinical Trials

M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Q1: Stability Testing

Q2: Validation of Analytical Procedures

Q3: Impurity Testing

1.3. Scope of the guidance

Specific clinical study issues addressed include: (1) considerations when initiating a paediatric programme for a medicinal product; (2) timing of initiation of paediatric studies during medicinal product development; (3) types of studies (pharmacokinetic, pharmacokinetic/pharmacodynamic (PK/PD), efficacy, safety); (4) age categories; and (5) ethics of paediatric clinical investigation. This guidance is not intended to be comprehensive; other ICH guidance, as well as documents from regional regulatory authorities and paediatric societies, provide additional detail.

1.4. General principles

Paediatric patients should be given medicinal products that have been appropriately evaluated for their use. Safe and effective pharmacotherapy in paediatric patients requires the timely development of information on the proper use of medicinal products in paediatric patients of various ages and, often, the development of paediatric formulations of those products. Advances in formulation chemistry and in paediatric study design will help facilitate the development of medicinal products for paediatric use. Drug development programmes should usually include the paediatric patient population when a product is being developed for a disease or condition in adults and when it is anticipated the product will be used in the paediatric population. Obtaining knowledge of the effects of medicinal products in paediatric patients is an important goal. However, this should be done without compromising the wellbeing of paediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole.

2. GUIDANCE

2.1. Issues when initiating a paediatric medicinal product development programme

Data on the appropriate use of medicinal products in the paediatric population should be generated unless the use of a specific medicinal product in paediatric patients is clearly inappropriate. The timing of initiation of clinical studies in relation to studies conducted in adults, which may be influenced by regional public health and medical needs, is discussed in section 2.3. Justification for the timing and the approach to the clinical programme needs to be clearly addressed with regulatory authorities at an early stage and then periodically during the medicinal product development process. The paediatric development programme should not delay completion of adult studies and the availability of a medicinal product for adults.

The decision to proceed with a paediatric development programme for a medicinal product, and the nature of that programme, involve consideration of many factors, including:

• the prevalence of the condition to be treated in the paediatric population;

• the seriousness of the condition to be treated;

• the availability and suitability of alternative treatments for the condition in the paediatric population, including the efficacy and the adverse event profile (including any unique paediatric safety issues) of those treatments;

• whether the medicinal product is novel or one of a class of compounds with known properties;

• whether there are unique paediatric indications for the medicinal product;

• the need for the development of paediatric-specific endpoints;

• the age ranges of paediatric patients likely to be treated with the medicinal product;

• unique paediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues;

• the potential need for paediatric formulation development.

Of these factors, the most important is the presence of a serious or life-threatening disease for which the medicinal product represents a potentially important advance in therapy. This situation suggests relatively urgent and early initiation of paediatric studies.

Information from nonclinical safety studies to support a paediatric clinical programme is discussed in ICH M3, section 11. It should be noted that the most relevant safety data for paediatric studies ordinarily come from adult human exposure. Repeated dose toxicity studies, reproduction toxicity studies and genotoxicity tests would generally be available. The need for juvenile animal studies should be considered on a case-by-case basis and be based on developmental toxicology concerns.

2.2. Paediatric formulations

There is a need for paediatric formulations that permit accurate dosing and enhance patient compliance. For oral administration, different types of formulations, flavours and colours may be more acceptable in one region than another. Several formulations, such as liquids, suspensions, and chewable tablets, may be needed or desirable for paediatric patients of different ages. Different drug concentrations in these various formulations may also be needed. Consideration should also be given to the development of alternative delivery systems.

For injectable formulations, appropriate drug concentrations should be developed to allow accurate and safe administration of the dose. For medicinal products supplied as single-use vials, consideration should be given to dose-appropriate single-dose packaging.

The toxicity of some excipients may vary across paediatric age groups and between paediatric and adult populations, e.g., benzyl alcohol is toxic in the preterm newborn.

Depending on the active substance and excipients, appropriate use of the medicinal product in the newborn may require a new formulation or appropriate information about the dilution of an existing formulation. International harmonisation on the acceptability of formulation excipients and of validation procedures would help ensure that appropriate formulations are available for the paediatric population everywhere.

2.3. Timing of studies

During clinical development, the timing of paediatric studies will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatments. Since development of paediatric formulations can be difficult and time consuming, it is important to consider the development of these formulations early in medicinal product development.

