KLH-22 version 3 Requirements Governing the Text of Patient Information Leaflet Trial Subject Information Sheet /Informed Consent Form

With effect as of 14th September 2017, the Guideline supersedes guideline KLH-22 version 2.

The guideline is issued on the basis and in accordance with the provisions of Section 51 (2) of Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals), as amended, and Annex No. 2 to Decree No. 226/2008 Coll., on the Good Clinical Practice and More Detailed Conditions for Clinical trials on Pharmaceuticals as amended.
The Guideline is for recommendation.

Introduction

Trial subject (patient, healthy volunteer) information sheet/informed consent is a document safeguarding the provision of information about the basic principles of the concerned clinical trial (hereinafter referred to as "CT") and about the voluntary nature of participation therein to the aforementioned persons (their representatives or guardians). **It does not concern a document drafted for the purposes of protection of the sponsor's interest, it is a document the objective of which is to inform the trial subject about the CT in which he/she is offered participation**. Investigators should take into consideration that obtaining consent from the subject is a certain process taking some time rather than a mere act of attaching the subject's and investigator's signatures to the informed consent document. If practicable with a view to the type of the CT, the patient/healthy volunteer has to be given sufficient time to consider his/her participation in the CT.

The extent of the text of basic information for adult trial subjects and for parents/guardians is determined at the **maximum of 8 pages (in specific cases, as many as 10 pages may be acceptable)**, using a standard font size (such as Times New Roman 12, Arial 11, etc.) and a straightforward break-down of the text into chapters and paragraphs. Where treatment and age groups with reduced ability to read and perceive (details below) are concerned, the text should be shorter and the font size larger.

The text of the information sheet shall be clear and in a language the trial subject well understands; it should not contain foreign expressions, specialised terminology, unexplained abbreviations and complicated definitions. Where abbreviations are used, these are to be mentioned at the beginning of the text, i.e. after the first occurrence of the expression in the text – e.g. magnetic resonance imaging (hereinafter referred to as "MRI"). The text should be written in a friendly and sensitive manner, it is advisable to avoid words like "you have to" "you must not", "you suffer" etc. It is strongly recommended to conduct a language review of the final text to correct grammatical and text errors.

Pages shall be numbered (e.g. "1/6" or "1 (of 6)", etc.) and each page should be identified by the relevant version number, date of issue and CT identification (protocol number or EudraCT number).

The requirements governing the trial subject information sheet/informed consent are based upon:

- Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended (hereinafter referred to as the "Act on Pharmaceuticals")
- Decree No 226/2008 Coll., on Good Clinical Practice and Details of Clinical Trials on Medicinal Products, as amended (hereinafter referred to as the "GCP Decree")

Basic related documents:

- Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine
- International Conference on Harmonisation – E 6 – Good Clinical Practice: Consolidated Guideline, published by the European Medicines Agency (EMA) as guideline CPMP/ICH/135/95, part 4.8
- Act No 101/2000 Coll., on Personal Data Protection and on Amendments to Some Acts, as amended
- Act No 372/2011 Coll., on Health Services and the Terms and Conditions for the Providing of Such Services, as amended (hereinafter referred to as the "Act on Healthcare Services")
- Helsinki Declaration of the World Medical Association
- Belmont Report of 1978

Used terms

- **SÚKL** – Státní ústav pro kontrolu léčiv (State Institute for Drug Control)
- **CT** – Clinical Trial
- **GCP** – Good Clinical Practice
- **EC** – Ethics Committee
- **AR** – Adverse Reaction
- **SmPC** – Summary of Product Characteristics
- **IC** – Informed Consent

Explanation of basic terms for the purposes of this Guideline:

A clinical trial shall mean a systematic testing of one or more investigational medicinal products with the objective to verify the safety or efficacy of the medicinal product which is conducted in trial subjects for the purposes to:

1. determine or verify clinical, pharmacological or pharmacodynamic properties;
2. determine adverse reactions;
3. study the absorption, distribution, metabolism or excretion of one or more investigational medicinal products

in order to verify the safety or efficacy of the concerned medicinal product(s).

A trial subject shall mean a natural person (patient or healthy volunteer) who participates in the CT, either as a recipient of the investigational medicinal product or as a member of a comparator or control group.

Informed consent shall mean the expression of the trial subject's will to participate in the CT.

Explanation of legislative requirements:

1. A notification that the clinical trial is a research activity

In the introduction to the text it should be mentioned that the CT is a research activity and that the trial subject is being offered participation in the CT. It shall be stated that the patient or healthy volunteer may discuss his/her participation with close persons and take the information sheet home to study, before he/she decides whether to participate in the CT. It shall be specified who the sponsor of the CT is and, in case the sponsor is a commercial entity, it shall be stated that the investigator receives remuneration for this work.

