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Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations of intraocular lenses for the correction of aphakia

Implants ophtalmiques — Lentilles intraoculaires —

Partie 7: Investigations cliniques de lentilles intraoculaires pour la correction de l'aphakie

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This fourth edition cancels and replaces the third edition (ISO 11979-7:2014). It also cancels and replaces the first edition of ISO 11979-9:2006 and its amendment ISO 11979-9:2006/Amd 1:2014.

The main changes compared to the previous edition are as follows:

— Integration of the multifocal intraocular lens document (ISO 11979-9:2006);

— Technical updates concerning the safety and efficacy of the intraocular lens subtypes monofocal, multifocal, toric and accommodating;

— Recommendations for the clinical investigations of novel lens models; and

— The separation of guidance for intraocular lenses used in cases of aphakia, and intraocular lens used for the correction of ametropia in phakic patients.

A list of all parts in the ISO 11979 series can be found on the ISO website.

Introduction

Intraocular lenses (IOLs) are used to correct residual refractive errors in subjects who have aphakia. Such residual refractive errors typically include sphere and astigmatism, but can also include accommodation. Different designs of IOLs can be used to correct for specific refractive errors. In the case where an IOL is designed to provide more than one type of refractive correction, that IOL will have to satisfy each of the separate requirements of those correction designs.

This document provides requirements and recommendations for intraocular lens investigations of new IOL models. In the case where an IOL model is a modification of a parent IOL model, a risk analysis can be used in order to determine the appropriate level of testing.

Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations of intraocular lenses for the correction of aphakia

1 Scope

This document specifies the particular requirements for the clinical investigations of intraocular lenses that are implanted in the eye in order to correct aphakia.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11979-1, *Ophthalmic implants — Intraocular lenses — Part 1: Vocabulary*

ISO 11979-10:2018, *Ophthalmic implants — Intraocular lenses — Part 10: Clinical investigations of intraocular lenses for correction of ametropia in phakic eyes*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms, definitions and abbreviated terms

3.1 Terms and definitions

For the purposes of this document the terms and definitions given in ISO 11979-1 and ISO 14155 apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at https://www.iso.org/obp

3.2 Abbreviated terms

UDVA	uncorrected distance visual acuity
UIVA	uncorrected intermediate visual acuity
UNVA	uncorrected near visual acuity
CDVA	corrected distance visual acuity
CIVA	corrected intermediate visual acuity

CNVA corrected near visual acuity

DCIVA distance corrected intermediate visual acuity

DCNVA distance corrected near visual acuity

4 Justification for a clinical investigation

A risk analysis shall be implemented in accordance with ISO 14971. If the risk analysis identifies the need for a clinical investigation, the requirements of ISO 14155 shall apply, with additional requirements given in this document.

If a new IOL model is a modification of a parent IOL for which the safety and performance have already been established through clinical investigation in accordance with this document, then a limited or no additional clinical investigation can suffice. ISO/TR 22979[1] provides guidance in determining the need for a clinical investigation.

5 Ethical considerations

For clinical investigations of medical devices for human subjects, the ethical requirements in ISO 14155 apply.

6 General requirements

6.1 General

There are four main categories of intraocular lenses that are determined by optical design:

a) monofocal (IOL);

b) multifocal (MIOL);

c) toric (TIOL); and

d) accommodating (AIOL).

The same basic requirements apply to all of the IOL types. Additional requirements apply to MIOL, TIOL, and AIOL.

There is a further subdivision depending on anatomic placement of the IOL:

— posterior chamber; and

— anterior chamber.

Posterior chamber lenses are placed behind (posterior to) the iris. Anterior chamber lenses are placed in front of (anterior to) the iris. Additional requirements apply in the case of anterior chamber lenses.

6.2 Design of a clinical investigation

6.2.1 Requirements for all types of IOLs

A clinical investigation shall be designed to compare the rates of adverse events and visual acuities above defined thresholds of the model IOL to the results of historical data. Annex A provides general guidance for the design of a clinical investigation of IOLs. Historical data can be found in Annex E.