2.3.1. Medicinal products for diseases predominantly or exclusively affecting paediatric patients

In this case, the entire development programme will be conducted in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults. Some products may reasonably be studied only in the paediatric population even in the initial phases, e.g., when studies in adults would yield little useful information or expose them to inappropriate risk. Examples include surfactant for respiratory distress syndrome in preterm infants and therapies targeted at metabolic or genetic diseases unique to the paediatric population.

2.3.2. Medicinal products intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options

The presence of a serious or life-threatening disease for which the product represents a potentially important advance in therapy suggests the need for relatively urgent and early initiation of paediatric studies. In this case, medicinal product development should begin early in the paediatric population, following assessment of initial safety data and reasonable evidence of potential benefit. Paediatric study results should be part of the marketing application database. In circumstances where this has not been possible, lack of data should be justified in detail.

2.3.3. Medicinal products intended to treat other diseases and conditions

In this case, although the medicinal product will be used in paediatric patients, there is less urgency than in the previous cases and studies would usually begin at later phases of clinical development or, if a safety concern exists, even after substantial postmarketing experience in adults. Companies should have a clear plan for paediatric studies and reasons for their timing. Testing of these medicinal products in the paediatric population would usually not begin until Phase 2 or 3. In most cases, only limited paediatric data would be available at the time of submission of the application, but more would be expected after marketing.

The development of many new chemical entities is discontinued during or following Phase 1 and 2 studies in adults for lack of efficacy or an unacceptable side effect profile. Therefore, very early initiation of testing in paediatric patients might needlessly expose these patients to a compound that will be of no benefit. Even for a non-serious disease, if the medicinal product represents a major therapeutic advance for the paediatric population, studies should begin early in development, and the submission of paediatric data would be expected in the application.

Lack of data should be justified in detail. Thus, it is important to carefully weigh benefit/risk and therapeutic need in deciding when to start paediatric studies.

2.4. Types of studies

The principles outlined in ICH E4, E5, E6, and E10 apply to paediatric studies. Several paediatric specific issues are worth noting. When a medicinal product is studied in paediatric patients in one region, the intrinsic (e.g., pharmacogenetic) and extrinsic 1[1][1] (e.g., diet) factors that could impact on the extrapolation of data to other regions should be considered.

When a medicinal product is to be used in the paediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and paediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of paediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of paediatric doses that will produce blood levels similar to those observed in adults. If this approach is taken, adult pharmacokinetic data should be available to plan the paediatric studies.

When a medicinal product is to be used in younger paediatric patients for the same indication(s) as those studied in older paediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger paediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of paediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for paediatric use.

An approach based on pharmacokinetics is likely to be insufficient for medicinal products where blood levels are known or expected not to correspond with efficacy or where there is concern that the concentration-response relationship may differ between the adult and paediatric populations.

In such cases, studies of the clinical or the pharmacological effect of the medicinal product would usually be expected. Where the comparability of the disease course or outcome of therapy in paediatric patients is expected to be similar to adults, but the appropriate blood levels are not clear, it may be possible to use measurements of a pharmacodynamic effect related to clinical effectiveness to confirm the expectations of effectiveness and to define the dose and concentration needed to attain that pharmacodynamic effect. Such studies could provide increased confidence that achieving a given exposure to the medicinal product in paediatric patients would result in the desired therapeutic outcomes. Thus, a pharmacokinetic and pharmacodynamic approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies.

In other situations where a pharmacokinetic approach is not applicable, such as for topically active products, extrapolation of efficacy from one patient population to another may be based on studies that include pharmacodynamic endpoints and/or appropriate alternative assessments. Local tolerability studies may be needed. It may be important to determine blood levels and systemic effects to assess safety.

When novel indications are being sought for the medicinal product in paediatric patients, or when the disease course and outcome of therapy are likely to be different in adults and paediatric patients, clinical efficacy studies in the paediatric population would be needed.

2.4.1. Pharmacokinetics

Pharmacokinetic studies should generally be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

Relative bioavailability comparisons of paediatric formulations with the adult oral formulation typically should be done in adults. Definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the medicinal product is likely to be used should be conducted in the paediatric population.

Pharmacokinetic studies in the paediatric population are generally conducted in patients with the disease. This may lead to higher inter-subject variability than studies in normal volunteers, but the data better reflect clinical use.

For medicinal products that exhibit linear pharmacokinetics in adults, single-dose pharmacokinetic studies in the paediatric population may provide sufficient information for dosage selection.

