Pursuant to Article 10 of the Ordinance on Clinical Trials on Medicinal Products and Good Clinical Practice (Official Gazette No. 25/15), the Central Ethics Committee at its 193rd session on 14 September 2016 adopts the following

RULES OF PROCEDURE

ON THE CENTRAL ETHICS COMMITTEE

I. GENERAL PROVISIONS

Article 1

The Rules of Procedure regulate the responsibilities and scope of work of the Central Ethics Committee (hereinafter: CEC), the manner of work and decision-making, the rights and obligations of CEC members, as well as other issues influencing the work of CEC.

Article 2

The provisions of the Rules of Procedure are mandatory for all the members of CEC, as well as other persons involved in its work. The president of CEC shall ensure the proper implementation of the Rules of Procedure.

Article 3

CEC works in sessions.
The sessions shall be convened by the president of CEC.

Article 4

CEC is an independent body of 19 members, healthcare professionals and other members of the nonmedicinal profession. The president, deputy president and members of the Central Ethics Committee are appointed by the Minister of Health.

Article 5

CEC shall be constituted at its first session.

II. THE RESPONSIBILITIES AND SCOPE OF WORK OF CEC

Article 6

The responsibility of CEC 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 scope of work of CEC is regulated by the Medicinal Products Act (Official Gazette, No. 76/13 and 90/14), Medical Devices Act (Official Gazette, No. 76/13), the Ordinance on Clinical Trials on Medicinal Products and Good Clinical Practice (Official Gazette, No. 25/15 and 124/15),

Article 7

The Central Ethics Committee is responsible for:

- issuing opinions in the procedure of granting approvals for clinical trials of medicinal products and medical devices, including academic clinical trials;
- issuing opinions in the procedure of granting approvals for non-interventional trials of medicinal products and medical devices;
- accepting non-substantial amendments and updates to previously approved clinical and non-interventional trials;
- issuing opinions in the procedure of granting approvals for substantial amendments to the approved clinical and non-interventional trials; and
- accepting final clinical and non-interventional trial reports.

When granting approvals for clinical trials, CEC verifies the compliance with the requirements laid down in Articles 11 and 16 of the Ordinance on Clinical Trials on Medicinal Products and Good Clinical Practice (Official Gazette No. 25/15 and 124/15) and the Ordinance on Clinical Trials and Good Clinical Practice (Official Gazette No 121/07) (hereinafter: the Ordinance).

When granting approvals for non-interventional trials, CEC verifies compliance with the requirements laid down in Article 32 of the Ordinance.

Following the completion of the clinical trial, the applicant or sponsor shall submit a summary final report in accordance with Article 30 of the Ordinance to CEC and the Minister of Health, within a year of the completion of the clinical trial.

Article 8

All documents and materials referred to in Article 7 of the Rules of Procedure shall be considered a business secret, regulated by legal provisions on the protection of confidentiality.

III. THE RIGHTS AND OBLIGATIONS OF CEC MEMBERS

Article 9

A member of CEC has the following rights:

1. to participate in the work of CEC;
2. to submit proposals and raise issues related to the scope of work of CEC;
3. to participate in the preparation and creation of materials related to the work of CEC;
4. to be rewarded for their work in CEC.

A member of CEC has the following obligations:

1. to inform other members about a case assigned to him/her by the president of CEC at a session of CEC;
2. to inform on possible conflicts of interest when discussing certain cases (a member of CEC who has a conflict of interest shall not participate in the discussion and issuing of opinions about the case), and sign a statement confirming the conflict;
3. to consider all the information he/she obtains at work, at sessions of the Committee or outside of them, as a business secret and sign a Non-Disclosure Agreement;
4. to regularly attend the CEC sessions.

If a member of CEC misses three CEC sessions in a row without justification, he/she shall be considered to have resigned as a member of CEC.

The president of CEC shall initiate the procedure for the dismissal of the member in case of misconduct.

IV. THE MANNER OF WORK OF CEC

Article 10

No later than seven days before the session, the members of CEC shall receive a written request with the draft of the agenda and the minutes of the previous session, and the rapporteur on a case shall also receive documents.

Article 11

The sessions shall be chaired by the president of CEC or, in his/her absence, by the deputy president.
The president of CEC shall draft the agenda and decide on rapporteurs for cases.

Article 12

Two rapporteurs shall each prepare a report on one case independently and report on it at a CEC session.

Article 13

CEC can make legitimate decisions if more than half of the members are present at a session.

