EUROPEAN AND NATIONAL REQUIREMENTS FOR THE SLOVAK REPUBLIC -PART II – CLINICAL TRIAL APPLICATION (REGULATION (EU) NO 536/2014)

18.07.2024

VERSION	EFFECTIVE DATE	REASON
1.0.	24.08.2022	Initial document: Incorporation of new national requirements for part II - new site suitability form for clinical trials - "Site suitability form."
1.1.	28.02.2023	Incorporation of new national requirements for Part II: Documents intended for clinical trial participants. Clarification on signature requirements for CV, DoI, Site suitability Form: obligation of the clinical trial sponsor to ensure that an identical signed version is available for inspection within the clinical trial site and also available at the clinical trial sponsor as needed. Adding requirements for the suitability of the principal investigator providing information on the completion of GCP - Good clinical practice (stated in CV).
1.2.	27.03.2023	Clarification on national requirements for part II: Documents intended for clinical trial participants - They are uploaded to part I (according to Annex II of the document "Regulation (EU) No. 536/2014 Questions & Answers, version 6.4 from February 2023", they are submitted in English). If they are available in the Slovak language, they can be uploaded to Part I.
1.3.	15.06.2023	Clarification on requirements for recruitment materials: e.g. informational and advertising materials intended for future participants and clinical trial participants).
1.4.	13.10.2023	Clarification on requirements for patient documents: "Patient facing documents" are submitted in English and Slovak* and are uploaded to Part I according to the most recently updated Annex II of the document, "Regulation (EU) No. 536/2014 Questions & Answers". *"Patient facing documents", which are intended for clinical trial participants. Reference to "§ 29a par. 9 Act No. 362/2011".

VERSION	EFFECTIVE DATE	REASON
1.5.	18.07.2024	Clarification on requirements for recruitment materials, informed consents (underage participants). Adding the requirements of informed consent for national minorities. Deletion of disputed provision *"Patient facing documents", which are intended for clinical trial participants. Reference to § 29a par. 9 Act No. 362/2011 Coll. Addition: "Patient facing documents" are submitted in English and Slovak **and are uploaded to Part I (related to the final primary and secondary protocol endpoints)** according to the updated Annex II document, "Regulation (EU) No. 536/2014 Questions & Answers". Adding clarification on: • Questionnaires intended for the participant of the clinical trial, which will be filled out by the investigator • Electronic questionnaires and screenshots (paper versions) • Investigator´s CV • Insurance certificate (list of trial sites does not have to be listed on the insurance certificate) • Site suitability form • Financial compensation for the subjects • Compliance with the applicable rules for the collection, storage and further use of the participant's biological samples Addition of the "version overview". Addition of "other relevant requirements".

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
K. RECRUITMENT ARRANGEMENTS (CTIS section - Recruitment arrangements)	**A document that describes recruitment of the clinical trial participants** • **Slovak language or English language** Unless described in the protocol, a separate document shall describe in detail the procedures for inclusion of subjects and shall provide a clear indication of what the first act of recruitment is. The content and data in the document must be consistent with the protocol and other documents used in the trial. It is possible to use the template that can be found on the link in Chapter 1 (Chapter I) - **EudraLex - Volume 10 - *„Recruitment and Informed consent procedure template„.***

Documents Regulation 536/2014	**Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document**
	Where the recruitment of subjects **is done through advertisement, copies of the advertising material shall be submitted, including any printed materials, and audio or visual recordings.** The procedures proposed for handling responses to the advertisement shall be outlined. This includes copies of communications used to invite subjects to participate in the clinical trial and arrangements for information or advice to the respondents found not to be suitable for inclusion in the clinical trial. In the document **"Recruitment and Informed consent procedure template"** must stated how and by which media the potential clinical trial participant will be approached. • **Slovak language**
L. SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE (CTIS section - Subject information and informed consent form)	**Informed Consent Forms (ICF) and other documents intended for trial participants** • **Slovak language** When enrolling clinical trial participants **who are citizens of the Slovak Republic and belong to the national minorities or foreigners** (if such a situation arises), it is required to **submit the ICF in understandable language** of the potential clinical trial participant (in accordance with ICH GCP). The sponsor is responsible for ensuring that the wording of this ICF corresponds to the submitted Slovak version of the ICF. The document can also be submitted after approval of the Slovak version, within the next Substantial Modification - (SM).