Most CTs do not concern treatment within the scope of regular clinical practice. Mostly, a to-date non-approved medicinal product is administered, in which case the effects of the product may not be known and the safety profile of the new therapy may not be clearly established, either. The characteristics of the investigational medicinal product shall be provided; briefly and in a manner understandable for non-professionals. Where the efficacy of the new product has not been evidenced to date, it is not possible to declare benefit from participation in the CT to the patient, even if the sponsor anticipates benefit with a view to the mechanism of action. If the investigational product has already been authorised in any country, it is possible to mention the country and indication. In case the product is available for the concerned indication in the Czech Republic, it is necessary to mention that it is available to patients also in case they do not participate in the CT.

Where inclusion in the CT is preconditioned by discontinuation of patient's previous therapy, it is necessary to mention that such therapy may be discontinued only in case it is not sufficiently effective or safe for the patient. (Please note: The investigator must not discontinue such therapy solely for the purposes of patient's inclusion in the CT.)

2. Objectives of the clinical trial

The document shall specify the purpose of the CT, whether the research is conducted with the objective to determine the efficacy and/or safety of the concerned medicinal product. The document shall not list inclusion and exclusion criteria; compliance therewith is the responsibility of the investigator.

3. Treatment procedures and notification of the likelihood of being randomly assigned to individual groups with different treatments

The document shall describe the course of treatment (or the administration of the investigational product) within the scope of the CT. If placebo is administered in the CT, it is necessary to provide its clear definition (such as "a tablet without the active substance"). The administration of placebo in a CT cannot be defined as "treatment". The likelihood of being assigned to individual groups shall be clearly explained, including the likelihood of being included in the placebo arm (e.g. "the likelihood of getting placebo is 1:3", or "you have a 25% chance of getting placebo", or "1 in 4 patients will get placebo", etc.). The patient has to clearly understand from the text that he/she may be assigned to the placebo arm. It is not possible to state that the patient will be given the new investigational medicinal product and some other patients may be given placebo.

For CTs, where patients are concurrently given standard treatment which they have not been receiving prior to the commencement of the CT (e.g. oncological CTs), this treatment has to be specified. Any potential deviations from the standard treatment within the scope of regular clinical practice shall be mentioned. If, however, the patient receives standard treatment and is to continue such treatment in the CT, this information shall be emphasised, nevertheless, the risks associated with the use of the standard medication shall not be detailed as the patient should already be familiar with them.

If it is possible to use rescue medication in the course of the CT, the rules of its use shall be specified.

4. Processes and procedures in the course of the clinical trial

A schedule of individual assessments, ideally in the form of a straightforward table and explanation of individual types of assessments shall be provided. The frequency and duration of visits as well as any potential deviations from routine practice have to be obvious from the text. The anticipated total amount of blood drawn in the course of the CT shall be specified in ml (comparisons of the amount of

blood drawn to teaspoons, spoons, etc. are not to be used); for children, the total amount of blood drawn has to comply to official recommendations (guidelines), see e.g. document "Blood sample volumes in child health research: review of safe limits":

http://www.who.int/bulletin/volumes/89/1/10-080010/en/

and the relevant table: http://www.who.int/bulletin/volumes/89/1/BLT-10-080010-table-T2.html.

Where invasive and demanding assessments are to be performed, also the degree of discomfort, potential risks and duration thereof shall be mentioned and, if applicable, it shall be emphasised that more details will be provided to the trial subject by the investigator. The description of routine assessments (such as blood draws, non-invasive pressure measurements, ECG, etc.) shall not be provided. If a procedure the conduct of which is not planned in the Czech Republic its description shall not be mentioned.

Where the CT requires hospitalisation of the trial subject (and such hospitalisation probably would not be required by routine clinical practice), it has to be emphasised.

5. Trial subject's responsibilities

It shall be mentioned in the document that if the trial subject agrees with participation in the CT, he/she undertakes to follow the instructions of the investigator and study team and instructions specified in the information sheet.

Furthermore, it shall be mentioned that the trial subject is to consult the investigator in advance about any other treatment outside study medication which he/she would like to use. In case the use of some medicinal products is prohibited in the course of the CT, it has to be mentioned (again, in a manner suitable for non-professionals, i.e. using formulations like "In this clinical trial it is not allowed to take some medicines, such as medicines for the treatment of high blood pressure", rather than by the name of the active substance). In case a trial subject in an emergency does use a medication which he/she did not consult with the investigator in advance, he/she shall inform the investigator of such fact as soon as practicable.