Article 14

In the process of approving clinical and non-interventional trials, CEC can issue the following opinions:

1. Favourable opinion – the request is professionally and ethically justified with all the necessary documents submitted.
2. Conditional favourable opinion – the request is approved with minor amendments. The president of CEC can approve the request after submitting updated documents.
3. Postponed – the discussion is postponed because substantial amendments and/or updates to the documents are needed. After the documents have been updated, the request is discussed again at a CEC session.
4. Negative opinion – the trial cannot be approved based on the documents submitted.

Each opinion is issued on a uniform form, followed by the reasons for issuing it.

If the documents submitted during the process of approving a clinical or non-interventional trial are not complete, CEC sends a memorandum to the applicant listing all the documents he/she must submit.

Pursuant to Article 12 of the Ordinance, if the documents submitted during the process of approving a clinical trial are not complete and/or CEC informs the applicant/sponsor of the reasons for disapproval of the request, the applicant/sponsor of the trial can update the documents only once.

Article 15

The president of CEC approves all amendments and updates of a previously approved clinical trial if the amendments and updates of the clinical trial are not substantial, while substantial amendments and updates are subject to the approval of CEC and the Minister of Health.

The secretary-general shall consult with the president of CEC and report at CEC sessions on the documents received that do not require approval from CEC.

Substantial amendments and updates of a previously approved clinical trial are reported on by one of the rapporteurs at a CEC session.

Article 16

The president of CEC gives consent to conduct a clinical trial in additional legal persons to the applicant who was previously issued a positive opinion of CEC for the clinical trial.

V. MINUTES FROM THE SESSION

Article 17

Minutes from CEC sessions are kept.

Every member has the right to comment and propose amendments to the minutes from one session at the following session.

The merits of the comments are decided upon at the session. Accepted comments are entered in the minutes from the current session. If no comments are made to the minutes, they shall be considered adopted. The adopted minutes are signed by the president of CEC and the minutes-keeper.

The original minutes from the sessions and all the materials are kept in the Agency for Medicinal Products and Medical Devices.

Article 18

Administrative activities for the operation of CEC are conducted by the Agency for Medicinal Products and Medical Devices.

Pursuant to Article 27 of the Ordinance, the Agency for Medicinal Products and Medical Devices is responsible for keeping records of all reported adverse drug reactions during the clinical trial and annual summary reports about adverse reactions and informing CEC and the Ministry of Health about them. An employee of the Pharmacovigilance Department of the Agency participates in the sessions and reports, in a written and oral manner, on the information collected in the period between the two sessions.

The CEC documents on clinical trials shall be kept for 20 years from the end of the year in which the clinical trial was completed.

VI. FINAL PROVISIONS

Article 19

The president of CEC annually reports to the Minister of Health about the operation of CEC.

Article 20

The components of the Rules of Procedure are:

1. CEC Application Form for Clinical Trials of Medicinal Products and Medical Devices
2. Form_Synopsis of the Trial
3. Form_Schedule of the Clinical Trial (timeline of procedures and examinations)
4. Form_Report on the Review of the Clinical Trial
5. Form for Registration and Review of a Non-interventional Trial

Article 21

The Rules of Procedure shall be adopted by the Central Ethics Committee.
The amendments and updates on the Rules of Procedure shall be adopted in the same way as the Rules of Procedure.

Article 22

On the entry into force of these Rules of Procedure, the CEC Rules of Procedure of 19 February 2008, amended and updated on 3 June 2009, shall cease to have effect.

The president of the Central Ethics Committee

Assoc. Prof. Suzana Mimica-Matanović, M.D., Ph.D.

Central Ethics Committee (CEC) Application Form for Clinical Trials of Medicinal Products and Medical Devices – Annex 1

– to be filled out by the sponsor or the applicant responsible for the accuracy of the data included

– the principal investigator signs only the review of the informed consent

Sponsor:

Applicant:

CEC – registration number EUDRACT number	
Date of receiving the full 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, value date
Certificate of fees paid	
Summary of the trial (version and date)	Based on the special form of CEC
B. Identification of the investigators	
Principal investigator in the Republic of Croatia	
Address*	
Telephone and telefax	
Email	
The 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?	

Countries 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	
Summary of nonclinical 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 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

Synopsis of the trial (to be submited to all members of CEC) – Annex 2
(To be filled out by the sponsor or the applicant)

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 and the date	

CODE OF THE TRIAL: TITLE OF THE TRIAL:

SCHEDULE OF THE CLINICAL TRIAL (timeline of procedures and examinations)

Examination	Week 1	Week 2	Week 3	Week 4	Week 5	etc.
First examination (non-screening visit)	**X**					
Follow-up appointment		**X**		**X**		
Haematology*	**X**			**X**		
Biochemistry*	**X**					
Other examinations (specify which)						
ECG	**X**	**X**	**X**			
Brain CT scan	**X**					**X**
Chest						
etc.						
etc.						