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
	ICFs are prepared on the basis of **Methodical guidance 131/2021 (State Institute for Drug´s Control)** - Metodické pokyny | ŠÚKL (sukl.sk). **ICF with the use of samples for future research not related to the clinical trial** (either a separate document or a separate signature page included in the informed consent) • **Slovak language** In the case of a **minor age clinical trial participant or an underage pregnant partner** of an clinical trial participant, the person authorized to grant consent is the legal representative, **which as per local Family Act is father and mother**, or the legal representative determined by the court. In case of **an incapacitated clinical trial participant**, the legally designated representative appointed by the court is the authorized person to grant consent. If the ICF is submitted to a person who is not an enrolled clinical trial participant, for example the participant's pregnant partner, this must contain data on the identity of the participant and the partner at the same time (first and last name, because the assigned number in the clinical trial is not sufficient data to confirm the identity) and also information, where the signed ICF will be stored.

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
	The provision of data on a born child is the provision of data on a minor subject and requires a procedure in accordance with the participation of a minor age. The Ethics Committee (EC) requires the division of the signature page into two parts, consent to monitor the participant's/partner's pregnancy and the second part: consent to monitor the child's state of health/ provision of data on the minor subject. From a formal point of view, ICF must contain: • EC contact details (Name, addresss, email address, telephone contact – available on EC website • Link to the EU clinical trials page • EU CT number, protocol number

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
	Patient facing documents "**Patient facing documents"** related to the final primary and secondary endpoints of the protocol **are submitted in English and Slovak** and are uploaded to **Part I** according to the updated Annex II document, "Regulation (EU) No. 536/2014 Questions & Answers". **Questionnaires intended for the clinical trial participant**, which will be filled out by the investigator, can be submitted **in English only.** In the case of using **electronic questionnaires**, it is necessary to submit screenshots (if available at the time of the submission). In case of unavailability of screenshots, it is possible to submit their texts in word or pdf format, etc. The ICF must contain information on the number of used questionnaires/diaries and estimated time required to complete the questionnaires and diaries. In case of using electronic questionnaires, it is necessary to submit screenshots or to submit their paper versions. In the event that the paper versions are identical to the subsequently used screenshots, it is sufficient to submit the screenshots **as "non-substantial modification".**

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
M. SUITABILITY OF THE INVESTIGATOR (CTIS section - Suitability of the investigator)	**Curriculum vitae (CV) of the principal investigator** • **Slovak or English language** The use of this CV template is recommended, but all types of professional CVs are accepted as long as CV includes: • complete data on the medical education, relevant degrees and qualifications - it is sufficient to include this information in the CV • experience obtained from work with clinical trials and patient care • educational activity on GCP Training (Good Clinical Practice) together with the date of completion If the principal investigator does not have experience with the clinical trials in the required field, it is sufficient to include in the CV attestation or specialization within the required field. It is necessary to fulfill the national requirements regarding the qualification of the principal investigator - the necessity of certification in the field, resulting from Act no. 362/2011 on medicines and medical devices, § 29l "Requirements for the principal investigator, requirements for the investigator and requirements for the workplace where clinical trials of human medicines are carried out" and from "Regulation of the Government of the Slovak Republic no. 296/2010" on professional competence for the performance of the health profession, the method of further education of health workers, the system of specialized fields and the system of certified work activities.

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
	A CV uploaded to the CTIS (Clinical Trial Information System) portal will be accepted without a signature*, however it must be ensured that the identical signed version **is kept in accordance with GCP.** **Declaration of Interest (DoI) of the principal investigator** • **English language** **DoI** uploaded to the CTIS (Clinical Trial Information System) portal will be accepted without a signature*, however it must be ensured that the identical signed version **is kept in accordance with GCP.** Template – (Chapter I EudraLex - Volume 10 - Clinical trials guidelines)
N. SUITABILITY OF THE FACILITIES (CTIS section - Suitability of the facilities)	**"Site suitability form"** • **Slovak language or English language**