This can be corroborated, if indicated, by sparse sampling in multidose clinical studies. Any non-linearity in absorption, distribution, and elimination in adults and any difference in duration of effect between single and repeated dosing in adults would suggest the need for steady state studies in the paediatric population. All these approaches are facilitated by knowledge of adult pharmacokinetic parameters. Knowing the pathways of clearance (renal and metabolic) of the medicinal product and understanding the age-related changes of those processes will often be helpful in planning paediatric studies.

Dosing recommendations for most medicinal products used in the paediatric population are usually based on milligram (mg)/kilogram (kg) body weight up to a maximum adult dose. While dosing based on mg/square metre body surface area might be preferred, clinical experience indicates that errors in measuring height or length (particularly in smaller children and infants) and calculation errors of body surface area from weight and height are common. For some medications (e.g., medications with a narrow therapeutic index, such as those used in oncology), surface-area-guided dosing may be necessary, but extra care should be taken to ensure proper dose calculation.

Practical considerations to facilitate pharmacokinetic studies

The volume of blood withdrawn should be minimised in paediatric studies. Blood volumes should be justified in protocols. Institutional Review Boards/Independent Ethics Committees

(IRB's/IEC's) review and may define the maximum amount of blood (usually on a millilitres (ml)/kg or percentage of total blood volume basis) that may be taken for investigational purposes. Several approaches can be used to minimise the amount of blood drawn and/or the number of venipunctures.

• use of sensitive assays for parent drugs and metabolites to decrease the volume of blood required per sample;

• use of laboratories experienced in handling small volumes of blood for pharmacokinetic analyses and for laboratory safety studies (blood counts, clinical chemistry);

• collection of routine, clinical blood samples wherever possible at the same time as samples are obtained for pharmacokinetic analysis;

• the use of indwelling catheters, etc., to minimise distress as discussed in section 2.6.5;

• use of population pharmacokinetics and sparse sampling based on optimal sampling theory to minimise the number of samples obtained from each patient. Techniques include:

• sparse sampling approaches where each patient contributes as few as 2 to 4 observations at predetermined times to an overall "population area-under-the-curve";

• population pharmacokinetic analysis using the most useful sampling time points derived from modelling of adult data.

2.4.2 Efficacy

The principles in study design, statistical considerations and choice of control groups detailed in ICH E6, E9, and E10 generally apply to paediatric efficacy studies. There are, however, certain features unique to paediatric studies. The potential for extrapolation of efficacy from studies in adults to paediatric patients or from older to younger paediatric patients is discussed in section 2.4. Where efficacy studies are needed, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. Measurement of subjective symptoms such as pain requires different assessment instruments for patients of different ages. In paediatric patients with chronic diseases, the response to a medicinal product may vary among patients not only because of the duration of the disease and its chronic effects but also because of the developmental stage of the patient. Many diseases in the preterm and term newborn infant are unique or have unique manifestations precluding extrapolation of efficacy from older paediatric patients and call for novel methods of outcome assessment.

2.4.3. Safety

ICH guidance on E2 topics and ICH E6, which describes adverse event reporting, applies to paediatric studies. Age-appropriate, normal laboratory values and clinical measurements should be used in adverse event reporting. Unintended exposures to medicinal products (accidental ingestions, etc.) may provide the opportunity to obtain safety and pharmacokinetic information and to maximise understanding of dose-related side effects.

Medicinal products may affect physical and cognitive growth and development, and the adverse event profile may differ in paediatric patients. Because developing systems may respond differently from matured adult organs, some adverse events and drug interactions that occur in paediatric patients may not be identified in adult studies. In addition, the dynamic processes of growth and development may not manifest an adverse event acutely, but at a later stage of growth and maturation. Long-term studies or surveillance data, either while patients are on chronic therapy or during the post-therapy period, may be needed to determine possible effects on skeletal, behavioural, cognitive, sexual, and immune maturation and development.

2.4.4. Postmarketing information

Normally the paediatric database is limited at the time of approval. Therefore, postmarketing surveillance is particularly important. In some cases, long-term follow-up studies may be important to determine effects of certain medications on growth and development of paediatric patients. Postmarketing surveillance and/or long-term follow-up studies may provide safety and/or efficacy information for subgroups within the paediatric population or additional information for the entire paediatric population.

