Bratislava
26. 11. 2024

Subject: General inquiry_Clinical Trial_e-consent requirements

To Whom It May Concern,

Please refer to our national requirements available on our website https://www.health.gov.sk/?Eticka-komisia-pre-klinicke-skusanie. You may find Ethics committee´s (EC) response below:

EC would like to emphasize that neither the Ethics Committee for Clinical Trials nor the State Institute for Drug Control is obligated to provide interpretations of legal provisions. They do not have the authority to offer binding legal interpretations. This is based on Article 2, paragraph 2 of the Constitution of the Slovak Republic, which stipulates that state authorities may act only on the basis of the Constitution, within its limits, and to the extent and in the manner prescribed by law.

Providing binding interpretations of legal norms is an integral part of the judicial decision-making process, which involves applying abstract legal norms to specific circumstances of individual cases (i.e., the application of law as a significant form of law realization).

Furthermore, according to Article 152, paragraph 4 of the Constitution of the Slovak Republic, the interpretation and application of constitutional laws, laws, and other generally binding legal regulations must be in accordance with the Constitution. This is also supported by the position of the Supreme Court of the Slovak Republic as expressed in the rationale of the judgment, file No. (Rs) 8 Sžp 1/2010

Consequently, in consideration of the submitted inquiry and the identified terms, we can provide only an opinion regarding the possible interpretation of the relevant legal provisions, which is not legally binding.

Is it an acceptable way of obtaining consent per national regulation?

EC: In accordance with regulation 536/2014 article 29 par 1: "Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness.

In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial".

Currently, e-consent for clinical trials conducted under regulation 536/2014 in Slovakia is possible. However, ***Ethics Committee (EC) recommends the use of qualified electronic signatures (QES) or advanced electronic signatures (AES) in terms of e-IDAS regulation****. This is because these types of signatures provide a higher level of security and authenticity than other types of electronic signatures.*

The technical implementation of the e-consents remains within the competence of clinical trial sponsors as well as healthcare facilities. Information systems in healthcare facilities must enable the secure storage of electronic documents.

Standard Operating Procedures (SOPs) should establish the process for using electronic signatures, ensuring compliance with relevant regulations and standards. These procedures should clearly outline how electronic signatures are to be obtained, validated, and securely stored throughout the clinical trial process. Additionally, they should ensure that electronic documents associated with the clinical trial are securely stored and maintained in compliance with data protection and retention requirements.

If electronic signatures (QES or AES) are adopted, it is crucial to guarantee the inclusion of all relevant parties, including the investigator, clinical participant, witness, and any legal representatives etc. The onus to accommodate this requirement falls upon the sponsor and study sites.

Despite its advantages, this approach faces several challenges that must be addressed to comply with all legal requirements. For example, the site must maintain secure electronic storage for all relevant documents throughout the required retention period and provide patients with a copy.

Additionally, sponsor/study sites should consider the possibility that some patients may request an in-person consultation with the investigator (a remote consultation may not be sufficient) or may wish to sign the Informed Consent Form on paper. ***Such requests should be accommodated. Electronic consent has to be an option, and paper consent must be available for those unable to access the internet, or for those who do not agree to provide consent electronically.***

Are there any specific/additional documents that should be submitted in CTIS as part of the initial CTA?

EC: please refer to our national requirements available https://www.health.gov.sk/?Eticka-komisia-pre-klinicke-skusanie

Should the PIL-ICF be submitted in a particular format? *Please refer to our national requirements*

Are there any additional submissions outside of CTIS that should be performed?

EC: Please refer to our national requirements

Regarding the process of signature:

EC: there is no national process put in place with regards e –consent.

Is it required for the patient to have physical meetings with the PI or is it acceptable for the discussion occurring before the consent to be done remotely as well (e.g video, phone)?

EC: There are no national provisions with regards physical meetings. Remote discussion e.g. via video, phone is possible.

With regards to the requirement for qualified electronic signature, is there a specific type/software for signature required, other than the fact that it should comply with the e-IDAS regulation?