Documents Regulation 536/2014	**Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document**
	A written statement describing the suitability of the clinical trial sites, issued by a statutory representative of the healthcare facility. The procedures and examinations established by the protocol must be stated in the document and it must be defined that the site is capable of conducting the clinical trial. If necessary, the document must include the availability of all (including external) providers of diagnostic and therapeutic procedures that are listed in the protocol. **Site suitability form** uploaded to the CTIS (Clinical Trial Information System) portal will be accepted without a signature*, however it must be ensured that the identical signed version **is kept in accordance with GCP.** **Local modified bilingual version** is available on https://www.health.gov.sk/?Eticka-komisia-pre-klinicke-skusanie The template is available in the downloads section - ”dokumenty na stiahnutie” of the Ministry of Health website, Ethics Committee for Clinical Trials. **A list of the planned clinical trial sites with the name and position of the principal investigators with full site addresses, where the clinical trial is conducted and with the planned number of subjects at the sites or with the total planned subjects in Slovakia** • **Slovak or English language**

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
	EC requests that site address consistency is fulfilled within the following documents: • Curriculum Vitae (CV) of the Principal Investigator • Site Suitability Form • List of Participating Clinical Trial Sites Inaccuracies in the addresses of clinical trial sites listed in the "Trial Sites" section of CTIS, originating from the data automatically transmitted from the Organization Management Service system (hereinafter referred to as "OMS"), will not be commented by EC.
O. PROOF OF INSURANCE COVER OR INDEMNIFICATION (CTIS section - Proof of insurance cover or indemnification)	**Insurance certificate** • **Slovak language, multilingual version is also acceptable** It must contain information about the sponsor, the name and identification of the clinical trial and the duration of the insurance (beginning/end of the insurance period). The list of clinical trial sites can be replaced by a general wording in the sense of "*all participating clinical trial sites in Slovakia*" or *„Investigators/clinical trial sites based on a contractual relationship with the sponsor, which are authorized to participate in this clinical trial“* in order to avoid administrative burden. **The sponsor is responsible for securing insurance for the clinical trial sites in accordance with local legislation " (§ 29n paragraph 3 letter 3 of Act No. 362/2011 Coll.)."**

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
P. FINANCIAL AND OTHER ARRANGEMENTS (CTIS section - Financial and other arrangements)	**<u>Financial compensations paid to the subject are included either in the ICF or as a separate document</u>** • **<u>Slovak language (in ICF)</u>** • **<u>English language (if separate document)</u>** If this information is not provided in the ICF, it is necessary to provide: • description of the reimbursement method (cash, vouchers, payment cards...) • payment amount • timetable for the payment of financial compensation (ongoing) In the case of using payment cards, the subject must not incur expenses associated with card usage with the use of the card additionally, subjects must be offered an alternative method for receiving financial compensation. The value of compensation provided should be balanced with the average expenditure of funds typically associated with trial participation. However, the Ethics Committee recommends considering exceptional cases where a significant and justified increase in participant costs occurs.

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION LAW ON DATA PROTECTION (CTIS section - Compliance with national requirements on Data Protection)	**A statement by the sponsor or sponsor´s representative** that data will be collected and processed in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council – Personal data protection • **English language** The statement will be uploaded in the CTIS when completing the clinical trial application form. Submission in part II CTIS section - Compliance with national requirements on Data Protection is not needed.
COMPLIANCE WITH THE APPLICABLE RULES FOR THE COLLECTION, STORAGE AND FUTURE USE OF BIOLOGICAL SAMPLES OF THE SUBJECT. (CTIS section - Compliance with use of Biological samples) - If the information is not provided in the protocol	**Article 7, point 1(h) of Regulation (EU) No 536/2014** The sponsor shall submit a completed template, which can be found on the EudraLex website - Volume 10 - Clinical trials guidelines, in the link in Chapter I (Chapter I) "Compliance with applicable rules for biological samples", where it shall provide information not only on samples for future research, but also on samples taken as part of the clinical trial. • **English language**

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
General requirement for compliance with the good documentation practice - (page numbering, document date, document version and document name)	

Documents Regulation 536/2014	Document - Language requirements and a reference to applicable legislation or guidelines, EU recommendations and other information regarding the document
COVER LETTER	Reference: Regulation (EU) No 536/2014 - Annex I (Section B) - Local regulation reference: § 29a para 9 of Act No. 362/2011 Coll. It is recommended to include a list of submitted documents. • **English and Slovak or bilingual document**

Links:

https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en

*Electronic submission of the CTA to CTIS by the sponsor is regarded as equivalent to signing the document in accordance to Annex I.3. CTR is a regulation, which is directly applicable and ensures complete harmonisation of the sector, national laws should be set out to support its full implementation.