It is also appropriate to draw attention to unsuitable dietary supplements, as the doctor may not know about the OTC medicines and dietary supplements. Furthermore, it is necessary to specify any potential regimen measures (such as "during treatment with the investigational product you must not sunbathe"; "do not drink citrus fruit juices throughout the treatment"; "do not carry out these activities…", etc.).

In relevant cases it is appropriate to mention whether the investigational product affects driving and operating of heavy machinery and to instruct the trial subject to this effect.

6. Emphasising those elements of the clinical trial which are of the nature of research

Differences in treatment and assessments from routine clinical practice shall be mentioned, i.e. usually more visits to the doctor, more assessments, which are conducted for the purposes of the CT.

7. Foreseeable risks or discomfort for the trial subject

A list of adverse reactions to the study treatment shall be provided, in a straightforward (possibly tabular) and comprehensive manner, if practicable; it is not appropriate to use specialised terminology

in the text. Where such terminology cannot be avoided, it is necessary to explain it. Only real risks are to be mentioned.

Do not specify adverse reactions of treatment that is already known to the patient (e.g. the patient has been treated with the basic treatment prior to entry to the CT).

With a view to the fact that the trial subject usually does not know the structure of clinical trials, in the document the incidence of ARs should not be stratified to those which occurred in previous CTs in healthy volunteers and those that occurred in previous CTs in patients. It is not appropriate to mention the details of results of research in animals, either; nevertheless, the association between these data and potential occurrence of an AR in humans may be briefly mentioned.

The text should contain information that in case of adverse reactions occurrence the trial subject is to contact the investigator.

8. Information about risks for foetus or infant; contraception

The document shall mention the risks of treatment for fetus or breastfed child.

In case women of child-bearing potential participate in the CT, they shall use adequate contraception methods. Criteria for contraception listed in the information sheet / informed consent should be in accordance with the criteria in the protocol, which should be based on the CTFG Recommendations for contraception: (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf), unless other contraceptive methods are clearly justified. Contraceptive requirements should be given in a concise and comprehensible form for a layman. More detailed explanation should always be provided by the investigator and gynecologist.

In case children aged 15-17 years participate in the CT, a mention of the birth control requirements shall be provided also in the version for parents/guardians. However, at the same time, it shall be mentioned that birth control is to be applied only where such teenager is sexually active. Sexual abstinence is also considered to be a highly reliable method of contraception if it is followed during the entire period of risk associated with the study treatment. It is not appropriate to cite sterilization methods as a contraceptive option for this subject age group (15-17 years).

Information sheets for children under 15 years of age shall not include information about birth control. However, if the medicinal product used in the CT has a teratogenic potential, this information on the negative impact on the fetus / unborn child should be reported in the information sheet (12-14 years) as an adverse reaction of the product.

In case of phase IV CTs where the authorised product is used in compliance with the marketing authorisation, also contraception shall be applied as referred to by the SmPC.

9. Expected benefits; trial subjects shall be notified also in cases where no clinical benefits for them are anticipated

The document shall explain potential benefits of the subject's participation in the CT. It is appropriate to mention that the condition of the patient may also deteriorate in the course of the CT. Where such information is provided in the beginning of the document, it is not necessary to repeat it.

10. Alternative treatments, if the patient does not participate in the clinical trial

The document has to specify the options for the patient's treatment in routine clinical practice if he/she does not participate in the CT. Only products available in the Czech Republic shall be mentioned. It is appropriate to call the chapter “Other Available Treatment Options” (In Czech language: „Jiné dostupné možnosti léčby“).

Patients cannot be recommended participation in another CT or the option to give up any treatment.

11. Treatment and conditions of compensation in case of a trial-related injury

The following shall be mentioned in the document, ideally in the established wording: “All participants of the clinical trial have been insured in compliance with effective legislation of the Czech Republic.” (In Czech language: „Všichni účastníci klinického hodnocení jsou pojištěni podle platné legislativy ČR.“) The name of the insurance company may be provided. It has to be stated that the trial subject is to contact the investigator in case of a health damage due to his/her participation in the CT, that adequate medical care will be organised and reimbursed for the patient, and that the patient is entitled to compensation of damages pursuant to effective legal regulations.

It is not possible to state that reimbursement of such medical care will be provided only beyond the personal patient's health insurance coverage, etc. It is not sufficient to mention only the statement that the trial subject will be compensated for damages in accordance with the legislation of the Czech Republic. The document shall not discuss the relationship among the institution, sponsor and insurance company.