2.5. Age classification of paediatric patients

Any classification of the paediatric population into age categories is to some extent arbitrary, but a classification such as the one below provides a basis for thinking about study design in paediatric patients. Decisions on how to stratify studies and data by age should take into consideration developmental biology and pharmacology. Thus, a flexible approach is necessary to ensure that studies reflect current knowledge of paediatric pharmacology. The identification of which ages to study should be medicinal product-specific and justified.

If the clearance pathways of a medicinal product are well established and the ontogeny of the pathways understood, age categories for pharmacokinetic evaluation might be chosen based on any “break point” where clearance is likely to change significantly.

Sometimes, it may be more appropriate to collect data over broad age ranges and examine the effect of age as a continuous covariant. For efficacy, different endpoints may be established for paediatric patients of different ages, and the age groups might not correspond to the categories presented below. Dividing the paediatric population into many age groups might needlessly increase the number of patients required. In longer term studies, paediatric patients may move from one age category to another; the study design and statistical plans should prospectively take into account changing numbers of patients within a given age category.

The following is one possible categorisation. There is, however, considerable overlap in developmental (e.g., physical, cognitive, and psychosocial) issues across the age categories. Ages are defined in completed days, months, or years.

• preterm newborn infants;

• term newborn infants (0 to 27 days);

• infants and toddlers (28 days to 23 months);

• children (2 to 11 years);

• adolescents (12 to 16-18 years, dependent on region).

2.5.1. Preterm newborn infants

The study of medicinal products in preterm newborn infants presents special challenges because of the unique pathophysiology and responses to therapy in this population. The complexity of and ethical considerations involved in studying preterm newborn infants suggest the need for careful protocol development with expert input from neonatologists and neonatal pharmacologists. Only rarely will it be possible to extrapolate efficacy from studies in adults or even in older paediatric patients to the preterm newborn infant.

The category of preterm newborn infants is not a homogeneous age group. A 25-week gestation, 500-gram (g) newborn is very different from a 30-week gestation newborn weighing 1,500 g.

A distinction should also be made for low-birth-weight babies as to whether they are immature or growth retarded.

Important features that should be considered for these patients include: (1) gestational age at birth and age after birth (adjusted age); (2) immaturity of renal and hepatic clearance mechanisms; (3) protein binding and displacement issues (particularly bilirubin); (4) penetration of medicinal products into the central nervous system (CNS); (5) unique neonatal disease states (e.g., respiratory distress syndrome of the newborn, patent ductus arteriosus, primary pulmonary hypertension); (6) unique susceptibilities of the preterm newborn (e.g., necrotizing enterocolitis, intraventricular haemorrhage, retinopathy of prematurity); (7) rapid and variable maturation of all physiologic and pharmacologic processes leading to different dosing regimens with chronic exposure; and (8) transdermal absorption of medicinal products and other chemicals.

Study design issues that should be considered include: (1) weight and age (gestational and postnatal) stratification; (2) small blood volumes (a 500-g infant has 40 mL of blood); (3) small numbers of patients at a given centre and differences in care among centres; and (4) difficulties in assessing outcomes.

2.5.2. Term newborn infants (0 to 27 days)

While term newborn infants are developmentally more mature than preterm newborn infants, many of the physiologic and pharmacologic principles discussed above also apply to term infants. Volumes of distribution of medicinal products may be different from those in older paediatric patients because of different body water and fat content and high body-surface-area-to weight ratio. The blood-brain barrier is still not fully mature and medicinal products and endogenous substances (e.g., bilirubin) may gain access to the CNS with resultant toxicity. Oral absorption of medicinal products may be less predictable than in older paediatric patients. Hepatic and renal clearance mechanisms are immature and rapidly changing; doses may need to be adjusted over the first weeks of life. Many examples of increased susceptibility to toxic effects of medicinal products result from limited clearance in these patients (e.g., chloramphenicol grey baby syndrome). On the other hand, term newborn

infants may be less susceptible to some types of adverse effects (e.g., aminoglycoside nephrotoxicity) than are patients in older age groups.

2.5.3. Infants and toddlers (28 days to 23 months)

This is a period of rapid CNS maturation, immune system development and total body growth. Oral absorption becomes more reliable. Hepatic and renal clearance pathways continue to mature rapidly. By 1 to 2 years of age, clearance of many drugs on an mg/kg basis may exceed adult values.

The developmental pattern of maturation is dependent on specific pathways of clearance. There is often considerable inter-individual variability in maturation.