Other relevant requirements	
ANNUAL PROGRESS REPORTS	Send electronically to: eticka.komisia@health.gov.sk trial-sukl@sukl.sk Annual progress report template will be available on SUKL website https://www.sukl.sk/ Reference : § 29n (paragraph 3, letter d) of Act no. 362/2011
TRANSITION APPLICATIONS (Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation)	Note: Administrative fees **do not apply to TRANSITION applications.** **Minimum Requirements:** • **Most recent informed consents approved under Directive** 2001/20/EC (hereinafter referred to as the "Directive") The transition process for conducting a clinical trial under Regulation (EU) No 536/2014 is guided by the following European guidelines: • **https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en** • Guidance for the Transition of Clinical Trials from the Clinical Trials Directive to the Clinical Trials Regulation • CTCG Best Practice Guide for Sponsors

Other relevant requirements	
FIRST SUBSTANTIAL MODIFICATION APPLICATION (PART II) AFTER THE AUTHORISATION OF THE TRANSITION APPLICATION	Note: Administrative fees **apply as for a regular substantial amendment - Act No. 145/1995 Coll. on Administrative Fees** Links to European guidelines: Requirements are harmonized across member states: • https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en • Guidance for the Transition of Clinical Trials from the Clinical Trials Directive to the Clinical Trials Regulation • CTCG Best Practice Guide for Sponsors **Requirements for the first submission of a substantial modification after approval of a "transition trial"** • Declaration of Interest of the Principal Investigator • Updated CVs *(only if the previous ones are already obsolete)* • List of clinical trial sites • Compliance with the applicable rules for the collection, storage and future use of biological samples of the subject – only if this information is not provided in the clinical trial protocol • **GCP certificates are not required,** however, the principal investigator's curriculum vitae must include information on their completion

Other relevant requirements	
	• **Site suitability forms are not required - this does not apply to new sites that are newly added as part of a substantial modification.** Note: The Ethics Committee for Clinical Trials reserves the right to comment on documents intended for the clinical trial participants if they do not meet current requirements. The sponsor is not requested to upload a new template for documents for procedures in the trial that were already completed, e.g. if recruitment of trial participants has ended.

Legislative local framework:

Domov - SLOV-LEX

- **Act No. 362/2011 Coll.** - Act on Medicinal Products and Medical Devices
- **Act No. 576/2004 Coll.** - Act on Health Care, Services Related to the Provision of Health Care
- **Act No. 18/2018 Coll.** - Act on the Protection of Personal Data and on Amendments
- **Act No. 580/2004 Coll.** - Act on Health Insurance and on Amendments and Supplements to Act No. 95/2002 Coll. on Insurance
- **Act No. 581/2004 Coll.** - Act on Health Insurance Companies, Supervision of Health Care
- **Act No. 36/2005 Coll.** - Act on the Family
- **Act No. 270/1995 Coll.** - Act on the State Language of the Slovak Republic

- **Act No. 578/2004 Coll.** - Act on Providers of Health Care, Health Care Workers, Professional Organizations in Health Care
- **Act No. 363/2011 Coll.** - Act on the Scope and Conditions of Reimbursement for Medicinal Products, Medical Devices and Dietetic Foods on the Basis of Public Health Insurance
- **Act No. 395/2002 Coll.** - Act on Archives and Registries
- **Act No. 147/2001 Coll.** - Act on Advertising
- **Act No. 145/1995 Coll.** - Act on Administrative Fees

European Regulatory Framework:

European Guidelines:

- https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en
- Questions and Answers Document - Regulation (EU) 536/2014
- Guidance for the transition of clinical trials
- Quick Guide on CTR (Clinical Trials Regulation)
- CTIS: how to get started and how to transition a trial (CTIS stands for Clinical Trials Information System)
- CTCG best practice guide and annex for sponsors (CTCG likely refers to Clinical Trials Coordination Group)
- Chapter 5 of the CTIS Sponsor Handbook
- Module 23 of the CTIS online training programme