The chapter has to be worded briefly, it is not appropriate to use complex legal phrases which the trial subject does not understand.

It shall be mentioned that by signing this informed consent, the trial subject does not waive any of his/her legal rights.

12. Anticipated amount of remuneration for participation in the clinical trial

Trial subjects may be remunerated only in phase I CTs, bioequivalence and pharmacokinetics CTs. If the sponsor plans to remunerate the trial subject for participation, this fact has to be mentioned in the information sheet. Pursuant to law, however, remuneration may not be provided to vulnerable subjects (for examples, please refer to the Act on Pharmaceuticals, Section 52, paragraph (2)).

13. Anticipated expenses of the subject associated with the subject’s participation in the clinical trial

The text shall explain that the products administered to trial subjects and assessments carried out within the scope of the CT are paid for by the sponsor (do not use wording such as “you will not pay anything for the medicines and assessments”, “your participation is free of charge”, etc.). Where commercial CTs are concerned, it is not possible to state that products which are administered as investigational in the CT, but the patient would receive them also as part of routine clinical practice, will be paid either by the patient or his/her health insurance company. Likewise, it is not possible to mention that assessments which would be performed for the patient also as part of routine clinical practice are to be paid for by the patient or his/her health insurance company in the CT. The sponsor shall also pay for any above-standard procedures required for the patient at the time of the CT (such as the costs of sending SMS messages, etc.).

The document shall discuss the reimbursement of the trial subject's expenses for participation in the CT; this concerns adequate compensation of particularly travel expenses, the costs of meals, lost wages, and, where applicable, adequate compensation for the time intensity of assessments, visits to the doctor, discomfort of painful assessments (e.g. biopsy), and hospitalisation, where applicable. Detailed information about the method of reimbursement of expenses shall be provided to the trial subject by the investigator. The amount of compensation has to be adequate; it should be specified in the text, either as a flat-rate amount or based upon receipts presented to the investigator, or as exact rules for its determination.

14. Trial subject's participation is voluntary

The information sheet shall specify that the subject may freely decline participation in the CT and that this will not affect the relationship between the patient and the doctor or the patient's treatment. It is necessary to mention that the subject may withdraw from the CT at any time and without giving any reasons, and that this will not result in any adverse consequences or loss of benefits to which the subject is otherwise entitled. Despite this it would be appropriate to recommend to the subject to consult the early discontinuation of the investigational treatment with the investigator, particularly in those cases where immediate termination of treatment may adversely affect the trial subject's health.

15. Direct access to original clinical documentation and

16. Keeping of records about trial subjects

The document shall specify that monitors, auditors, representatives of the EC and authorised staff of competent authorities have direct access to source documentation. Confidentiality of subject information shall be maintained in compliance with legal regulations. It is desirable to use the following text. The following wording which has been drafted in cooperation with the Office for Personal Data Protection (ÚOOÚ) should be used:

“Any records will be stored and handled in compliance with effective legal regulations. Your personal data will be processed by administrators, who are the sponsor of the clinical trial (specify the name and identification details) and providers of healthcare services, as referred to by Act No 101/2000 Coll., on Personal Data Protection. Your explicit consent with the processing of these data should be granted after you are informed about the purpose of the processing and about the personal data to which the consent applies, and about the administrator and period for which it is valid. The provision of personal data is necessary for participation in the clinical trial. After the completion of the clinical trial or after the completion of your participation in the clinical trial the data will remain with the administrators, so that the validity of data obtained from the clinical trial is not compromised, for a period necessary to achieve the purpose of the clinical trial. Only the investigator and authorised representatives of the sponsor (such as the monitor and auditors), persons appointed by national control authorities of the states (in the Czech Republic the State Institute for Drug Control - SÚKL) and ethics committees, i.e. persons authorised to carry out surveillance over the course of the clinical trial, will have access to your personal records in the medical files. These persons are bound by mandatory confidentiality. Any data and samples collected in the clinical trial will be sent to the sponsor in a coded form only. Hence data on the basis of which it would be possible to establish your identity will not leave the workplace of the investigator. You have the right to view your medical files and the documentation of the clinical trial which is relevant to you and should you disagree with the processing of your data, e.g. due to their inaccuracy, you can ask the administrator to rectify them.”

In Czech language: “Veškeré záznamy budou uchovávány a bude s nimi nakládáno v souladu s platnými právními předpisy. Vaše osobní údaje budou zpracovávány správci, kterými jsou zadavatel klinického

hodnocení (uvést název a identifikační údaje) a poskytovatelé zdravotních služeb, v souladu se zákonem č. 101/2000 Sb., o ochraně osobních údajů. Váš výslovný souhlas se zpracováním těchto údajů by měl být udělen po sdělení, pro jaký účel zpracování a k jakým osobním údajům je souhlas dáván, jakému správci a na jaké období. Poskytnutí osobních údajů je nezbytné pro účast v klinickém hodnocení. Po ukončení klinického hodnocení, nebo po ukončení Vaší účasti v klinickém hodnocení zůstávají údaje správcům, aby nebyla narušena validita dat získaných v klinickém hodnocení a to po dobu nezbytnou k dosažení účelu klinického hodnocení. Do Vašich osobních záznamů ve zdravotnické dokumentaci má přístup pouze zkoušející lékař a pověření zástupci zadavatele (např. monitor a auditoři), osoby pověřené národními kontrolními úřady států (v ČR Státní ústav pro kontrolu léčiv - SÚKL) a etické komise, tzn. osoby pověřené dohledem nad průběhem klinického hodnocení. Tyto osoby jsou vázány povinnou mlčenlivostí. Všechny údaje a odebrané vzorky získané v klinickém hodnocení budou odeslány zadavateli pouze v kódované podobě. Údaje umožňující zjistit Vaši totožnost tak neopustí pracoviště zkoušejícího lékaře. Do Vaší zdravotnické dokumentace a dokumentace ke klinickému hodnocení týkající se Vaší osoby máte právo nahlédnout a v případě nesouhlasu se zpracováním svých údajů, např. z důvodu jejich nepřesnosti, můžete na správci požadovat nápravu stavu.“

This information, including its extent, is completely sufficient for the purposes of this document in cases where personal data are not transferred outside EU.

Contacts for family members and friends must not be requested from trial subjects across the board, but only in case it is a requirement specified by the protocol and the patient/healthy volunteer agrees with it. Only the trial site team is allowed to contact the trial subject.

Where reference to the American database of clinical trials clinicaltrials.gov is provided, it should follow only after references to SÚKL's database of clinical trials http://www.sukl.cz/modules/evaluation/ and the European database http://clinicaltrialsregister.eu/.

References to American legislation which is not relevant for the trial subject shall not be made; exceptionally, in case such reference is made, SÚKL requires that it follows only after a reference to Czech/EU legislation.

Until the adequacy decision of the European Commission, the EU-US Privacy Shield, which replaces the original decision of Safe Harbor, is put in place, the US is considered a country with insufficient level of data protection. Applicable legislation states that personal data can only be transferred to countries outside the EU and the EEA when an adequate level of protection is guaranteed.

For those cases, modified text of the consent should be used:

My personal data, which are sent to the sponsor may be transferred to countries including the US and Japan. Those, countries don’t have such strict laws on data protection as the Czech Republic; but the sponsor obligated to ensure an adequate level of protection for personal data as within the EU.

In Czech language:

„Informace o mé osobě, které jsou zasílány zadavateli, mohou být předávány do dalších zemí včetně USA a Japonska, kde nemusejí platit tak přísné zákony na ochranu osobních údajů jako v České republice; avšak zadavatel má povinnost na území těchto zemí zajistit adekvátní úroveň ochrany osobních údajů jako na území EU.“

17. Subject's consent with being informed immediately if information which could be of relevance for the subject's decision to continue to participate in the clinical trial becomes available

It shall be mentioned that information will be communicated to the trial subject without any delay particularly where it concerns an influence on the subject's safety. In such a case, the patient/healthy volunteer should be subsequently asked to sign a consent with continued participation in the CT by an amendment to the patient information sheet/informed consent form.

18. Contact for persons from whom the subject may obtain further information

A contact details of the investigator or a doctor appointed by the sponsor shall be specified.

Please note: GCP Decree, Section 12, paragraph (7): “For trial subjects and their guardians, the sponsor shall appoint a properly qualified and easily accessible doctor for the provision of consultations about health problems and about issues arising in association with the clinical trial.“

In respect of ethical aspects and rights of trial subjects in the CT a trial subject may contact the ethics committee.

19. Foreseeable circumstances and reasons for which the subject's participation in the clinical trial may be terminated

The given circumstances, particularly safety reasons or failure to comply with study procedures by trial subject, etc. shall be mentioned.

20. Anticipated duration of subject's participation in the clinical trial

The total maximum duration of participation of a single subject (not the time of duration of the entire CT) shall be specified, which includes not only the treatment period, but also the screening period and the period of follow-up visits, if applicable.

21. Approximate number of subjects to participate in the clinical trial

It is appropriate to specify the number of subjects both in the Czech Republic and worldwide.

Informed consent – general recommendations

At the start of the text it is appropriate to address the patient/healthy volunteer.

Points in an informed consent form shall be worded briefly, as it concerns a summary of the most important issues, it is not necessary to repeat information provided in the previous text in an extensive manner.

It has to be specified that by signing this informed consent the trial subject does not waive any of his/her legal rights.

Furthermore, it shall be mentioned that the subject’s general practitioner will be informed about the subject's participation in the clinical trial (in compliance with the requirement set forth by Annex 2 to the GCP Decree and the Act on Healthcare Services – Section 45, Rights and Obligations of the Provider, paragraph (2): "The provider shall be obliged to submit a report on provided healthcare services to the registering provider in the field of general medicine or in the field of general paediatric medicine").

This shall not apply in case of CTs of other than therapeutic, preventative or diagnostic purpose, where the trial subject (voluntary patient or healthy volunteer) is not provided with healthcare services, i.e. to pharmacokinetics and bioequivalence CTs and phase I CTs).

It is not appropriate to use checkboxes of the “YES/NO” type in the informed consent, as the trial subject will sign the informed consent only if he/she agrees with all of its points.

In compliance with Section 7, paragraph 2 of the GCP Decree, the following has to be specified:

- the date, name and signature of the trial participant (or, in specific cases, the signature of his/her guardian or signature of an independent witness - see below); in justified cases the participant will also note down the time of signing;

and

- the date, name and signature of the investigator. The words "signature of the person who obtained consent" may not be used in place of the investigator. In the Czech Republic, the patient's/volunteer’s consent with participation in the CT has to be always obtained by the investigator.

The signature of the subject cannot be obtained by sending the patient information sheet/informed consent form thereto by mail, etc.

After the document is signed both by the trial participant and the investigator, the subject shall receive a counterpart of the document (rather than a copy).

Information for parents/guardians of a child or a court-appointed guardian of the child (i.e. may be the child's surrogate or adoptive parent)

The scope of the document shall be similar as in the case of an information sheet for adult patients. In addition to the aforementioned points, the following specific features of the document shall be taken into account:

The purpose of the CT and the offer of participation for the child shall be specified. The child's participation is voluntary and the child's opinion should be taken into consideration.

In the document, it is necessary to provide a balanced information of the risks of the child's participation in the CT compared to the potential benefit of the new treatment. The patient must be guaranteed not to have worse treatment then in routine clinical practice. It is necessary to provide a clear and comprehensible explanation and to give the parents enough time to make their decision.

The method of evidencing efficacy and safety shall be described. Information about the medicine and to-date experience from the product development shall be provided. It is necessary to specify the likelihood of the child being assigned to individual treatment groups, or, if applicable, to explain the blinding of the treatment and, in justifiable cases, the use of placebo. It is necessary to explain adverse reactions, also those to any other products used in the CT (this shall not apply to medication used by the patient prior to his/her inclusion in the CT). The time intensity of assessments and visits shall be explained as well as the degree of discomfort for the child. Compensation of costs shall be specified and it shall be stated that the child will not be in any way remunerated for participation in the CT. The parent may terminate the child's participation in the CT at any time and without giving any reasons, but should always inform the investigator of such decision in advance.

The document shall be signed by both parents. The informed consent may be signed only by one parent if the other parent is not listed in the child's birth certificate, has died or is younger than 18 years. Exceptionally, one parent may be relieved from parental responsibility by a court decision (no longer acts as the child's guardian), in such a case the informed consent would be signed by the other parent.

Where the child's parents (or one of them) are foreign nationals, the information sheet shall be presented in bilingual format. Concurrently, the foreign-language version of the patient information sheet/informed consent which shall be a certified translation of the approved Czech version shall be submitted to SÚKL and to the ethics committee for approval.

Information sheet for paediatric patients

Information sheet for paediatric patients (i.e. the child's will to participate in the CT) shall not replace the consent of parents/guardians which shall be decisive for the child's participation in the CT. The child's opinion, however, has to be taken into account.

The information sheet has to specify the purpose of the CT and that it concerns research. Participation in the CT has to be offered to the child and the child shall have the right to ask anything that is unclear to him/her at any time. The child shall have the right to discuss participation with parents and anyone else and have enough time to think about his/her decision. The information sheet has to clearly specify what procedures are going to be conducted in the course of the CT and what discomfort will be implied by the participation for the child compared to routine practice (e.g. more frequent blood sampling, injection administration of the product, a higher degree of assessments, possibly more frequent absences from school, etc.). The benefits and risks of participation shall be briefly mentioned. With a view to the fact that a child cannot be remunerated for participation in the CT, the document may not contain any information about remuneration, either. The child may express a wish to terminate participation in the CT at any time.