6.2.2 Additional requirements for toric IOLs (TIOLs)

Prior to any clinical investigation of a toric intraocular lens, the rotational stability of a mechanically and geometrically equivalent non-toric version of that IOL model shall be demonstrated.

The following performance criteria for rotational stability shall be fulfilled.

The IOL rotation is defined as the difference in postoperative orientation of the meridian defined by the IOL axis indicator between that intended on the day of surgery (Form 0) and that measured at Form 4 and subsequent Forms. (See A.3 for recommendations on reporting periods). The absolute value of the rotation shall be less than 10° in 90 % of the cases and less than 20° in 95 % of the cases.

Subsequently, if found necessary by risk analysis (e.g. to assess the clinical performance of low cylinder power TIOLs), a clinical investigation can be performed using the toric version of the model.

Subjects that undergo a secondary surgery to correct postoperative IOL rotational misalignment shall have their clinical results prior to the secondary surgery carried forward as the final results for that subject, and examinations scheduled later in the clinical investigation shall be performed prior to the secondary surgery, wherever possible. (See Annex D.)

Additional elements for investigations of TIOLs are outlined in Annex B.

6.2.3 Additional requirements for multifocal IOLs (MIOLs)

For multifocal designs with two or more intended foci, a clinical investigation shall evaluate the safety and performance of vision at far as well as any additional intended focal distances.

The clinical investigation plan shall include a defocus evaluation.

A phased enrolment as outlined in Annex C shall be considered.

Additional elements for MIOLs are outlined in Annex C.

6.2.4 Additional requirements for accommodating IOLs (AIOLs)

A controlled clinical investigation of an AIOL shall evaluate the accommodative amplitude and the additional safety and performance aspects related to the risk assessment. Annex D identifies safety and performance aspects for consideration. The clinical investigation plan shall include at least one objective method to measure accommodative amplitude.

The investigation enrolment shall consist of two phases (see Annex D). The second phase shall begin only if the first phase has demonstrated that the IOL design provides an average of at least 1,0 D of objective accommodation. In order for the design to be designated as an AIOL, the overall investigation shall demonstrate objective accommodation of 1,0 D or more at the point of accommodative stability (see Annex D).

Additional elements for AIOLs are outlined in Annex D.

6.2.5 Additional requirements for anterior chamber IOLs

A clinical investigation of an anterior chamber IOL shall evaluate the change in endothelial cell density, hexagonality and coefficient of variation of endothelial cell area, the clearance between the surfaces of the anterior chamber IOL and the posterior surface of the cornea and the iris, the anterior chamber angle (including observations of pigment and synechiae), and any additional safety and performance aspects related to the risk assessment.

6.3 Characteristics of clinical investigations

6.3.1 General

The clinical investigation plan shall provide information regarding characteristics to be studied, and instructions regarding the methods and documentation of these characteristics. Whenever possible, objective methods, such as photographic imaging, shall be used.

If additional claims are to be made, additional corresponding characteristics shall be studied.

If several types of IOLs are combined, the characteristics of each IOL subtype in the combination shall be fully considered.

6.3.2 Characteristics to be studied for all types of IOLs

The following characteristics shall be considered:

a) CDVA;

b) visual acuity at all intended distances with far correction;

c) intraocular pressure;

d) corneal status;

e) signs of inflammation:

- anterior chamber cells,
- anterior chamber flare,
- cystoid macular oedema,
- hypopyon, and
- endophthalmitis.

f) pupillary block;

g) retinal detachment;

h) status of anterior and posterior capsule;

i) IOL decentration[2];

j) IOL tilt[2];

k) IOL discoloration; and

l) IOL opacity.

6.3.3 Additional characteristics to be studied for TIOLs

a) IOL rotational stability; and

b) corneal astigmatism:

- prior to surgery;
- intended surgical position (Form 0); and
- post-surgical.

6.3.4 Additional characteristics to be studied for MIOLs

a) uncorrected visual acuity at all intended focal distances;

b) contrast sensitivity;

c) defocus evaluation;

d) pupil size under photopic and mesopic conditions; and

e) fundus visualization.