2.5.4. Children 2 to 11 years

Most pathways of drug clearance (hepatic and renal) are mature, with clearance often exceeding adult values. Changes in clearance of a drug may be dependent on maturation of specific metabolic pathways.

Specific strategies should be addressed in protocols to ascertain any effects of the medicinal product on growth and development. Children achieve several important milestones of psychomotor development that could be adversely affected by CNS-active drugs. Entry into school and increased cognitive and motor skills may affect a child's ability to participate in some types of efficacy studies. Factors useful in measuring the effects of a medicinal product on children include skeletal growth, weight gain, school attendance, and school performance.

Recruitment of patients should ensure adequate representation across the age range in this category, as it is important to ensure a sufficient number of younger patients for evaluation.

Stratification by age within this category is often unnecessary, but it may be appropriate to stratify patients based on pharmacokinetic and/or efficacy endpoint considerations.

The onset of puberty is highly variable and occurs earlier in girls, in whom normal onset of puberty may occur as early as 9 years of age. Puberty can affect the apparent activity of enzymes that metabolize drugs, and dose requirements for some medicinal products on an mg/kg basis may decrease dramatically (e.g., theophylline). In some cases, it may be appropriate to specifically assess the effect of puberty on a medicinal product by studying pre- and post-pubertal paediatric patients. In other cases, it may be appropriate to record Tanner stages of pubertal development or obtain biological markers of puberty and examine data for any potential influence of pubertal changes.

2.5.5. Adolescents (12 to 16-18 years, dependent on region)

This is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development.

In certain studies, pregnancy testing and review of sexual activity and contraceptive use may be appropriate.

This is also a period of rapid growth and continued neurocognitive development. Medicinal products and illnesses that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt and, by changing the pattern of growth, may affect final height. Evolving cognitive and emotional changes could potentially influence the outcome of clinical studies.

Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.

Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect appearance. In clinical studies compliance checks are important.

Recreational use of unprescribed drugs, alcohol and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centres knowledgeable and skilled in the care of this special population.

2.6. Ethical issues in paediatric studies

The paediatric population represents a vulnerable group of participants. Therefore, special measures are needed to protect the rights of paediatric study participants and to shield them from undue risk. The purpose of this section is to provide an ethical framework for paediatric studies.

To be of benefit to those participating in a clinical study, as well as to the rest of the paediatric population, a clinical study must be properly designed to ensure the quality and clarity of the data obtained. In addition, participants in clinical studies are expected to benefit from the clinical study except under the special circumstances discussed in ICH E6, section 4.8.14.

2.6.1. Institutional Review Board/Independent Ethics Committee (Committee)

The roles and responsibilities of the Committee as detailed in ICH E6 are critical to the protection of study participants. When protocols involving the paediatric population are reviewed, there should be Committee members or experts consulted by the Committee who are knowledgeable in paediatric ethical, clinical, and psychosocial issues.

2.6.2. Recruitment

Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)/legal guardian or the study participant.

Reimbursement and subsistence costs may be covered in the context of a paediatric clinical study. Any compensation should be approved by the Committee.

When studies are conducted in the paediatric population, an attempt should be made to include individuals representing the demographics of the region and the disease being studied, unless there is a valid reason for restricting enrolment.

2.6.3. Consent and assent

As a rule, a paediatric subject is legally unable to provide informed consent. Therefore paediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand. Where appropriate, participants should assent to enrol in a study (age of assent to be determined by the Committee or be consistent with local legal requirements).

Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form or the written informed consent. In all cases, participants should be made aware of their rights to decline to participate or to withdraw from the study at any time. Attention should be paid to signs of undue distress in patients who are unable to clearly articulate their distress.

Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a paediatric patient would be jeopardised by his or her failing to participate in the study. In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study. Emancipated or mature minors (defined by local laws) may be capable of giving autonomous consent.

Information that can be obtained in a less vulnerable, consenting population should not be obtained in a more vulnerable population or one in which the patients are unable to provide individual consent. Studies in handicapped or institutionalised paediatric populations should be limited to diseases or conditions found principally or exclusively in these populations, or situations in which the disease or condition in these paediatric patients would be expected to alter the disposition or pharmacodynamic effects of a medicinal product.

2.6.4. Minimising risk

However important a study may be to prove or disprove the value of a treatment, participants may suffer injury as a result of inclusion in the study, even if the whole community benefits. Every effort should be made to anticipate and reduce known hazards. Investigators should be fully aware before the start of a clinical study of all relevant preclinical and clinical toxicity of the medicinal product. To minimise risk in paediatric clinical studies, those conducting the study should be properly trained and experienced in studying the paediatric population, including the evaluation and management of potential paediatric adverse events.

