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Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations

Implants ophtalmiques — Lentilles intraoculaires —

Partie 7: Investigations cliniques

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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 documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2. www.iso.org/directives

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This second edition cancels and replaces the third edition (ISO 11979-7:2006), which has been technically revised. It also incorporates the Amendment ISO 11979-7:2006/Amd1:2012 .

ISO 11979 consists of the following parts, under the general title *Ophthalmic implants — Intraocular lenses*:

— *Part 1: Vocabulary*

— *Part 2: Optical properties and test methods*

— *Part 3: Mechanical properties and test methods*

— *Part 4: Labelling and information*

— *Part 5: Biocompatibility*

— *Part 6: Shelf-life and transport stability testing*

— *Part 7: Clinical investigations*

— *Part 8: Fundamental requirements*

— *Part 9: Multifocal intraocular lenses*

— *Part 10: Phakic intraocular lenses*

Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations

1 Scope

This part of ISO 11979 specifies particular requirements for clinical investigations for posterior and anterior chamber intraocular lenses (IOLs).

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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: Phakic intraocular lenses*

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

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

4 Justification for a clinical investigation

If the need for a clinical investigation is identified, the requirements of ISO 14155 shall apply, with additional requirements given below.

If a new IOL model is a modification of a model for which the safety and performance have been established through clinical investigation in accordance with this part of ISO 11979 no or limited clinical investigation is needed. ISO/TR 22979[1] provides guidance in determining whether or not a modification is minor.

5 Ethical considerations

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

6 General requirements

6.1 General

The requirements for a clinical investigation given in ISO 14155 shall apply, with additional requirements given below.

6.2 Design

6.2.1 General

A clinical investigation shall be designed to compare results to historical data on adverse events and visual acuity rates. Annex A provides general guidance for the design of a clinical investigation. Historical data can be found in Annex B.

6.2.2 Additional requirements for toric IOLs

For all toric IOLs, the rotational stability of a non-toric version that is mechanically and geometrically equivalent to the toric IOL shall be demonstrated.

The following performance criteria for rotational stability shall be fulfilled: the rotation of the meridian defined by the IOL axis indicator as measured and compared between Day 0 (the day of surgery) post-operative examination and the form 4 examination shall be less than 10° in 90 % of the cases, less than 20° in 95 % of the cases, and less than 30° in 99 % of the cases.

Then, if necessary due to risk analysis, a clinical investigation shall be performed using the toric version of the model.

In the event that a toric IOL clinical investigation is required due to risk analysis, the subjects that undergo secondary surgery to correct IOL axis mark rotation shall have their clinical results prior to the secondary surgery carried forward as the final results for that subject. In the case of examinations scheduled to be performed later in the clinical investigation, the sponsor shall consider requiring each of these examinations to be performed prior to the secondary surgery, if possible.

Additional elements for toric IOLs are outlined in Annex C.

6.2.3 Additional requirements for accommodating IOLs

A controlled clinical investigation of an accommodating IOL shall evaluate the additional safety and performance concerns, specifically including the evaluation of accommodative amplitude using at least one objective method. Guidance on clinical investigation of accommodating IOLs is outlined in Annex D. It shall consist of two phases, with phase two beginning only after the first phase has demonstrated that the accommodating IOL provides an average of at least 1 D of objective accommodation. The overall study shall demonstrate that the accommodating IOL also provides 1 D of objective accommodation at the point of stabilization.

6.3 Characteristics

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

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

6.3.1 General characteristics

a) best spectacle corrected visual acuity (BSCVA);

b) subjective refraction;

c) intraocular pressure;

d) corneal status;

e) signs of inflammation:

   1) anterior chamber cells;

   2) anterior chamber flare;

   3) cystoid macular oedema;

   4) hypopyon;

   5) 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;

l) IOL opacity.

6.3.2 Toric IOL characteristics

a) uncorrected visual acuity;

b) keratometry;

c) IOL mark axis rotation.

6.3.3 Accommodating IOL characteristics

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

b) visual acuity at near and intermediate with best distance correction;

c) best corrected near visual acuity;

d) additional refraction (over best distance subjective correction) required to achieve best corrected near acuity;

e) objective accommodative amplitude;

f) contrast sensitivity;

g) subject questionnaire;

h) pupil size.

6.3.4 Additional characteristics

If justified by the risk analysis, these additional characteristics shall be considered.

a) cycloplegic refraction;

b) specular microscopy;

c) gonioscopic examination;

d) pupil size;

e) anterior chamber depth measurement.