6.3.5 Additional characteristics to be studied for AIOLs

a) objective accommodative amplitude;

b) uncorrected visual acuity at distance, intermediate and near;

c) visual acuity at near and intermediate using far correction;

d) additional refraction (over distance correction) required to achieve any improvement in near visual acuity;

e) contrast sensitivity;

f) defocus evaluation; and

g) pupil size.

6.3.6 Additional characteristics applying to anterior chamber IOLs

a) specular microscopy;

b) anterior chamber depth measurement; and

c) gonioscopy.

6.3.7 Additional characteristics

If justified by the risk analysis, the following additional characteristics shall be considered:

a) cycloplegic refraction;

b) specular microscopy;

c) gonioscopic examination;

d) pupil size; and

e) anterior chamber depth measurement.

6.4 Duration of the investigations

Consult ISO/TR 22979[1] for guidance on investigation duration for modifications of lens models for which safety and performance have previously been established through clinical investigation.

For posterior chamber IOLs that are not modifications of a model for which safety and performance data have been previously established through clinical investigation, the minimum duration of the clinical investigations shall be Form 5 (see Annex A for recommended visit window tolerances).

For anterior chamber IOLs that are not modifications of a model for which safety and performance data have been previously established through clinical investigation, the minimum duration of the clinical investigations shall be 3 years (see Annex A for recommended visit window tolerances).

For all TIOLs, a study of the non-toric version of the IOL shall be performed to ensure rotational stability through Form 4. TIOLs that are not a modification of a respective parent IOL shall require a full clinical investigation through Form 5 for posterior chamber IOLs, and 3 years duration for anterior chamber IOLs.

For TIOLs that are a modification of an IOL parent, the rotational stability assessment shall have a duration through Form 4. If a subsequent clinical investigation of the TIOL is performed, it shall also have a duration through Form 4.

For all AIOLs, the minimum clinical study duration shall be Form 5, but can require up to 3 years, based on accommodative stability.

All subjects in a clinical investigation that have not been discontinued shall complete all visits of the investigation. The clinical investigation shall be considered completed when all subjects who have been enrolled in the investigation, including subjects whose IOL was removed repositioned or replaced, have either completed follow up according to protocol or have passed the final visit window.

6.5 Enrolment

To minimize the risks associated with the clinical investigation of a new IOL, subject enrolment shall occur in stages. The subject data from each stage shall be evaluated and found acceptable by the sponsor and the coordinating investigator (and by the regulatory body, where applicable) prior to the continuation of the next phase of the clinical investigation. Guidance on phased enrolment is included in Annex A (monofocal IOLs), Annex B (TIOLs), Annex C (MIOLs), and Annex D (AIOLs).

A risk analysis shall be performed to determine if an earlier additional phase (before Phase 1 listed in the Annexes above) is needed to address specific safety issues associated with the IOL design.

6.6 Bilateral implantation

Any plans for fellow eye implantation shall be clearly described in the clinical investigation plan. Only the first eye of each subject shall be included in the primary statistical analysis. When implantation of fellow eyes is permitted, the clinical investigation plan shall specify the time period between implantation of the first eye and the fellow eye. A risk analysis shall be used to guide necessary safety and efficacy data requirements.

Bilateral implantation shall not be implemented until initial safety and performance data have been collected, evaluated and found acceptable by the sponsor and coordinating investigator (and regulatory body, where applicable).

The review of data from at least 50 eyes with six months of follow-up is recommended prior to fellow eye implantation. Risk analysis can allow an earlier implantation in fellow eyes if sufficiently justified by previous clinical experience.

6.7 Surgical technique

The clinical investigation plan shall contain descriptions of the surgical technique, the intraoperative use of ophthalmic viscosurgical devices, and the use of preoperative, intraoperative and postoperative medications. Any deviations shall be recorded on the case report forms.

6.8 Examination and treatment of subjects

The reporting periods are described in Annex A.

The clinical investigation plan shall describe how subject visits and ophthalmic adverse events that occur between standard reporting periods will be handled in the data analyses.

6.9 Adverse events reports

Refer to ISO 14155.

6.10 Inclusion and exclusion criteria

6.10.1 General

The general inclusion criteria in 6.10.1.1 and the general exclusion criteria in 6.10.1.2 shall be considered. Additional criteria as given in 6.10.2, 6.10.3 and 6.10.4 shall be considered depending on the risk analysis for the particular IOL model.

6.10.1.1 General inclusion criteria

a) adult;

b) cataract;

c) calculated IOL power is within the range of the investigational IOL;

d) signed informed consent form; and

e) clear intraocular media other than cataract.

6.10.1.2 General exclusion criteria

a) previous intraocular or corneal surgery;

b) traumatic cataract;

c) pregnancy or lactation;

d) concurrent participation in another drug or device investigation;

e) instability of keratometry or biometry measurements; and

f) irregular astigmatism.

Subjects shall be discontinued when certain conditions are present at the time of surgery, including:

— zonular instability;

— need for iris manipulation;

— capsular fibrosis or other opacity; and

— inability to fixate IOL in desired position.

In such cases, the subject shall be followed until the condition has stabilized.

6.10.2 Additional inclusion criteria for TIOLs

a) corneal astigmatism within the range defined in the clinical investigation plan;

b) stability of the corneal astigmatism (for a minimum of 4 weeks); and

c) dilated pupil size large enough to visualize TIOL axis markings postoperatively.

6.10.3 Additional exclusion criteria for MIOLs

a) more than 1 D of pre-operative corneal astigmatism.

6.10.4 Additional exclusion criteria for anterior chamber IOLs

The criteria for the specific anterior chamber IOL platform shall comply with the specific intended IOL design as described in this subclause, including TIOL, AIOL and MIOL.

a) angle abnormalities;

b) glaucoma or ocular hypertension;

c) angle or anterior chamber anatomy unsuitable to accept IOL design safely;

d) minimum anterior chamber depth related to design;

e) endothelial issues:

— endothelial cell density less than listed in ISO 11979-10:2018, Table 1;

— percent hexagonality of endothelial cell shape ≥45 %;

— coefficient of variation of endothelial cell area <0,45;

— any endothelial conditions putting the cornea at risk of failure.

f) corneal oedema.

Annex A
(informative)

General elements in the clinical investigation of IOLs

A.1 General

This Annex provides elements of a clinical investigation plan (CIP) which can assist in collecting data for the purpose of determining the safety and performance of all types of IOLs.

A.2 Investigation design and duration

A.2.1 General

The suggested clinical investigation design is an uncontrolled study to compare outcomes with the historical safety and performance endpoints in Annex E at the final follow-up.

NOTE 1 In case of an investigation with a concurrent control group, the number of subjects will have to be calculated to be sufficient to detect differences in the safety and performance endpoints in Annex E with similar statistical power to the study mentioned above.

NOTE 2 Any additional claims beyond those for safety and performance require separate calculations of an appropriate sample size for each of such claims.

To take into account that some subjects are lost to follow-up during the course of the clinical investigation (including deceased subjects and subjects who have the IOL explanted), enrol as a target (see also 6.4):

a) 340 subjects in the one-year investigation;

b) 420 subjects in the three-year investigation.

If risk analysis determines that a limited clinical investigation is sufficient (see ISO/TR 22979[1]), then enrol a target of 115 subjects to achieve a goal of 100 completed subjects.

In order to minimize exposure to the risks of a new IOL, significantly larger numbers of subjects than above should not be enrolled.

To assist in achieving a balance in the number of subjects from each investigator, each surgeon should contribute a minimum of 20 subjects, but no more than 25 % of the total subjects in the investigation.

A.2.2 Enrolment

To minimize potential risks, the clinical investigation consists of two phases:

a) Phase 1: A maximum of 100 subjects are included for the initial investigation. After at least 50 of those have reached case report Form 4, their data are evaluated. If the results are acceptable, the next phase can begin.

b) Phase 2: The remainder of the subjects are included.

In the case of the limited clinical investigation, the investigation is not phased.