In designing studies, every attempt should be made to minimise the number of participants and of procedures, consistent with good study design.

Mechanisms should be in place to ensure that a study can be rapidly terminated should an unexpected hazard be noted.

2.6.5. Minimising Distress

Repeated invasive procedures may be painful or frightening.

Discomfort can be minimised if studies are designed and conducted by investigators experienced in the treatment of paediatric patients.

Protocols and investigations should be designed specifically for the paediatric population (not simply re-worked from adult protocols) and approved by the Committee as described in section 2.6.1.

Practical considerations to ensure that participants' experiences in clinical studies are positive and to minimise discomfort and distress include the following:

• personnel knowledgeable and skilled in dealing with the paediatric population and its age appropriate needs, including skill in performing paediatric procedures;

• a physical setting with furniture, play equipment, activities, and food appropriate for age;

• the conduct of studies in a familiar environment such as the hospital or clinic where participants normally receive their care;

• approaches to minimise discomfort of procedures, such as:

• topical anaesthesia to place IV catheters;

• indwelling catheters rather than repeated venipunctures for blood sampling;

• collection of some protocol-specified blood samples when routine clinical samples are obtained.

The Committee should consider how many venipunctures are acceptable in an attempt to obtain blood samples for a protocol and ensure a clear understanding of procedures if an indwelling catheter fails to function over time. The participant's right to refuse further investigational procedures must be respected except as noted in section 2.6.3.

ANNEX III

REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT IN THE REPUBLIC OF CROATIA TO THE HEALTH MINISTER

– To be filled in by the sponsor or the applicant responsible for the accuracy of the data included

Sponsor:

Applicant:

*Date of receiving the file: *Date of receiving the full set of documents:	
A. General information	
Title of the trial:	
Protocol code number:	
EUDRACT number:	
Phase of the trial (I, II, III, IV)	
List of states in which the clinical trial has been authorised and/or in which the clinical trial is planned before the date of submitting the request to the ministry competent for health	
Version and date of the protocol	
Investigator's Brochure	
Informed consent	
Document on insurance Insurance policy number, date of issue, term of insurance	
B. Identification of the investigators	
Principal investigator in the Republic of Croatia	
Address:	
Telephone/telefax	
Email	
Informed consent, version and date, signed by the principal investigator	
Heads of trial centres participating in the trial (investigators)	

C. Investigational substance related data	
Does the investigational medicinal product to be used in the trial have a marketing authorisation in the Republic of Croatia?	
States that have granted marketing authorisation for the investigational substance	
Generic name	
Trade name	
Manufacturer	
Dosing and administration of the investigational medicinal product in this trial	
Results of non-clinical trials (or reasons why there are none)	
Primary hypothesis of the trial (and secondary, if relevant)	
Ethical considerations concerning the trial (to identify and specify problems, if any; to present new information that could be generated in the trial, and the relevance of such information; to evaluate the potential risk of injuries or other hazards to the participants; to present an evaluation of the risk/benefit ratio)	
If planned, give reasons for the inclusion of persons pertaining to particularly vulnerable groups, such as minors, people who are unconscious, people who are not able to make their own informed decisions, people with disability	
Description of trial subject recruitment procedures (all materials to be used must be attached)	
Procedures for providing information to and obtaining the consent from potential trial subjects (parents or legal guardians– if included)	
Procedures in the trial, specifying any deviations from the habitual practice that might be necessary	
Risk assessment, the unintended risks of treatment and procedures to be used (including pain, discomfort, breach of personal integrity, and the way(s) of avoiding and/or managing unintended/unwanted events)	
Previous experience in conducting similar procedures in the legal person(s) where the clinical trial is to be conducted	