This is only an example of the schedule, which must be in line with the protocol.
* Every examination must be listed in its cell correctly.

CENTRAL ETHICS COMMITTEE

REPORT ON THE REVIEW OF THE CLINICAL TRIAL

Basic information on the clinical trial

Title of the clinical trial in the Croatian language:	
Title of the clinical trial in the English language:	
Code of the protocol:	
EudraCT number:	
Name and address of the sponsor:	
Name and address of the applicant:	
The location of the clinical trial:	

Documents submitted:

Review of the clinical trial *(to be filled out by the rapporteur)*

Protocol of the clinical trial:	YES	NO	
Includes all the materials compliant with the Guideline for Good Clinical Practice:			Comment:
It is appropriate, and the foreseeable hazards and risks in relation to the anticipated benefits for the subjects are justified:			Comment:
The arrangements for the recruitment of subjects in the clinical trial are adequate.			Comment:
The procedures of the clinical trial are clearly described and justified:			Comment:
Other comments:			
Proposal of necessary documents corrections/clarifications/updates			

Investigator's Brochure:	YES	NO	
Includes all the materials compliant with the Guideline for Good Clinical Practice:			Comment:
The available nonclinical and clinical information on the investigational product is adequate to support the proposed clinical trial:			Comment:
The information is presented in a brief, simple, objective, and balanced manner:			Comment:
Not older than one year:			
Other comments:			
Proposal of necessary documents corrections/clarifications/updates			

Informed consent form in the Croatian language:	YES	NO	
Includes all the materials compliant with the Guideline for Good Clinical Practice:			Comment:
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:
Information about compensation for subjects, including the methods, amounts, and schedule of payment, is set forth in the informed consent and is appropriate: *(delete if not applicable):*			Comment:
Other comments:			
Proposal of necessary documents corrections/clarifications/updates			

Other written documents for trial subjects:	YES	NO	
The content is appropriate and in terms that the patient is able to understand:			Comment:
The text is correct in terms of language, orthography and spelling:			Comment:
Other comments:			
Proposal of necessary documents corrections/clarifications/updates			
Proposed principal investigators:	YES	NO	
Are qualified by education, training and experience to conduct the clinical trial:			Comment:
Have documented training in Good Clinical Practice:			Comment:
Simultaneously conduct no more than five clinical trials in the phase of actively enrolling subjects:			Comment:
Other comments:			
Proposal of necessary documents corrections/clarifications/updates			

Financial plan of the trial:	YES	NO	
Contains the financial structure:			Comment:
Contains information about the distribution of compensation between the establishment and the investigator:			Comment:
Other comments:			

Proposal of necessary documents corrections/clarifications/updates			
Proof of insurance of subjects:	YES	NO	-
The insurance conditions are appropriate:			Comment:
The certificate contains the title of the trial, the names of the establishment and the investigators, as well as the number of subjects covered by the insurance:			Comment:
Other comments:			
Proposal of necessary documents corrections/clarifications/updates			
Other professional documents:	YES	NO	
In line with the protocol:			Comment:
The purpose is clear:			Comment:
Proposal of necessary documents corrections/clarifications/updates			

<u>Recommendation of the rapporteur for the issuing of an opinion of CEC at the session (please state the date of the session):</u>

(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: Rapporteur's signature:

CENTRAL ETHICS COMMITTEE

FORM FOR REGISTRATION AND REVIEW OF A NON-INTERVENTIONAL TRIAL

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

Title of the non-interventional trial in the Croatian language:	
Title of the non-interventional trial 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 is to be conducted (the number of establishments and investigators):	*The list is in the Annex of this form and forms an integral part thereof.*
Objectives of the trial:	
Inclusion criteria:	
Planned number of patients to be monitored:	
Planned duration of the trial in the Republic of Croatia:	

Documents submitted (to be filled out by the applicant)

Protocol (code, version and date):	
Authorised summary of product characteristics in the Croatian language (authorisation date):	
Authorised package leaflet in the Croatian language (authorisation date):	
Marketing authorisation (date):	
Informed consent form for the subject in the Croatian language (version and date):	
Informed consent form for the subject in the English language (version and date):	
Financial plan of the trial:	
Other documents (please specify which, and indicate the version and the date of the documents):	
Certificate of payment of the costs pertaining to the issuing of an opinion of CEC:	

Signature of the responsible person of the applicant and the date:

Review of the documents *(to be filled out 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 CEC 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: Rapporteur's signature: