ZP-21 Inspection of the conduct of clinical evaluations on medical devices in the premises of healthcare providers

This guideline supersedes guideline SÚKL PZT-16 as of November 1, 2004.

The purpose of this guideline is to inform healthcare providers on the current status of legislation governing clinical evaluations and clinical investigations of medical devices. The text should not provide an exhaustive information and, with the exception of quoted legal regulations, should be considered a recommendation.

KEYWORDS, TERMS, AND ABBREVIATIONS

Clinical evaluation, clinical investigation, literary research, sponsor, healthcare provider, investigator, medical device, ethics committee, quality system

SÚKL – State Institute for Drug Control (Státní ústav pro kontrolu léčiv)

MoH – Ministry of Health of the Czech Republic

ÚZIS – Institute of Health Information and Statistics (Ústav zdravotnických statistických informací)

MD – medical device

AIMD – active implantable medical device

Sponsor – the manufacturer or its authorised representative (a person established in an EU Member State who has been authorised by the manufacturer in writing to act on its behalf with respect to the requirements implied for the manufacturer by this Act and by special regulations)

MDD – Council directive 93/42/EEC on medical devices

AIMD – Council directive 90/385/EEC on active implantable medical devices

ČSN EN ISO - identification of the Czech version of international standards, e.g. ČSN EN ISO 13485/2003 Medical devices - quality management system

ČSN EN ISO 14155-1: 2003 Clinical investigation of medical device for human subjects – Part 1: General requirements (published on November 1, 2003, currently available in the English language)

ČSN EN ISO 14155-2: 2003 Clinical investigation of medical device for human subjects – Part 2: Clinical investigation plans (published on November 1, 2003, currently available in the English language)

Act No 123/2000 Coll., on medical devices and on amendment to some related acts, as amended (no. 346/2003 Coll.)

Government Regulation no. 336/2004 Coll., on technical requirements governing medical devices, amending Government Regulation no. 251/2003 Coll., amending some government regulations published as implementing regulations for Act No 22/1997 Coll., on technical requirements for products and on amendments to some acts, as amended

Government Regulation no. 154/2004 Coll., on technical requirements governing active implantable medical devices, amending Government Regulation no. 251/2003 Coll., amending some government regulations published as implementing regulations for Act No 22/1997 Coll., on technical requirements for products and on amendments to some acts, as amended

CI – clinical investigation

CE – clinical evaluation

1. THE CURRENT STATUS OF LEGISLATION IN THE CZECH REPUBLIC AND RELATED DOCUMENTS

At present, **Act No 123/2000 Coll.,** on medical devices and on amendments to some related acts, as implied by amendments implemented by Act No 130/2003 Coll. and by Act No 274/2003 Coll. **is effective** (full text published as Act No 346/2003 Coll.).

Current Czech legislation and related documents relevant to clinical investigation and clinical evaluation:

1.1. Act No 123/2000 Coll., on medical devices, as amended

Article 8 General provisions

Paragraph 1 Verification of suitability for use in the provision of health care

Medical device must be suitable for use in the provision of health care; suitability of a medical device for the intended purpose of use must be verified by means of clinical evaluation or clinical investigation, except for

a) in vitro medical devices,
b) medical devices placed on the market in the European Communities Member States and bearing the CE conformity marking.

Paragraph 2 Definition of a clinical evaluation (CE)

Clinical evaluation of a medical device (hereinafter referred to as the "clinical evaluation") is understood to mean its expert evaluation by an investigator on the basis of the available professional publications, technical documentation and other documents in writing in order to review the safety of its use in the provision of health care and to respect the intended purpose of use specified by its manufacturer. If the clinical data and experience with the medical device have already been sufficiently and credibly documented to a necessary extent, only a clinical evaluation is required. The necessary clinical data is obtained from

a) the description of methodology and results of clinical investigation of the medical device, including clinical investigations on animals;

b) published clinical studies, especially

1. ***randomized (where the random recruiting for experimental and control groups is based on pre-established criteria such as age and sex, is comparable in basic parameters and cannot be applied retroactively on the basis of the already obtained results) controlled studies,***
2. ***various types of evaluable non-randomized studies, e.g. cohort studies (carried out in groups of individuals selected on the basis of certain common characteristics, a group exposed to the envisaged risk and a group not exposed to the envisaged risk, both groups are monitored and compared during a determined period of time, especially in the long-term; selection may be retroactive), multi-cohort (multiple cohort studies) or open controlled cohort studies;***
3. ***case studies;***
4. ***reports on controlled use of the medical device, after the obligation to notify stipulated by this Act has been met,***

c) background research or other evaluation of literary data published in the available national or foreign databases, or

d) data available from other persons, e.g. health insurance companies, bodies responsible for surveillance (vigilance), professional associations.

Paragraph 3 Definition of clinical investigation (CI)

Clinical investigation of a medical device (hereinafter referred to as the "clinical investigation") is understood to mean its systematic testing in accordance with its intended purpose of use and in the conditions determined by the manufacturer carried out by an investigator following a pre-established plan of clinical investigation, consisting in the application of the device in individuals in order to

e) prove whether the medical device is suitable for use in health care in accordance with its intended purpose of use, especially in terms of its safety and effectiveness;

f) identify its effects on the subject;

g) identify its adverse side effects and assess whether they represent risks which are acceptable for the subject.