Intended benefits for trial subjects	
Describe the relationship between trial subjects and investigators (e.g., patient-doctor, student-professor, etc.)	
Procedures conducted to verify whether potential trial subjects are at the same time taking part in another clinical trial or whether sufficient time has passed since participation in an earlier clinical trial (especially important in the case of inclusion of healthy trial subjects):	
Procedures used to ensure the protection of privacy of recorded data, source documents or samples:	
Plan for treatment or care after the end of trial (who will be responsible and where):	
Statistical considerations and reasons for the inclusion of the stated number of trial subjects	
Refundable costs and the trial subject refunding procedure (the amount and description of the costs paid during the trial, such as travel costs, the refund of loss of earnings, compensation for pain and discomfort, etc.):	
Rules for suspension (or premature termination) of a clinical trial in a legal person(s) where the clinical trial is to be conducted:	
Contract on direct access to data by the investigator, principles governing the publication of data, etc. (unless specified in the protocol):	
Sources of finance (unless specified in the protocol) and information on financial or other interests of the investigator.	
Monitor of the trial	
Person responsible for the clinical trial on the part of the applicant/sponsor of the clinical trial of a medicinal product	
Date:	
Signature:	

* To be filled in by the MH

ANNEX IV

Request for opinion from the Central Ethics Committee concerning the acceptability of a clinical trial on a medicinal product

– To be filled in by the sponsor or the applicant responsible for the accuracy of the data included

– Principal investigator's signature confirms only examination of the informed consent form

Sponsor:

Applicant:

Central Ethics Committee – Registration number EUDRACT number	
Date of receiving the complete set of documents	
A. General information	
Title of the trial, code	
Phase of the trial (I, II, III, IV.)	
Version and date of the protocol	
Investigator's Brochure (version and date)	
Informed consent (version and date)	
Document on insurance	Insurance policy number, date of issue, term of insurance
Certificate of fees paid	
Summary of the trial (version and date)	Based on the special form of the Central Ethics Committee
B. Identification of the investigators	
Principal investigator in the Republic of Croatia	
Address*	
Telephone and telefax	
Email	
Principal investigator has reviewed the translation of the informed consent	

state the version and date – as confirmed by signing this section	
Heads of trial centres participating in the trial (investigators), (addresses, telephone, fax, email)	
C. Investigational substance related data	
Does the investigational medicinal product to be used in the trial have a marketing authorisation in the Republic of Croatia?	
States that have granted a marketing authorisation for the investigational substance	
Generic name	
Trade name	
Manufacturer	
Dosing and administration of the investigational medicinal product in this trial	
Summary of non-clinical trials (only for trials in phases I and II)	
Known side-effects	
Known contraindications	
Known interactions	
D. Use of placebo	Yes No
If yes: information on the existing effective therapeutic options, if approved, for this condition or disease	
Hazard to the subject in case of non-treatment or use of placebo in this disease or condition	
E. Supplying the medicinal product	
Will the patient and/or the establishment be receiving the medicinal product for the clinical trial free of charge	
Is a follow-up to the trial planned in the form an open trial; will the participants receive the medicinal product free of charge, and for how long?	

* Address of the principal investigator which is at the same time the address for all communication between the Central Ethics Committee and the investigator in the trial

ANNEX V

Synopsis of the trial
(To be filled out by the sponsor or the applicant responsible for the accuracy of the data)

Sponsor:

Applicant:

Title of the trial	
Establishment(s) in which the trial is to be conducted	
Total number of centres	
Protocol code, EUDRACT	
Trial phase I. II. III. IV.	
Indications	
Objectives (comparators)	Primary: Secondary objective:
Population of trial subjects, diagnosis, and main inclusion criterion	
Duration of the trial	
Beginning and end of the trial (in Croatia, elsewhere)	
Criteria used to measure the effects of the trial	
Methodology (type of trial)(tick)	open, double blind, placebo-controlled
Number of visits, controls	
Side effects	
Administration and dosage	
Special remarks	
The principal investigator has reviewed the translation of the informed consent (please state the version and the date) and the summary of the protocol as confirmed by his/her signature on this form of the Central Ethics Committee	
Signature of the applicant/sponsor and the date	

ANNEX VI

CENTRAL ETHICS COMMITTEE **FORM FOR REGISTRATION AND APPRAISAL OF A NON-INTERVENTIONAL TRIAL ON A MEDICINAL PRODUCT**

Basic information on the non-interventional trial (to be filled in by the applicant)

Title of the non-interventional trial on a medicinal product in the Croatian language:	
Title of the non-interventional trial on a medicinal product in the English language:	
Code of the protocol:	
Name and address of the sponsor:	
Name and address of the applicant:	
Principal investigators and establishments in which the non-interventional trial of a medicinal product will be conducted (the number of establishments and investigators)	*The list is attached to this form as a schedule and forms an integral part hereof*
Objectives of the trial	
Inclusion criteria:	
Planned number of subjects to be monitored:	
Planned duration of the trial in the Republic of Croatia:	

Documents submitted (to be filled in by the applicant)

Protocol (code, version and date):	
Authorised summary of product characteristics in the Republic of Croatia (authorisation date)	
Authorised package insert in the Republic of Croatia (authorisation date):	
Marketing authorisation (date):	
Informed consent form for the subject in the Croatian language (version and date):	
Original informed consent form in the English language (version and date):	
Financial plan of the trial:	
Other documents (please specify which, and indicate the version and date of such	

documents):	
Certificate of payment of the costs pertaining to the issuing of an opinion of the Central Ethics Committee:	

Signature of the responsible person of the applicant and date:

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Appraisal of the documents (to be filled in by the rapporteur)

Protocol	**YES**	**NO**	
The medicinal product is prescribed in accordance with the terms of the marketing authorisation:	∑	☐	Comment:
Assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice:	∑	☐	Comment:
The prescription of the medicine is clearly separated from the decision to include the patient in the study:	∑	☐	Comment:
No additional diagnostic or monitoring procedures are applied to the patients (other than those that are part of the habitual practice):	∑	☐	Comment:
Epidemiological methods are used for the analysis of collected data:	∑	☐	Comment:
The trial does not promote the prescription of the medicine that is monitored:	∑	☐	Comment:
Informed consent form in the Croatian language:	**YES**	**NO**	
The text clearly describes the implementation of the trial by providing all data necessary to make a decision:	∑	☐	Comment:
The text of the informed consent form is in terms that the patient is able to understand:	∑	☐	Comment:
The text of the informed consent form is correct in terms of language, orthography and spelling:	∑	☐	Comment:

Other documents submitted:	**YES**	**NO**	
In line with the protocol:	∑	☐	Comment:

Financial plan of the trial:	**YES**	**NO**	
The financial plan of the trial is clear:	∑	☐	Comment:
Compensation to investigators is adequate in terms of the planned scope of work:	∑	☐	Comment:

Recommendation of the rapporteur for the issuing of an opinion of the Central Ethics Committee at the session (please state the date of the session):

(please delete the following as appropriate; if b, c or d is given, please provide reasons)

a. favourable opinion

b. conditional favourable opinion

c. postponed

d. negative opinion

Reasons:

Date of the report Signature of the rapporteur:

[1]1[1] In the ICH- E5 Guideline relating to the Ethnic Factors in the Acceptability of Foreign Clinical Data, factors that can produce a different response to a medicinal product in various populations may be classified as either intrinsic or extrinsic ethnic factors. In this document, the categories are referred to simply as intrinsic or extrinsic factors.

ANNEX VII

AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES OF CROATIA
FORM FOR REGISTRATION AND APPRAISAL OF A NON-INTERVENTIONAL TRIAL

Basic data on the non-interventional trial (to be filled in by the applicant)

Title of the non-interventional trial in the Croatian language:	
Title of the non-interventional trial in the English language:	
Name of the active ingredient (INN):	
Name of the medicinal product:	
Code of the protocol:	
Name and address of the marketing authorisation holder:	
Name and address of the sponsor:	
Name and address of the applicant:	
Name and surname of the local person responsible for pharmacovigilance:	
Principal investigators and establishments in which the non-interventional trial is to be conducted (the names of establishments and the names of investigators):	
Objectives of the trial:	
Inclusion criteria:	
Exclusion criteria:	
Planned number of patients to be monitored:	
Planned duration of the trial in the Republic of Croatia:	
States in which the non-interventional trial is already in progress:	
States in which a request for the implementation of the non-interventional trial has been submitted	
EU PAS Register number*	
Joint PASS**	

* Please indicate whether the PASS is registered with the EU PAS Register.

** If several marketing authorisation holders participate in the planning and implementation of the PASS.

Documents submitted (to be filled in by the applicant)

Protocol (code, version and date):	
Case report form (version and date):	
Authorised summary of product characteristics in the Croatian language (authorisation date):	
Authorised package insert in the Croatian language (authorisation date):	
Marketing authorisation (date):	
Informed consent form for the subject in the Croatian language (version and date):	
Original informed consent form in the English language (version and date), if applicable:	
Financial plan of the trial:	
Proposed notice to the director of the establishment on the implementation of a non-interventional trial	
Other documents (please specify which, and indicate the version and the date of the documents):	
Opinion of the Central Ethics Committee:	

Signature of the responsible person of the applicant and date

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[1] This Directive does not regulate non-interventional trials.