SÚKL and the ethics committees require written patient information sheet/informed consent form for children from the age of 12. The used language and stylistics have to be as simple as possible, particularly for younger children. Texts should be submitted for the following age groups:

- 12 – 14 years incl.: Simple language, extent of text no longer than 4 pages. Information sheet for children under the age of 15 may not contain any information regarding contraceptives. The informal (“ty”) (specific for Czech language) form of address should be used, it is not acceptable to write the information in the first-person form.
- 15 – 17 years incl.: This may be of the extent of an information sheet for adults, a document for this age group shall include information about the necessity to use contraception in case the trial subject is sexually active. Adolescents should be addressed using the formal (“vy”) (specific for Czech language) form of address.

If the patient turns 18 in the course of the CT, he/she has to newly sign the patient information sheet/informed consent with participation in the CT – full version for adults. As of the date of becoming a adult, the consent with the minor’s participation in the CT granted by his/her parents or guardian shall cease validity.

Information sheet for patients with reduced ability to perceive the content of the document

The extent of the document has to reflect the ability of a patient in a particular physical and mental condition to read and perceive the information without any problems. Specific approach and abbreviated extent of information shall be employed for patients with psychiatric disorders, patients

with dementia, seniors, patients with painful conditions, and generally patients in acute and severely deteriorated conditions (such as myocardial infarction, acute-stage cardiac failure, stroke, etc.). For the last aforementioned group of patients, it is necessary to submit two versions: 1) an abbreviated version which shall contain basic information and shall be presented to the patient in his/her deteriorated clinical condition, nevertheless, shall contain a very brief description based upon the 20 points established in GCP and reflected in Annex 2 of the GCP Decree (no more than 1 page), and 2) a basic version which shall be submitted to the patient once his/her clinical condition is stabilised (consent with continued CT).

Information for guardians (in Czech language "opatrovníky") **(persons appointed by court who express legally relevant informed consent) in case of participation of partially legally incapacitated persons in the CT**

It is necessary to assess who is to sign the legally relevant consent, whether it is to be the patient himself/herself or his/her representative (a court appointed guardian (in Czech language "opatrovník") shall grant a legally relevant informed consent where, in its ruling about restricted legal capacity, the court directly states that the patient cannot decide about issues related to the provision of healthcare services[1]. Where the court ruling does not contain any such restriction, a partially legally incapacitated patient may express informed consent with participation in the CT.

It is, therefore, necessary to take into account that a patient, although partially legally incapacitated, is a vulnerable subject and hence rules for inclusion in the CT stipulated by the Act on Pharmaceuticals apply to him/her.

Information for guardian shall be drafted in the same extent as information for adult patients participating in a CT, the only difference being language adaptations reflecting that the guardian expresses consent on behalf of the person for whom he/she acts.

Information for caregivers (i.e. persons caring for the patient not expressing legally relevant consent in relation to the patient) – particularly for psychiatric CTs

This concerns information for the caregiver who, in the course of the CT, helps the patient and the study team in conducting the treatment, visits to the doctor, and patient assessments in compliance with the rules of the CT. To safeguard the subject's safety and, concurrently, the validity of the evaluation of treatment efficacy, the caregiver should be in contact with the patient on a daily basis (sometime common household may be necessary), or several days a week, depending on the patient's condition and the intensity of the procedures within the CT.

The information sheet may be presented in full extent, specifying all of the important pieces of information for this person; the text has to well explain the role of the caregiver.

The caregiver signs "his/her" informed consent in which he/she expresses his/her consent with involvement in the CT (e.g. will come with the patient for follow-up visits, will visit the patient regularly, will e.g. inform the investigator about deterioration of the medical condition of the trial subject). By signing the informed consent the caregiver expresses his/her will to become involved in the CT, but does not have the authority to express the relevant consent with the trial subject's participation in the CT; the trial subject has to provide such consent himself/herself.

[1] It cannot be anticipated that the court ruling would explicitly mention a restriction of the patient's decision-making in respect of his/her participation in the clinical trial.

Information in case patients unable to provide consent (unconscious patients) are being enrolled

Act on Pharmaceuticals, Section 52, paragraph (9): "In acute cases when it is impossible to obtain the trial subject's informed consent prior to the inclusion in the clinical trial, the consent shall be requested from the subject's guardian in compliance with paragraph 3, letter (b). Where such guardian has not been assigned or is unavailable, the trial subject may only be included in the clinical trial if the inclusion procedure is specified in the protocol and the investigator has obtained a written favourable opinion from the trial's ethics committee which contains an explicit position on the procedure of including trial subjects."

The investigator shall obtain the informed consent with continued trial subject's participation in the CT from the trial subject or, where applicable, from the subject's guardian, as soon as it is possible with respect to the medical condition of the trial subject or availability of the guardian.

All of the aforementioned details shall be applicable to inclusion of a trial subject in acute condition; nevertheless, it is recommended to obtain a consent from a close person, if such person is available. This consent shall not replace the consent of the patient proper.

When documenting the inclusion of a trial subject who is not able to confirm it in writing a consent by an independent witness shall be required (see above); by attaching his/her signature, the witness shall confirm that the trial subject has been included in compliance with the procedure described in the protocol and approved by the ethics committee (date, name + signature).

Information in case patients unable to write and/or read are being enrolled

If the person is unable to write, the person's consent shall be confirmed by an independent witness (must not be a study team member) attaching his/her signature to the informed consent. In the informed consent, the witness shall state that the trial subject agrees with inclusion in the CT and shall attach his/her own name, date and signature.

If the person is unable to read, the fact that the text of the information sheet has been read to the patient shall be confirmed by an independent witness (must not be a study team member) attaching his/her signature. The independent witness shall provide his/her name, date and signature. In the informed consent, the witness shall state that the patient information sheet has been read to the trial subject, the investigator provided further information about the CT to the trial subject and answered the subject's questions. In case the trial subject agrees with participation in the CT, he/she shall sign the informed consent.

Information for trial subjects regarding participation in a substudy

The substudy has to be described in the protocol. If participation in the substudy is optional for trial subjects, independently of the main part of the CT, a separate trial subject information sheet/informed consent form shall be submitted. The document shall explain the circumstances of the substudy, the intensity of assessments or other procedures above the scope of the main part of the CT. The trial subject shall be offered to participate. It is not necessary to repeat information from the main information sheet in the document, only different information shall be presented. It is, however, appropriate to mention that any information from the main document still remain valid.

It shall be mentioned that even if the trial subject declines participation in the substudy, he/she may still participate in the main part of the CT. Consent with participation in the substudy shall be expressed by the trial subject by attaching his/her signature to the informed consent. If the trial subject does not

wish to take part in the substudy, he/she shall not sign the document (in this case it is not possible to use checkboxes with rejection of participation and signature).

Consent with storage and use of samples for future research – such information sheet shall be approved by SÚKL only where such research is defined in the protocol and is associated with the treatment and specified procedures or with the basic diagnosis of patients enrolled in the CT.

Information sheet versions newly submitted in the course of the clinical trial

Updated versions of patient information sheets/informed consent forms shall be submitted to SÚKL for assessment with highlighted changes, so called "revisions". It has to be apparent what amendments have been made to the document compared to the previous version. SÚKL requires that changes be highlighted against the previous version also in the document which is then directly presented to trial subjects who have already signed the previous version.

Any new version of the information sheet has to have a serial version number and a current date of its origin. When compiling new revised versions of the patient information sheet/informed consent form it is not possible to ignore and cancel previous changes which were requested by SÚKL or EC during approvals. Any changes requested upon the initial CT application have to be automatically reflected in any other versions.

In case the recruitment of new trial subjects to the CT has been completed, in specific cases the submission of mere amendments to the patient information sheet/informed consent form where only the changed facts are to be mentioned is required.

Other types of information for trial subjects:

SÚKL shall approve only such patient information sheets (or healthy volunteer, parent/guardian or custodian information sheets) which are relevant to the trial subject's consent with participation in the CT or, if applicable, in substudies defined by the protocol (e.g. a pharmacokinetic substudy).

Examples of other types of information documents which are not assessed and approved by SÚKL:

- Information sheet/informed consent form with the use of samples for future scientific research not associated with the concerned clinical trial;
- Declaration of withdrawal from the clinical trial;
- Information sheet/informed consent form with authority to contact the patient's/healthy volunteer's pregnant partner;
- Information sheet/informed consent form for partners of males participating in a clinical trial;
- Information sheet for pregnant partner and consent form for the provision of data;
- Information sheet/informed consent form with test magnetic resonance imaging for the purposes of scan quality evaluation;
- Information sheet/informed consent form for personal data processing;
- Statement of the patient/healthy volunteer upon end of study treatment;
- Information sheet/informed consent form for the use of optional text message service;
- Information sheet/informed consent form for the use of photographs for educational purposes.

Opinion on these documents shall be provided solely by the ethics committee.

Note:

Header and footer of patient information leaflet/informed consent form – text in English may be accepted by SÚKL, if properly updated.