*EC:**There are no specific requirements regarding the type or software** used to generate Qualified Electronic Signature (QES) or Advanced Electronic Signature (AES), **however, the QES/AES signatures must meet the technical requirements outlined in the eIDAS regulation**.*

In the Slovak Republic, communication with state institutions typically requires the use of a Qualified Electronic Signature (QES). This signature can be created using a Slovak identity card equipped with an electronic chip, also known as an eID card. For further information on obtaining and utilizing an eID card, please refer to the official government portal: Ako začať - UPVS (slovensko.sk)

With regards electronic systems/storage, we would also recommend to follow EMA Guideline on computerised systems and electronic data in clinical trials (EMA guideline) – available on https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf

Decentralised elements in clinical trials

https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu?utm_campaign=PostBeyond&utm_source=LinkedIn&utm_medium=363067&utm_term=Facilitating+Decentralised+Clinical+Trials+in+the+EU+-+European+Medicines+Agency

Should the process of signature be submitted as part of the initial CTA? If so, in which document is it recommended to have it included?

*EC: No, EC does not require signed documents to be submitted in the CTA. *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.*

Rationale:

Legislative framework:

1. Act No 362/2011 Coll. on Medicinal Products and Medical Devices (hereinafter referred to as the 'Medicinal Products Act'),
2. Act No 576/2004 Coll. on health care, services related to the provision of health care (hereinafter referred to as the 'Act on the provision of health care'),
3. Civil Code No 40/1964 Coll. ('the Civil Code'),
4. Regulation No. 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC ("Regulation No. 536/2014"),
5. Regulation (EU) No 910/2014 of the European Parliament and of the Council on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC (hereinafter referred to as the "eIDAS Regulation").
6. Guideline on computerised systems and electronic data in clinical trials - 9 March 2023 EMA/INS/GCP/112288/2023 Good Clinical Practice Inspectors Working Group (GCP IWG) (hereinafter referred to as the "Guideline")

Pursuant to Section 6(4), first sentence of Act No. 576/2004 Coll. on health care, services related to the provision of health care and on amendment and supplementation of certain acts, as amended (hereinafter referred to as "Act No. 576/2004 Coll."): "Informed consent is demonstrable consent to the provision of health care preceded by instruction pursuant to this Act.".

The actual regulation of the patient's instruction and informed consent to the provision of health care is contained in Section 6 of Act No. 576/2004 Coll. An important part of the patient's (in our case, the participant in the CC) instruction and informed consent is the record of the implementation or non-implementation.

According to § 6, paragraph 10, first sentence of Act No. 576/2004 Coll.: *"The method of instruction, the content of the instruction, the refusal of instruction, informed consent, the refusal of informed consent and the withdrawal of informed consent are part of the record in the medical record (§ 21)."*

Act No 576/2004 Coll. distinguishes between (i) an entry in the electronic health record book and (ii) an entry in the health record which is kept in written form.

Pursuant to Section 20(4) of Act No 576/2004 Coll.: "Health records shall be kept in written form or in electronic form with a qualified electronic signature, unless this Act provides that a written form is required (Section 6(5), Section 12(7))."

Pursuant to Article 26(2) of Act No 576/2004 Coll.: "Biomedical research shall be carried out under the conditions laid down in this Act; **this shall not apply to clinical trials of medical devices and in vitro performance studies of diagnostic medical devices, which shall be carried out under the conditions laid down in special regulations) and to clinical trials of medicinal products for**

human use, which shall be carried out under the conditions laid down in special regulations, unless otherwise provided for in Article 49r".

As of 31.01.2022, the amendment of Article 26(2) of Act No 576/2004 Coll. entered into force, **the current wording of which states that the conditions for conducting clinical trials of medicinal products for human use are not covered by the legal regulation of biomedical research contained in Act No. 576/2004 Coll.** The exclusion of the conditions of biomedical research regulated in Act No. 576/2004 Coll. to clinical trials of medical devices and clinical trials of medicinal products for human use cannot be interpreted as meaning that these types of research are not biomedical research, but should be understood as meaning that for clinical trials of medical devices and medicinal products, the regime regulated in the regulations referred to by the legislator in Article 26(2) of Act No. 576/2004 Coll. (i.e. the Medicinal Products Act and Regulation No. 536/2014) applies. Centralized Procedure for Clinical Trials of Medicinal Products for Human Use is regulated in Act No. 362/2011 Coll. on Medicinal Products and Medical Devices and on Amendments and Additions to Certain Acts, as amended (hereinafter referred to as the "Medicinal Products Act").

Pursuant to Article 29(13) of Act No 362/2011 Coll. on Medicinal Products and Medical Devices and on Amendments to Certain Acts, as amended: „*A participant shall be enrolled in a clinical trial on the basis of his/her consent to participate in the clinical trial. The consent of the participant shall be given voluntarily after having been thoroughly informed of the purpose, meaning, consequences and risks of the clinical trial in which he is to participate and after having signed an instruction (hereinafter referred to as 'informed consent'). The informed consent shall be in writing and dated and signed by a participant who is competent to give his consent. In the case of a participant who lacks capacity to consent, the informed consent must be signed by the participant's legal representative. Where the participant is a competent person but is unable to write, he may give his consent orally in the presence of at least one witness in a record which shall be signed by the witness present.*“

"For centralised clinical trials of medicinal products, the reference regulation is Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC (hereafter referred to as 'Regulation No 536/2014'), **therefore, we are of the opinion that Section 29(13) of the Medicinal Products Act does not apply to the centralised clinical trial procedure for a medicinal product for human use, as this section was applicable to the national clinical trial application procedure**. **Neither Regulation No 536/2014 nor the Medicinal Products Act contains provisions explicitly specifying what kind of electronic signature is necessary for the validity of the informed consent of a clinical trial participant. This issue is also not explicitly addressed by any other relevant Slovak legal norm.**

According to Article 2(21) of Regulation No 536/2014: „*Informed consent' means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial*"

According to Article 25 of of the e-IDAS Regulation: ***„An electronic signature shall not be denied legal effect and admissibility as evidence in legal proceedings solely on the grounds that it is in an electronic form or that it does not meet the requirements for qualified electronic signatures.“*** **We note that even if the signature is advanced electronic, this cannot be a reason for its invalidity.**

According to Article 29(1) of Regulation 536/2014: *„Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial.“*

Pursuant to the second sentence of Article 40(4) of Act No 40/1964 Coll., the Civil Code, as amended: 'The written form shall be preserved if the legal act is performed by telegraph, telegram or electronic means which make it possible to capture the content of the legal act and to identify the person who performed the legal act. The written form shall always be preserved if the legal act made by electronic means is signed by a guaranteed electronic signature or a guaranteed electronic seal.".

The conditions for electronic signatures are regulated in Regulation (EU) No 910/2014 of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC (hereinafter referred to as the "eIDAS Regulation"), which distinguishes basically three levels of signatures, namely:

a) **simple electronic signature**, i.e. a signature written in electronic form, without any further verification, or the name and surname at the end of the email,

b) **advanced electronic signature (AES) – shall meet the following requirements:**

- ✓ it is uniquely linked to the signatory;
- ✓ it is capable of identifying the signatory;
- ✓ it is created using electronic signature creation data that the signatory can, with a high level of confidence, use under his sole control; and
- ✓ it is linked to the data signed therewith in such a way that any subsequent change in the data is detectable.

c) **qualified electronic signature (QES)** – means an advanced electronic signature that is created by a qualified electronic signature creation device, and which is based on a qualified certificate for electronic signatures;

In the context of above we rely on the available guidelines that address the issue of electronic signatures in the context of clinical trials of medicinal products under the regime of Regulation No 536/2014 - **Article 4.8 of the Guideline on computerised systems states:**

„Whenever ICH E6 requires a document to be signed and an electronic signature is used for that purpose, the electronic signature functionality should meet the expectations stated below regarding authentication, non-repudiation, unbreakable link, and timestamp of the signature.

The system should thus include functionality to:

- ✓ *authenticate the signatory, i.e. establish a high degree of certainty that a record was signed by the claimed signatory;*
- ✓ *ensure non-repudiation, i.e. that the signatory cannot later deny having signed the record;*
- ✓ *ensure an unbreakable link between the electronic record and its signature, i.e. that the contents of a signed (approved) version of a record cannot later be changed by anyone without the signature being rendered visibly invalid;*
- ✓ *provide a timestamp, i.e. that the date, time, and time zone when the signature was applied is recorded.*

Electronic signatures can further be divided into two groups depending on whether the identity of the signatory is known in advance, i.e. signatures executed in 'closed' and in 'open' systems.

For 'closed' systems, which constitute the majority of systems used in clinical trials and which are typically provided by the responsible party or by their respective service provider, the system owner knows the identity of all users and signatories and grants and controls their access rights to the system. Regulation (EU) No 910/2014 ('eIDAS') on electronic identification and trust services for

electronic transactions is not applicable for 'closed' systems ('eIDAS' article 2.2). The electronic signature functionality in these systems should be proven during system validation to meet the expectations mentioned above.

For 'open' systems, the signatories (and users) are not known in advance. For sites located in the EU, electronic signatures should meet the requirements defined in the 'eIDAS' regulation. Sites located in third countries should use electronic or digital signature solutions compliant with local regulations and proven to meet the expectations mentioned above.

Irrespective of the media used, in case a signature is applied on a different document or only on part of a document (e.g. signature page), there should still be an unbreakable link between the electronic document to be signed and the document containing the signature".

The aforementioned technical requirements are also met by advanced electronic signatures (AES), as defined in the eIDAS Regulation.

We would also like to draw attention to the case law of the Slovak courts, which, in general, could also be applied to other essential documents in clinical trials (e.g., the curriculum vitae of the principal investigator, the suitability form of the clinical trial site, the declaration of interest, etc.).

"According to the jurisprudence of the Supreme Court of the Slovak Republic (4Asan/3/2016), the sending of an e-mail, SMS or fax may also be considered a document, while the basic condition is that the text of the legal act has been captured on a tangible support from which it is possible to identify the content of the legal act and the person who made the legal act (in the given case, it was the saving of an SMS message in the memory of the phone).

The Supreme Court of the Slovak Republic (2Sžo/505/2009) extended the interpretation of the term electronic signature to "ordinary electronic signature", i.e. also to such forms of electronic signature which are not defined by the law, such as a simple indication of the sender's name and surname at the end of an e-mail communication, or a signature pattern which is automatically attached to the sent e-mail message, or any other signs and markings which the contracting parties or other parties consider to be an identification code in accordance with which they are able to identify the sender. The types of electronic signatures in question must be regarded as electronic signatures within the meaning of that term.

The Civil Code thus allows for the possibility of carrying out a legal act by electronic means, thereby equating documents made on paper with documents made electronically on a technical medium. **If the parties agree, even implicitly, to use electronic means of communication, there is no difference between the treatment of documents (data messages) and documents on paper."**

The patient's expression of intent is electronically recorded and stored as an attachment within information systems. Similar practices are already employed by other healthcare organizations, including private practices and health insurance companies..

In reference to the aforementioned legal provisions, we are of the opinion that a clinical trial participant under the CTR regime may provide informed consent through electronic means. Consequently, it can be concluded that the details of clinical trials of medicinal products not explicitly regulated by the Act on Medicinal Products are governed by the CTR. Therefore, it is not mandatory to require the informed consent exclusively in paper form.

In such cases, the use of electronic signatures for informed consent may be applied in accordance with the eIDAS Regulation in combination with the EMA guidelines on computerized systems. The informed consent and other essential documents (e.g., the curriculum vitae of the principal investigator, the suitability form of the clinical trial site, the declaration of interest, etc.) may be signed using a Qualified Electronic Signature (QES) or an Advanced Electronic Signature (AES) that meets the technical requirements as described in the eIDAS Regulation. However, it is essential that the electronic signature is applied by all relevant parties, including the investigator, the patient, and, if applicable, a witness or legal representative.

Furthermore, all legal obligations must be upheld (e.g., ensuring the clinical trial site has a secure method of electronic storage for the required retention period and providing the participant with a copy of the document to retain at home).

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