1.2. Decree published on the basis of Act No 123/2000 Coll.

- Decree no. 316/2000 Coll., on the particulars of a final report on a clinical evaluation of a medical device

1.3. Other legislative requirements relevant to clinical evaluations and clinical investigations of medical devices

- Government Regulation no. 336/2004 Coll., on technical requirements governing medical devices (Article 15, Annex 8, Annex 10)
- Government Regulation no. 154/2004 Coll., on technical requirements governing active implantable medical devices (Article 14, Annex 6, Annex 7)

1.4. Standards relevant to clinical evaluation

- ČSN EN ISO 141551-1:2003 Clinical investigation of medical device for human subjects -– Part 1: General requirements
- ČSN EN ISO 14155-2: 2003 Clinical investigation of medical device for human subjects – Part 2: Clinical investigation plans

1.5. Standards relevant to quality systems for medical devices

- ČSN EN ISO 13485:2003 Medical devices - Quality Management System
  This standard focuses exclusively upon the quality systems of manufacturers of medical devices.

2. EU LEGISLATION AND RELATED DOCUMENTS

On the basis of the degree of importance, this area may be structured into the following parts:

2.1. Council directive 93/42/EEC on medical devices (hereinafter referred to as MDD) and Council directive 90/385/EEC on active implantable medical devices (hereinafter referred to as AIMD), where the area of clinical evaluations is mostly stipulated by:

- Article 15 (MDD) and Article 10 (AIMD);
- Annex I, II, III, VII, VIII, and X (MDD) and Annex I, II, III, VI, and VII (AIMD)

2.2. Standards relevant to quality systems for medical devices

- **EN ISO 13485:2003 Medical devices** – Quality Management System

This standard focuses exclusively upon the quality systems of manufacturers of medical devices.

2.3. Standards relevant to clinical evaluations

- **ČSN EN ISO 14155 – 1: 2003** Clinical investigation of medical device for human subjects – Part 1: General requirements
- **EN ISO ČSN 14155-2: 2003** Clinical investigation of medical device for human subjects – Part 2: Clinical investigation plans

2.4. Recommendations for the area of clinical evaluations

- NB-MED/2.7/Rec. 3 – Clinical data evaluation

3. SÚKL'S APPROACH TO INSPECTIONS OF THE CONDUCT OF CLINICAL EVALUATIONS AND CLINICAL INVESTIGATION OF MEDICAL DEVICES IN THE PREMISES OF HEALTHCARE PROVIDERS

SÚKL shall base its inspections of the conduct of a clinical evaluation or clinical investigation upon effective legislation, i.e. Act No 123/200 Coll., on medical devices, as amended. After the coming into force of the Treaty of Accession of the Czech Republic to the European Union, the provisions of Article 8, paragraph 1, letter (b) of Act No 123/2000 Coll. have taken effect, stipulating that **the suitability of a medical device for the intended purpose of use does not have to be verified by clinical evaluation (on the basis of a research) or by clinical investigation, if the medical device has been placed on the market in the European Communities Member States and bears CE conformity marking. The necessity to verify the suitability of a medical device by clinical evaluation or by clinical investigation is relevant only for those medical devices which are first placed on the market in the Czech Republic from non-EU countries and do not bear CE conformity marking.**
If a Czech manufacturer of a medical device obtains the CE mark from an EU notified body (i.e. outside the Czech Republic), they may place such medical device on the market without having to repeat the conduct of a clinical evaluation or clinical investigation in the Czech Republic. Where a Czech manufacturer of a medical device applies for conformity assessment and subsequent CE marking with a Czech notified body pursuant to a Czech government regulation, the suitability of the medical device for the intended purpose of use must then be verified by means of a clinical evaluation/clinical investigation pursuant to the above quoted Act No 123/2000 Coll. For procedure please refer to Annex 4.

Clinical evaluation and clinical investigation

a) ***Monitoring of clinical evaluation (CE) and clinical investigation (CI):***

In the inspections of clinical evaluations and clinical investigation SÚKL shall monitor the following recommended scheme of essential steps:

1. Contacts with the provider of health care (and with the sponsor, where applicable), sending of the inspection plan;
2. Commencement of the inspection in the presence of the director or his/her statutory representative, the investigator, and the sponsor, where applicable;
3. Review of the inspection plan, amendments and additional proposals, where applicable;
4. The inspection proper of the conduct of the clinical evaluation is set forth in *Annex 1*, that of clinical investigation in *Annex 2;*
5. Inspection completion, summary of conclusions, drafting of an inspection report;
6. Final inspection evaluation in the presence of the director or his/her statutory representative and the investigator, presentations of shortcomings, where appropriate;
7. Sending of the final protocol on the conduct and outcomes of the inspection.

Please note*:* The manufacturer or its authorised representative shall notify their intent to conduct the investigation to the MoH and to the Institute.

b) Verification of suitability of the medical device for the intended purpose of use:

(1) Article 8, paragraph 1 of the Act stipulates: "***Medical device must be suitable for use in the provision of health care; suitability of a medical device for the intended purpose of use must be verified by means of clinical evaluation or clinical investigation, except for***

a) in vitro medical devices,
b) medical devices placed on the market in the European Communities Member States and bearing the CE conformity marking.

c) Decision on the conduct of clinical investigation or clinical evaluation:

The following recommended scheme may be helpful in decision-making:
A clinical evaluation shall be regarded inadequate in the following instances:

- A new medical device with previously unknown components, properties or principles (method) of its action,
- An existing medical device modified in a way which may affect its effects upon the human body or its safe use in clinical practice;
- A medical device to be used for a purpose other than the current purpose of use;
- A medical device containing new or unknown materials which are to be in contact with the human body;
- Known materials contained in the medical device acting on a site previously inadequately tested in clinical practice;
- The effects of a medical device with known materials to be significantly longer than previously;
- A new, previously unverified manufacturer.

