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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

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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 document 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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This document was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 170, *Ophthalmic optics,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement)

This fifth edition cancels and replaces the fourth edition (ISO 11979-7:2018), which has been technically revised. The changes related herein for updating the document to the fifth edition apply to devices that will enter the marketplace after the date of publication of the fifth edition and are not designed or meant to limit any devices currently approved and marketed, nor those devices in the process of approval.

The main changes are as follows:

— development of definitions of non-accommodative posterior chamber “Simultaneous Vision Range” (SVIOL) lenses that include the subtypes of MIOL (Multifocal), EDF (Extended Depth of Focus) and FVR (Full Visual Range) IOLs, and defining each of these IOL types to allow differentiation among the lens types based on clinical and safety performance measures,

— establishment of guidelines for clinical testing of newly defined IOL types as listed above as well as related novel lens types, with alignment of testing methodologies among the lens types;

— ISO 11979-1, ISO 11979-2, ISO 11979-4 and ISO/TR 22979 are under revision and, when published, will be aligned with this edition of ISO 11979-7.

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

Any feedback or questions on this document should be directed to the user’s national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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 may also correct for a lack of 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, *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 and 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 terminology databases for use in standardization at the following addresses:

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

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

3.2 Abbreviated terms

UDVA	uncorrected distance visual acuity
UIVA	uncorrected intermediate visual acuity
UNVA	uncorrected near visual acuity
CDVA	corrected distance visual acuity
CS	contrast sensitivity
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 shall suffice.

ISO/TR 22979[2] provides guidance in determining the need for a clinical investigation. The outcomes of optical evaluation performed according to in ISO 11979-2[1] can be used to include or exclude characteristics to be studied in 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 and/or clinical characteristics or performance:

a) monofocal (IOL);

b) toric (TIOL);

c) simultaneous vision lens (SVIOL): non accommodative lenses of three sub-categories that provide simultaneous vision at multiple distances with EDF and FVR IOLs classified as non-inferior to monofocal lenses at far:

   — multifocal (MIOL); lens implants that emphasize optical and functionally useful acuity levels at far, but when compared to the monofocal control lens, also have improved optical and clinical performances at near focal distances. Multifocal lenses (MIOLs) have additional requirements for near vision;

   — extended depth of focus (EDF IOL); lens implants that emphasize optical and functionally useful acuity levels at far but also from far through intermediate focal distances. Extended depth of focus lenses (EDF IOLs) have additional requirements for intermediate vision;

   — full visual range IOL (FVR IOL) lens implants that emphasize optical and functionally useful acuity levels at far but also from far through intermediate and up to near focal distances. Full visual range lenses (FVR IOLs) have additional requirements at intermediate and near vision

d) Accommodating (AIOL).

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

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 IOL

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. The requirements of Annex A shall apply 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 (TIOL)

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 to be performed 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 Simultaneous Vision IOL (SVIOL) including MIOL, EDF and FVR lenses

6.2.3.1 General

For SVIOL optical designs, a clinical investigation shall evaluate the safety and performance of vision at far as well as any additional intended defined focal distances (e.g., intermediate and/or near). Clinically significant acuity shall be defined as ≤ 0,20 logMAR. All visual acuity items in the table relate to mean monocular photopic visual acuity.

Intermediate visual performance shall be assessed with best distance correction at 66 cm. Near visual performance shall be assessed with best distance correction at 40 cm. Additional testing distances may be used based on the lens design.

In order to minimize pseudo-accommodation, the monofocal IOL used for the control group should be spherical aberration correcting, commercially available and one for which the selection has been justified.

For all types of SVIOLs, depth of focus testing shall be performed as described in F.3. Specifically for EDF IOLs, such testing is considered a performance requirement and shall meet the criterion listed in Table 1.

Visual acuity performance necessary to meet the requirements in Table 1 shall be obtained using visual acuity charts at distances listed in Table 1, or taken from the depth of focus curve which is generated as

described in F.3. The full depth of focus curve as described in F.3 shall be used to characterize the IOL performance with sufficient precision for inclusion in the labelling of the SVIOL.

The specific effectiveness requirements are related to the type of SVL as listed Table 1 shall be met.

Table 1 — Additional requirements for simultaneous visions IOLs

Category	FAR	INTERMEDIATE (66 cm)	NEAR (40 cm)
SVIOL all types	Δ (mesopic CS) ≤ 0,3 log units at any frequency[a]		
MIOL	CDVA ≤ 0,20 logMAR[b]		DCNVA superior to control
EDF IOL	CDVA non-inferior to control 0,10 logMAR level	DCIVA ≤ 0,20 logMAR	
EDF IOL		DCIVA superior to control	
EDF IOL	Negative defocus range at the 0,20 logMar threshold is ≥0,5 D greater than control[c]		
EDF IOL	*DCVA at 1,0 m ≤ 0,20 logMAR*		
FVR IOL	CDVA non-inferior to control 0,10 logMAR level		
FVR IOL		DCIVA ≤ 0,20 logMAR	DCNVA ≤ 0,20 logMAR
FVR IOL		DCIVA superior to control	DCNVA superior to control
FVR IOL	DCVA at 1,0 m and 50 cm ≤ 0,20 logMAR		

a. Δ (mesopic CS) is the difference of the mean contrast sensitivity of the test IOL group minus the mean contrast sensitivity of the control IOL group, each tested under monocular conditions without glare.

b. Visual performance shall meet or exceed 0,20 logMAR in order to prevent performance values to be rounded down to 0,20 logMAR.

c. Refer to Annex F for clinical testing and related references. Visual acuity performance necessary to meet the requirements in Table 1 may be obtained using visual acuity charts at distances listed in Table 1 or taken from the defocus curve which was generated as described in F.3. The full defocus curve as described in F.3 is required to characterize the defocus performance with sufficient precision for inclusion in the labelling for the SVIOL.

6.2.3.2 Depth of focus testing

Depth of focus evaluations shall be performed on all SVIOL types. See Annex F for additional guidance.

6.2.3.3 Safety requirements

The mean monocular far contrast sensitivity (without glare) for all SVIOL shall be no worse than 0,3 log units below that of the control at any test spatial frequency. Annex C identifies additional safety and performance requirements for consideration.

NOTE The 0,3 log unit at one spatial frequency is from review of the *Summary of Safety and Effectiveness Documents (SSED's)* of approved MIOL's in the US[3].

6.2.4 Additional requirements for accommodating IOLs (AIOL)

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. Annex F includes depth of focus testing guidance. The clinical investigation plan shall include at least one objective method to measure accommodative amplitude.

The investigation enrollment 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 IOL

The following characteristics shall be considered for all types of IOLs:

a) CDVA;

b) manifest (subjective) refraction;

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

d) intraocular pressure;

e) corneal status;

f) signs of intraocular inflammation:

   — anterior chamber cells;

   — anterior chamber flare;

   — cystoid macular oedema;

   — hypopyon; and

   — endophthalmitis;

g) pupillary block;

h) retinal detachment;

i) status of anterior and posterior capsule;

j) IOL decentration[4];

k) IOL tilt[4];

l) IOL discoloration;

m) IOL opacity;

n) glistenings in IOL;

o) visualization of posterior pole through IOL.

6.3.3 Additional characteristics to be studied for toric IOL

The following additional characteristics shall be considered for toric IOLs:

a) IOL rotational stability, and

b) measured surgical position (Form 0); and pre and post surgical corneal astigmatism.

6.3.4 Additional characteristics to be studied for SVIOLs

The following additional characteristics shall be considered for SVIOLs:

a) depth of focus testing;

b) uncorrected visual acuity at far and intermediate and/or near, as applicable to the type of IOL;

c) intermediate and/or near visual acuity with best distance correction, as applicable to the type of IOL;

d) patient reported outcome (PRO) survey to assess visual symptoms related to the optical properties of the IOL for bilateral implantation of SVIOL;

e) rate of secondary surgical interventions;

f) monocular contrast sensitivity (at far).

6.3.5 Additional characteristics to be studied for accommodating IOL

The following additional characteristics shall be considered for accomodating IOLs:

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) pupil size;

g) PRO survey to assess visual symptoms related to the optical properties of the IOL;

h) rate of secondary surgical interventions.

6.3.6 Additional characteristics applying to anterior chamber IOLs

The following additional characteristics shall be considered for anterior chamber IOLs:

a) specular microscopy;

b) anterior chamber depth measurement;

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;

e) anterior chamber depth measurement.

6.4 Duration of the investigations

Consult ISO/TR 22979[2] for guidance on investigation duration for modifications of lens models for which safety and performance have previously been established through clinical investigation.

For all types of 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, an investigation of the non-toric version of the IOL shall be performed to ensure rotational stability through Form 4. Toric IOLs 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 SVIOL that are a modification of an IOL parent, the minimum duration of the clinical investigation shall be through Form 4.

For all AIOLs, the minimum clinical investigation 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 IOL), Annex B (TIOL), Annex C (SVIOL), and Annex D (AIOL).

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 at Form 4 shall be performed 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 shall be as 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

See ISO 14155.

6.10 Inclusion and exclusion criteria

6.10.1 General

The general inclusion criteria in 6.10.2 and the general exclusion criteria in 6.10.4 shall be considered. Additional criteria as given in 6.10.3, 6.10.5 and in 6.10.6 shall be considered depending on the risk analysis for the particular IOL model.

6.10.2 General inclusion criteria

The following general inclusion criteria shall be considered:

a) adult;

b) cataract;

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

d) signed informed consent form;

e) clear intraocular media other than cataract.