Please note*:* The sponsor as well as the investigator may consult the selected procedure and requirements for the conduct of the clinical evaluation and investigation proper with the employees of the SÚKL Medical Devices Branch.

3.1. Clinical evaluation inspections in the premises of healthcare providers

In compliance with the requirements stipulated by Article 12, paragraph 1 of the Act, the inspection shall focus upon the following:

- Written contracts and agreements concluded by the investigator, healthcare provider, and sponsor;
- Set of documents containing necessary data on the medical device which is to be the subject of examination;
- Set of relevant information known prior to the commencement of the clinical evaluation;
- Final reports from the clinical evaluation of the medical device.

Annex 1 provides a recommended scheme for inspected materials.

3.2. Clinical investigation

The inspection shall focus upon compliance with the requirements in the scope defined by Article 12, paragraph 2 of the Act. The inspection of clinical investigation shall have two stages:

a) The inspection of documentation sent by the sponsor of the clinical investigation;
b) The inspection of the conduct of the clinical investigation in the premises of the healthcare provider. The inspection shall focus upon compliance with the procedures stipulated by the Act, the examination of documentation and any related materials relevant to the clinical investigation.

Annex 2 provides a recommended scheme for inspected materials.

Please note:

SÚKL shall also inspect the compliance with the requirements stipulated by the newly harmonised European standards ČSN EN ISO 14 155-1,2: 2003, particularly in terms of good clinical practice (GCP).

SÚKL recommends that manufacturers and their authorised representatives proceed in compliance with the above mentioned harmonised standards, as these standards comply with the requirements governing clinical investigations which form an integral part of conformity assessment and CE marking, as laid down by both relevant government regulations and European directives on medical devices effective in the Czech Republic.

Annex 1

Inspection of the conduct of clinical evaluation (without clinical investigation) - recommended scheme

(where applicable)

1. A certificate of competence of the workplace to conduct clinical evaluations

Examination of the MoH certificate of the workplace's competence to conduct clinical evaluations.

2. A written agreement of the sponsor and the healthcare provider on the conduct of the clinical evaluation

The identification of the contracting parties (sponsor/healthcare provider), CE specifications, MD specifications - name, manufacturer, any other relevant information necessary for the identification of the product where applicable, specification of the site where the clinical evaluation is to be conducted, start and end date of the clinical evaluation, signatures of the statutory body and of the healthcare provider.

3. A written agreement of the sponsor and investigator on the conduct of the clinical evaluation

The identification of the contracting parties (sponsor/investigator), CE specifications, MD specifications - name, manufacturer, any other relevant information necessary for the identification of the product where applicable, confidentiality obligations, start and end date of the clinical evaluation, signatures of the investigator and of the statutory body of the sponsor.

4. Certificate of professional qualification of the investigator

Examination of the documents of professional qualifications of the investigator (adequate qualifications, experience and knowledge of the use of the relevant medical device, licence of the investigator for the conduct of the relevant specialist activities).

5. A written declaration of the investigator

Examination of the written declaration of the investigator regarding:

a) the ability to conduct and complete the clinical evaluation;
b) the fact that he/she has no personal interest in the subject matter of the clinical evaluation which might result in a conflict of interest.

6. Other related documents

Certificates of quality system ISO EN 9000, ČSN EN ISO 13485, certificates compliant with technical standards, certificates of material of animal origin in respect of TSE/BSE risks (where applicable).

7. Package leaflet or instruction for use in the Czech language

Verification of consistency of instructions for use/package leaflet in the Czech language and in its original version (where applicable), and its verification by the investigator.

8. Preclinical and clinical data

Examination of e.g. the following:

- preclinical data incl. e.g. the description of methodology and results of clinical investigations in animals or *in vitro* tests;
- clinical documentation based for example upon published clinical studies, research of relevant specialist literature documenting data on the experience with the use of the medical device in clinical practice which may also be considered a literary source;
- and other data set forth in Article 8, paragraph 2, letter (d) of the Act.

Please note: In the assessment of source materials for a clinical evaluation, compliance with the following facts in particular shall be evaluated:

- the summary of available literature must be adequate to the period when the clinical evaluation is to be conducted, and, moreover:
- the medical device must be, in the published reports, used in the same population as the clinically evaluated medical device;
- the conditions of use of the medical device must be identical;
- the medical device must be used for identical clinical purpose (indications);
- the adequacy of data in decisive aspects of consistency must be objectively evidenced;
- literary data may be applied to the clinically evaluated medical device only if the similarity with the medical device in terms of technology and key operations is clearly demonstrated,
- the published data must be taken from well-established scientific sources.

9. Final report on the clinical evaluation of a medical device

The final report should contain:

a) registration-type data:
    - name of the healthcare provider where the clinical evaluation has been conducted;
    - name and registered office of the sponsor of the clinical evaluation;
    - name of the medical device, incl. its manufacturer;

- name and qualifications of the investigator;
- date of final report completion;

b) expert contents of the final report:
   - brief characteristics of the clinical evaluation;
   - data on the medical device, e.g. a brief description of the device, the intended purpose of use - indications, contraindications consistent with the instructions for use;
   - data on the assessment of suitability of the medical device for the intended purpose of use consistent with the instructions for use/package leaflet;
   - list of used specialist literature;
c) signatures of the statutory body of the healthcare provider, the statutory body of the sponsor of the clinical evaluation, and the investigator.

Dossiers incl. all associated source materials should be archived in a clearly organised and easily identifiable manner. The investigator shall store the documentation of the clinical evaluation of the medical device incl. the final report for the period of ten years.

***Recommendation**:*
Compliance with the scheme of the final report pursuant to ČSN EN ISO 14155-1: 2003 Annex C.

Annex 2

Inspection of the conduct of clinical investigation within the premises of the healthcare provider

A. Examination of clinical documentation - recommended scheme

1. **Name of the medical device, type/catalogue ID, batch no.**
   Examination of consistency of these details with data stated in all associated documents and with the labelling of the medical device.

2. **Intended purpose of use of the medical device**
   Review of consistency, e.g. indications, contraindications, areas of application, with the instructions for use.

3. **Manufacturer of the medical device**
   Address, telephone, fax, e-mail, contact person.

4. **Sponsor of the clinical investigation**
   Contact person, address, telephone, fax, e-mail.

5. **Written approval of the Ethics Committee**
   Examination of minutes of meeting of the Ethics Committee, e.g. examination of unequivocal nature of the position, identification of the medical device, dates and signatures of the members of the Ethics Committee.

6. **Written approval of the Ministry of Health of the Czech Republic**
   Random examination, e.g. examination of clear specification of the clinical investigation and medical device, dates, and signatures.

7. **Investigator's brochure**
   Examination of technical and clinical data on the investigated medical device (if applicable):
   - technical and clinical data on the investigated medical device;
   - an overview of literature and its evaluation (supporting the rationale of the expected purpose of use of the medical device and conduct of the clinical investigation);
   - general description of the medical device;
   - quantitative and qualitative chemical composition of the medical device;
   - results or preclinical, physical, and chemical tests;
   - test validations;
   - packaging and labelling of the medical device;
   - list of applied international and national standards;
   - results of risk analyses;
   - certificate of material of animal origin for use in the medical device in terms of BSE risk.

8. **Clinical investigation plan**
   Examination of detailed information, e.g. on the reasons, purpose, objectives, selection of subjects for the clinical investigations, methodology as well as on the management and monitoring of the clinical investigation. The plan must be signed by the investigator and by the sponsor.
   Recommendation: A clinical investigation plan should contain particulars in the scope specified by standard ČSN EN ISO 14155*-2:2003*.

9. **Information for subjects**
   Examination of e.g. comprehensibility, clarity, and completeness of the provided information within the scope established by Article 10, paragraph 2 of the Act (the informed consent should also be part of health records of a subject included in a clinical investigation).

10. **Individual Case Report Forms (CRF) for subjects of the clinical investigation**
    Examination of the design of the form, e.g. in terms of the form being unequivocal and clearly identifiable.

11. **Adverse incident forms**
    Examination of the design of the form.

B. Inspection of clinical investigation within the premises of the healthcare provider

1. **A written contract of the sponsor and healthcare provider and a written agreement of the sponsor and investigator**
   Random examination (e.g. date, signature, identification of the medical device, data protection, confidentiality obligation).

2. **Copies of certificates of qualification of the workplace issued by the Ministry of Health of the Czech Republic**

Examination of validity, scope of powers.

3. **Written approval of the Ethics Committee**
   Random examination of minutes of meeting of the Ethics Committee (a list of Committee members, identification of the medical device, documentation submitted by the sponsor, dates and signatures).

4. **Written approval of the Ministry of Health of the Czech Republic**
   Random examination (specification of the clinical investigation and medical device, dates, and signatures)

5. **Qualifications of the investigator**
   Examination of certificates of professional qualifications of the investigator (adequate qualifications, experience and knowledge of the use of the relevant medical device, licence of the investigator for the conduct of the relevant specialist activities).

10. 6. **A written declaration of the investigator**
   a) regarding the ability to conduct and complete the clinical investigation;
   b) regarding the fact that he/she has no personal interest in the subject of the clinical investigation which might result in a conflict of interest.

   Examination of date and signature.

7. **Investigator's brochure**
   Examination of consistency of technical and clinical data documentation on the investigated medical device and documentation submitted to the Institute (Annex 2, letter A, item 9 refers).

8. **Medical device intended for investigation**
   Examination of labelling, certificate of final inspection for the given batch of the medical device and hand-over protocol incl. batch data.

9. **Instructions for use/package leaflet**
   Examination of availability of the instructions for use to the user, comparison of the Czech version with the original version of the instructions for use (where applicable).

10. **Clinical investigation plan**
   Examination of formal particulars (such as signatures, dates) and additional amendments to the plan where applicable, approved by the sponsor of the clinical investigation, examination of the position of the Ethics Committee on the amendment of the plan.
   Recommendation*:* The clinical investigation plan should contain particulars within the scope specified by standard ČSN EN ISO 14155-2: 2003.

11. **Maintenance of records on the course of the clinical investigation**
   Examination to determine whether records are complete, up-to-date, legible, easily identifiable, and examination of record-keeping management, i.e. filing and archival, responsibilities and powers.

12. **Discontinuation and early termination of the clinical investigation**
   Examination to determine whether the discontinuation or early termination of the clinical investigation has been adequately justified, signed by responsible persons, and dated.

13. **Information for subjects**
   Examination for e.g. comprehensibility, clarity and completeness of the provided information.

14. **Informed consent of the subject of clinical investigation**
   Examination of signature, date, legibility, and method of archival.

15. **Proof of insurance/document on method of compensation for damages**
   Examination of the scope and purpose of insurance coverage and its validity.

16. **Individual Case Report Forms (CRF) for subjects in the clinical investigation**
   Examination of accuracy of records, identifier of the patient, statement of the type/batch of the medical device, legibility of the signature of the investigator or authorised person, furthermore examination of changes, dates of their implementation and signatures of persons who have carried out the changes, filing and archival.

17. **Adverse incidents**
   Examination of forms (e.g. for accuracy of their completion), examination of the procedure of mandatory notification (MoH, SÚKL, Ethics Committee, sponsor).

18. **Archival of documentation**
    Examination of the archival system - the investigator shall maintain the documentation of the clinical investigation of the medical device incl. the final report for the period of ten years.

19. **Notification duty**
    Examination of the notification of the intended conduct of the clinical investigation to the MoH and SÚKL (to be notified by the sponsor pursuant to Article 11, paragraph 5 of Act No 123/2000 Coll., and Article 15, item 1 of Government Regulation no. 336/2004 Coll.).

C. Final report on the clinical investigation of a medical device - recommended scheme

a) registration-type data:
- name of the healthcare provider where the clinical evaluation has been conducted;
- name and registered office of the sponsor of the clinical evaluation;
- name of the medical device, incl. its manufacturer;
- name and qualification of the investigator;
- start date of the clinical investigation;
- end date of the clinical investigation;
- date of final report completion;

b) expert contents of the final report:
- brief characteristics of the clinical evaluation;
- data on the medical device, e.g. a brief description of the medical device, indications, contraindications consistent with the package leaflet/instructions for use;
- data on the verification of suitability of the medical device for the intended purpose of use - Clinical Investigation Plan (e.g. the objectives of clinical investigation, rationale, selection of control group, criteria for inclusion of subjects in the clinical investigation, medical care provided to the subject of the clinical investigation, applied statistical methods, data on the evaluation of efficacy and safety of the medical device claimed by the manufacturer with a view to the intended purpose of use);
- list of used specialist literature;

c) signatures of the statutory body of the healthcare provider, the statutory body of the sponsor of the clinical investigation, and the investigator.

The investigator shall maintain the documentation of the clinical investigation of the medical device incl. the final report for the period of ten years.

Recommendation:
1. Decree no. 316/2000 Coll. may serve as a guideline for the preparation of the final report.
2. Another guideline which may be used is Annex C to the European harmonised standard ČSN EN ISO 14155-1:2003.

Recommendation:
- A translation of **NB-MED/2.7/Rec3: Clinical data evaluation** is available on the SÚKL website www.sukl.cz under section **Medical devices**
- **ČSN EN ISO 14155 – 1: 2003 Clinical investigation of medical device for human subjects – Part 1: General requirements**
- **EN ISO ČSN 14155-2: 2003 Clinical investigation of medical device for human subjects – Part 2: Clinical investigation plans**
  The texts of both standards are in the English language. The standards may be purchased in the office of the Czech Standards Institute, Biskupský dvůr 5, Prague (web site of the Institute: www.csni.cz). The Czech version of the above mentioned standards has been in print at the time of issue of this guideline.

Annex 3

Methods of evidencing the safety and suitability of medical devices
General provisions

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	A. Decree 93/42 EEC	B. ČSN EN ISO 14155 – 1,2: 2003
Article 8, paragraph 1	**Article 15**	**Article 14**	**Annex X, paragraph 1**	**Subject matter of the standard**
The medical device must be suitable for use in the provision of health care; the suitability of the medical device for the intended purpose of use must be verified by a clinical evaluation or clinical investigation with the exception of: a) *in vitro* medical devices; b) medical devices marketed in the EC member states and CE-marked for conformity.	*Item 3* **Clinical evaluations or clinical investigations must be carried out in compliance with the Act on medical devices, Annex 10 to this Regulation.** *Item 5* **Clinical evaluations or clinical investigations shall not be conducted** for medical devices in the instances established by the Act on Medical Devices. It is curious that the text of Article 15 concerns clinical investigations, although it regulates also clinical evaluations.	*Item 1* For active devices intended for clinical investigations, the manufacturer or the authorised representative shall submit to the Ministry and to the Institute, no later than 60 days prior to the commencement of the clinical investigations, a declaration pursuant to Annex 6 to this Regulation. *Annex 6* Provisions on active devices intended for special purposes *Annex 7* Clinical evaluations and clinical investigations Both annexes refer to Act No 123/2000 Coll.	With regard to the relevant harmonised standards the adequacy of clinical data, where appropriate, shall be based upon 1.1.1. the summary of normally available relevant scientific literature on the given purpose of use and applied methods, or, where applicable, upon a written critical evaluation of this summary or 1.1.2. the results of all conducted clinical investigations, incl. investigations conducted pursuant to paragraph 2 (procedures and methods of clinical investigations)	Subject-matter of the standard - protection of human subjects; - ensure scientific management of clinical investigations; - assistance for sponsors, sponsor's assistants, investigators, ethics committees, authorised bodies, and statutory bodies involved in conformity assessment in the field of medical devices
Temporary provisions - Article 52, paragraph 2 The authorisation to use a medical device in the provision of health care issued by the Ministry or by the Institute pursuant to Article 62, paragraph 3, of Act No 20/1966 Coll., on care for the health of the nation, as amended by Act No 548/1991 Coll., **shall be considered the certificate of compliance with the suitability of the medical device pursuant to Article 8.** This certificate shall be valid for the entire duration specified therein; where no such duration is specified, the expiry date for the use of the medical device in the provision of health				

care shall be December 31, 2005.				

<u>Clinical evaluation</u>
Collection of necessary data

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	C. Decree 93/42 EEC	D. ČSN EN ISO 14155 – 1,2: 2004
Article 8, paragraph 2	**Annex 10, item 1.3.**	**Annex 7, item 1**	**Annex X, paragraph 1**	
<u>Clinical evaluations on medical devices</u> – Where clinical data and experience pertaining to the medical device are documented beforehand in an adequate scope and in a credible manner a clinical evaluation shall be considered sufficient. Relevant clinical data shall be obtained from: a) the description of methodology and results of clinical investigation of the medical device, incl. clinical investigation in animals; b) published clinical studies: randomised, various types of evaluable non-randomised studies, case studies; c) research or other evaluation of published literature data from available domestic or foreign databases, or d) available data of other persons e.g. health insurance companies, bodies responsible for the conduct of surveillance (vigilance), professional associations.	The assessment of the adequacy of clinical data, *with regard to the relevant harmonised standards*, shall be based upon Article 8, paragraph 2 of the Act.	The necessary clinical data shall be obtained from a comparison of the summary of available scientific literature on the specific active device and the written critical assessment of this comparison.	***With regard to the relevant harmonised standards,* the adequacy of clinical data, where appropriate, shall be based upon** 1.1.1. the summary of normally available relevant scientific literature on the given purpose of use and applied methods, or, where applicable, upon a written critical evaluation of this summary.	Clinical evaluations are not the subject matter of the standard. Literature research serves as a basic source material for clinical investigations.

<u>Clinical investigation</u>
Purpose of the clinical investigation

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	E. Decree 93/42 EEC	F. ČSN EN ISO 14155 – 1,2: 2004
Article 8, paragraph 3	**Annex 10, paragraph 2**	**Annex 7, item 2.1.**	**Annex X, paragraph 2.1.**	**Item 3.4. (14155-1) and item 4.6. (14155-2)**

Clinical investigation of a medical device shall mean its systematic investigation in accordance with its intended purpose of use and in the conditions determined by the manufacturer carried out by an investigator following a pre-established plan of clinical investigation, consisting in the application of the device in individuals in order to a) prove whether the medical device is suitable for use in the provision of health care in accordance with its intended purpose of use, especially in terms of its safety and efficacy; b) identify its effects on the subject, identify its adverse side effects and assess whether they represent risks which are acceptable for the subject.	Clinical investigations must 2.1. be conducted in compliance with the Helsinki Declaration; 2.2. be conducted under circumstances similar to the normal conditions of use of the medical device; 2.3. include relevant characteristics of the medical device, incl. characteristics relevant to the safety and performance of the medical device and its influence on patients.	The purpose of the clinical investigations of an active device for the intended purpose of use under normal conditions shall be: 2.1.1. to verify whether their efficacy is in compliance with the requirements set forth in Annex 1, item 2; 2.1.2. to determine adverse reactions thereto and to evaluate whether they represent acceptable risks with a view to the efficacy of these devices.	The purpose of the clinical investigations shall be: - to verify whether the conduct of the clinical investigation of the medical device under normal conditions of use corresponds, in terms of its procedure, to the characteristics pursuant to Annex I, paragraph 3; and - to determine all adverse reactions under normal conditions of use and to evaluate whether they represent an acceptable risk with a view to the intended purpose of use of the medical device.	Item 3.4. Any expected and planned systematic investigation conducted in human subjects to verify the safety and/or functional adequacy of a specific medical device. Item 4.6. The plan of clinical investigations must clearly identify primary and secondary hypotheses and objectives of the clinical investigations together with the populations for which the medical devices are to be used in the clinical investigations.

Clinical investigation
Ethics Committee

Act No 123/2000 Coll.	**Government Regulation no. 336/2004 Coll.**	**Government Regulation no. 154/2004 Coll.**	**G. Decree 93/42 EEC**	**H. ČSN EN ISO 14155 – 1: 2004**
Article 9, paragraph 4		**Annex 7, item 2.3.**		**Item 3.10.**
The sponsor shall be obliged to notify the concerned Ethics Committee in advance and in writing of its intention to conduct clinical investigation; together with the notification the sponsor shall submit the relevant dossiers. The Ethics Committee shall approve or reject the conduct of the clinical investigation within 60 days of the delivery of the notification.	The government Regulation does not address the issue of approval/rejection of the clinical evaluation by the Ethics Committee. It only discusses the ethical aspects, such as compliance with the Helsinki Declaration.	Clinical investigations must be conducted in compliance with the plan of clinical investigations approved by the Ethics Committee. Moreover, there is a reference to Act No 123/2000 Coll., Article 8, paragraph 4 (reference to the plan) and Article 9, paragraph 3 (the healthcare provider to report to the Ministry of Health the resolutions of the Committee).	The Decree does not address the issue of approval/rejection of the clinical evaluation by The ethics Committee. It only discusses the ethical aspects, such as compliance with the Helsinki Declaration.	An Ethics Committee – an independent and properly established competent authority whose task is to responsibly ensure that the safety, mental wellbeing, and human rights of the subjects participating in the clinical investigations are maintained.

Clinical investigation
Informed consent

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	I. Decree 93/42 EEC	J. ČSN EN ISO 14155 – 1: 2004
Article 10, paragraph 1, 2, 3, and 4				**Item 6.7.**
The above mentioned Article clearly stipulates that - the information for the patient must be provided in writing, in a clear form and language well understandable to the subject, and must contain particulars stipulated by Article 10, paragraph 2, letters (a) to (f); - the information forms part of the informed consent. For the purpose of the clinical investigation, the investigator shall be obliged to ensure that the informed consent is obtained from the subject of the clinical investigation - this obligation is imposed by **Article 14, paragraph 2, letter (c).**	The Government Regulation does not address the issue of patient information and informed consent.	The Government Regulation does not address the issue of patient information and informed consent.	The Decree does not address the issue of patient information and informed consent.	The above mentioned Item specifies in detail the following: - procedures governing the obtaining of the informed consent (item 6.7.2); - information provided to the subject in order to obtain their consent (item 6.7.3); - declaration on the informed consent (item 6.7.4); - agreement on the informed consent (item 6.7.5).

<u>Clinical investigation</u>
Conditions governing the conduct of clinical investigations

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	K. Decree 93/42 EEC	L. ČSN EN ISO 14155 – 1: 2003
Article 11, paragraph 1	**Annex 8, item 2.2.**	**Annex 7, item 2.3.**	**Annex X, item 2.3.**	**Item 6.6.**
Clinical investigation in subjects may start and proceed only if a) the predictable risks and inconveniences do not outweigh the expected benefits for the subject; b) an informed consent has been obtained from the subject; c) a written approval of the plan of clinical investigation has been obtained from the ethics committee;	Declaration of the manufacturer or its authorised representative on the medical device intended for investigation shall contain: 2.2.1. details allowing for the identification of this device; 2.2.2. the plan of clinical investigations; 2.2.3. position of the concerned Ethics Committee; 2.2.4. name and surname of the person who commissions the	Clinical investigations must 2.3.1. be conducted in compliance with the plan of clinical investigations approved by the Ethics Committee; 2.3.2. contain an adequate number of comparisons in order to guarantee scientific validity of conclusions; 2.3.3. be conducted under circumstances adequate to those of normal conditions of use of	2.3.1. Clinical investigations shall be conducted on the basis of a relevant plan. Investigations must contain an adequate number of observations in order to ensure scientific validity of conclusions. 2.3.2. Procedures applied in investigations must be adequate. 2.3.3. Clinical investigations must be conducted under circumstances adequate to those	No clinical investigations may be initiated until: a) a plan of clinical investigations is compiled and signed; b) the position and/or approval has been obtained from the Ethics Committee; c) a statutory authorisation or approval has been obtained where applicable.

d) it starts and is carried out under the management of an investigator; e) whenever applicable, the biological safety test has been conducted, and the suitability of use of the medical device in terms of safety and technical standards has been proven.	conduct of the clinical investigation and the surname of the physician conducting the clinical investigation; 2.2.5. the site, start date, and planned duration of the clinical investigation; 2.2.6. declaration to the effect that the medical device in question complies with the essential requirements with the exception of aspects which are the subject matter of the investigations.	the active device; 2.3.4. verify the relevant characteristics of the active device and the effects of the device on patients; 2.3.5. include procedures adequate for the active device for which the clinical investigations are conducted.	of normal conditions of use of the device. 2.3.4. All relevant characteristics of the device shall be tested, incl. those relevant to the safety and performance of the device and its effects on patients. 2.3.5. All adverse incidents shall be recorded and reported to the concerned authority.	

Clinical investigation
Notification duty

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	M. Decree 93/42 EEC	N. ČSN EN ISO 14155 – 1,2: 2003
Article 11, paragraph 5	**Article 15, item 1**	**Article 14, item 1**	**Article 15**	
Before the start of the clinical investigation, a written notification of the intent to conduct clinical investigation is to be sent to the Ministry or to the concerned authority of the EU Member State where the clinical investigation is to be conducted.	The manufacturer or its authorised representative shall notify the Ministry and the Institute of their intention to carry out a clinical investigation.	No later than 60 days before the commencement of the clinical investigations the manufacturer or its authorised representative shall submit to the Ministry and to the Institute a declaration pursuant to Annex 6 to this regulation.	A manufacturer or its authorised representative established in the EU shall proceed in compliance with Annex VIII and inform the concerned authorities of the Member States where the investigations are to be conducted.	Not addressed by the Standard.

Clinical investigation
Clinical investigation dossiers

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	Decree 93/42 EEC	ČSN EN ISO 14155 – 1,2: 2003
Article 12, paragraph 2	**Annex 8, items 2.2. and 3.2.**	**Annex 6, item 2.2.**	**Annex VIII, items 2.2. and 3.2.**	**Item 7 (14155-1), items 1 – 4 (14155-2)**
letter (a) - prior to the commencement of the clinical investigations 1. a contract concluded by the sponsor and the healthcare provider; 2. Investigator's brochure, which	Clinical investigation dossiers must include, for example: 3.2.1. a general description of the device; 3.2.2. design drawings, expected manufacturing technologies, particularly those concerning	Clinical investigation dossiers must include: 2.2.1. details allowing for the identification of this device; 2.2.2. the plan of clinical investigations (purpose, content, scope, and number of medical	The requirements governing the dossiers are based upon the declaration of the manufacturer or its authorised representative in the EU which contains, for example: - details necessary for the identification of the medical	Documentation stipulated under items 7.2 and 7.3 must be ready before the start of the clinical investigation. 7.2 The Investigator's brochure shall contain, for example: - a list of literature and evaluation

shall mean a set of relevant information known before the start of the clinical investigations, in particular information harmonised with the law and with EC recommendations (reference to Decree 93/42/EEC, ČSN EN 540); 3. the plan of clinical investigations; 4. a written approval of the Ethics Committee; 5. the informed consent; 6. a set of documents containing necessary information on the subjects and on the medical device; 7. a list of pharmaceuticals and the method of their administration to the subject; 8. a method of compensation should the health of the subjects be injured. **Letter (b) - during the clinical investigations, records on:** 1. activities conducted pursuant to the plan of the clinical investigations; 2. unexpected developments and measures implemented beyond the plan of clinical investigation; 3. adverse incidents, if any.	sterilisation, and, furthermore, drawings of individual parts, subsets and circuits; 3.2.3. descriptions and explanations necessary for the understanding of the above mentioned drawings, schemes, and function of the device in question; 3.2.4. results of risk analysis, a list of partially or fully applied harmonised standards, and a description of solutions adopted to comply with the essential requirements where these standards have not been applied, results of design calculations, conducted controls, technical tests, and other measures where applicable.	devices); 2.2.3. name of the doctor and name of the healthcare facility or the business name of the company of the person authorised to provide health care pursuant to special legal regulations who is responsible for the conduct of the clinical investigation, date of the planned commencement of this investigation, and its duration; 2.2.4. a declaration to the effect that this medical device complies with essential requirements with the exception of those aspects which are the subject matter of the clinical investigation and that with regard to these aspects preliminary measures have been taken to protect the health and safety of the individual in whom the clinical investigation is to be conducted.	device; - the plan of clinical investigations, purpose and number of medical devices; - the position of the ethics committee; - name of the doctor or other authorised person and institution responsible for the investigation; - the site, start date, and duration of the investigation; - a declaration to the effect that the medical device in question complies with essential requirements with the exception of those aspects which are the subject matter of the clinical investigation and that with regard to these aspects all preliminary measures have been taken to protect the health and safety of the patient.	supporting the justification of the intended purpose of use of the medical device and the design of the clinical investigation; - a general description of the medical device; - a description of mechanisms of action of the medical device together with supporting scientific literature, instructions for use, and, moreover, manufacturer's instructions for installation where relevant; - a description of expected clinical properties; - a description of materials; - preclinical investigations; - risk analysis results. 7.3 Other documents, such as: - the plan of clinical investigation - described in detail in 14155-2 (items 1 – 4); - up-to-date CVs of the investigators; - name of the institution where the clinical investigation is to be conducted; - a written position of the Ethics Committee; - correspondence with authorities as required by national legislation (notification duty).

<u>Clinical investigation/clinical evaluation</u>
Competence of workplaces to carry out clinical evaluations or clinical investigations

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	Decree 93/42 EEC	ČSN EN ISO 14155 – 1,2: 2003
Article 15				
If the workplace is competent to conduct clinical evaluations/investigations, the MoH	The competence of the workplace to conduct clinical evaluations/investigations is not	The competence of the workplace to conduct clinical evaluations/investigations is not	The competence of the workplace to conduct clinical evaluations/investigations is not	The competence of the workplace to conduct clinical evaluations/investigations is not

shall issue a certificate.	addressed.	addressed.	addressed.	addressed.

Clinical investigation
Final report

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	Decree 93/42 EEC	ČSN EN ISO 14155 – 1:2003
Article 12, paragraph 2, letter (b)	**Annex 10, item 3**	**Annex 7, item 3**	**Annex X, item 2.3.7.**	**Annex C**
The final report on clinical investigations shall contain, in particular, a description of methodology and design of the clinical investigation, an analysis of all data collected from all workplaces involved, incl. the critical assessment of their clinical evaluation and the relevant statistical analysis, data from all subjects, while no subject may be identifiable from this report or from the published results. To be signed by the investigator, the statutory body of the sponsor, and the statutory body of the healthcare provider (Decree no. 316/2000 Coll. refers).	Refers to Act No 123/2000 Coll.	Following the completion of clinical investigations, a final report shall be processed which must contain a critical assessment of all data collected in the course of the clinical investigation or clinical evaluation. The person to sign the report is not specified (there is no reference to Act No 123/2000 Coll.).	A written report signed by the investigator must contain a critical assessment of all data collected in the course of the clinical investigations.	This Annex specifies the structure and content of the final report C.2 Title page C.3 Summary C.4 Table of contents C.5 Introduction C.6 Materials and methods C.7 Results C.8 Discussion and overall conclusions C.9 Abbreviations and definitions C.10 Ethics C.11 Investigators and administrative structure of clinical investigations C.12 Signature block C.13 Annexes to the report The Annex details the individual items.

Clinical investigation and clinical evaluation
Period of dossier archival

Act No 123/2000 Coll.	Government Regulation no. 336/2004 Coll.	Government Regulation no. 154/2004 Coll.	Decree 93/42 EEC	ČSN EN ISO 14155 – 1: 2003
Article 14, paragraph 1, letter (d), paragraph 2, letter (c), item 2.	**Annex 8, item 4**		**Annex VIII, Article 4**	**Item 8.2., letter (n)**
The investigator shall be obliged to store the dossiers for the clinical evaluations and clinical investigations for the period of ten years.	Information contained in the declaration pursuant to this Annex shall be kept by the person who has issued the declaration, for the period of five years.	The Government Regulation does not address the issue of dossier archival.	Information contained in the declaration pursuant to this Annex shall be kept by the person who has issued the declaration, for the period of five years.	The sponsor must collect, keep, safely maintain and ensure together with the relevant parties the completion of documents stipulated under item 7 and, moreover: - a copy of signed and dated reports on examinations; - records of any adverse incidents

				and adverse reactions to the medical device which have been reported to the sponsor in the course of the clinical investigations; - any statistical analyses for related supporting data; - the final report from the clinical investigation. The standard does not stipulate the period of archival.

Annex 4

Approach to the conduct of clinical evaluation and clinical investigation after May 1, 2004