6.4 Investigation duration

The minimum duration of the clinical investigations shall be one year (see Annex A for visit window tolerance) for aphakic posterior chamber IOLs which are not modifications of a model for which safety and performance data have been established through clinical investigation.

The minimum duration of the clinical investigations shall be three years (see Annex A for visit window tolerance) for aphakic anterior chamber IOLs which are not modifications of a model for which safety and performance data have been established through clinical investigation.

For all toric IOLs, a six-month study of the non-toric version of the IOL shall be performed to ensure rotational stability. Then for toric IOLs that are a modification of an IOL that has met the requirements of all parts of ISO 11979, risk analysis may require that this rotational stability study is followed by a clinical investigation of the actual toric IOL for six months. Toric IOLs that are not a modification of an IOL that has met the requirements of all parts of ISO 11979 shall require a full clinical investigation of one year duration.

The minimum study duration for accommodating IOLs through clinical investigation shall be one year but may require up to three years based on the risk analysis.

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

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 that have been enrolled in the investigation, including subjects whose IOL was removed or replaced, have reached the final reporting period.

6.5 Enrollment

To minimize the risks associated with the clinical investigation of a new IOL, subject enrollment 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, if applicable) prior to the continuation of the clinical investigation. Guidance on phased enrollment is included in Annex A (monofocal IOL), Annex C (toric IOL) and Annex D (accommodating IOL).

Risk analysis should be used to determine if an earlier phase than the phase 1 listed in the Annexes above is needed to address safety issues associated with the IOL design.

6.6 Bilateral implantation

Any plans for fellow eye implantation shall be described in the clinical investigation plan. Bilateral implantation shall not be implemented until initial safety and performance data have been collected, evaluated and confirmed by the sponsor and coordinating investigator (and by the risk analysis, if applicable). Only the first eye of each subject shall be included in the primary statistical analysis.

When implantation of fellow eye is permitted, the clinical investigation plan shall specify time period between implantation of first eye and of fellow eye, based upon risk analysis.

NOTE The review of data from at least 50 eyes with six months of follow-up is recommended prior to fellow eye implantation. Risk analysis might 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 deviation shall be recorded on the case report forms.

For toric IOLs, the clinical investigation plan shall specify the type and location of the incision. The estimated effect of the incision on the corneal astigmatism shall be used in the protocol for choosing the appropriate cylindrical power.

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

Serious adverse events and all adverse device effects shall be reported using a special case report form and forwarded to the sponsor as required. All other ophthalmic adverse events shall be reported using either the standard visit case report form or specific adverse event forms and be collected during monitoring. Non-ophthalmic events that are non-serious are not required to be reported.

6.10 Inclusion and exclusion criteria

6.10.1 General

The following inclusion/exclusion criteria shall be considered. Additional criteria shall be included depending on the risk analysis for the particular IOL model.

6.10.1.1 Inclusion criteria

a) adult;

b) cataract (does not apply for phakic IOL);

c) best corrected visual acuity projected to be 0,2 logMAR or lower;

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

e) signed informed consent form.

6.10.1.2 Exclusion criteria

a) previous intraocular and corneal surgery;

b) traumatic cataract;

c) pregnancy and lactation;

d) concurrent participation in another drug or device investigation.

6.10.2 Additional criteria for toric IOL

6.10.2.1 Inclusion criteria

a) corneal cylindrical error within the range defined in the clinical investigation plan (CIP);

b) stability of the cornea has been demonstrated by keratometry;

c) expected dilated pupil size at least large enough to visualize the axis markings.

6.10.2.1.1 Additional inclusion criteria for phakic toric IOLs

a) the inclusion criteria described in ISO 11979-10 shall be considered.

6.10.2.2 Exclusion criteria

6.10.2.2.1 Additional exclusion criteria for phakic toric IOLs

The exclusion criteria described in ISO 11979-10 shall be considered.

Annex A
(informative)

Elements of a clinical investigation

A.1 General

The following are elements of a clinical investigation plan which can assist in collecting data for the purpose of determining the safety and performance of IOLs.

A.2 Number of subjects

The clinical investigation includes a minimum of 300 subjects when the results are compared to the safety and performance end points in Annex B. In the case of an investigation with a concurrent control group, calculate the number of subjects sufficient to detect differences in the safety and performance end points in Annex B with similar statistical power to the investigation mentioned above. Any additional claims, beyond those for safety and performance, require calculation of a sample size for that purpose.

To take into account that some subjects are lost during the course of the clinical investigation (including deceased subjects and subjects who have the IOL explanted), enrol about:

a) 390 subjects in the one-year investigation;

b) 500 subjects in the three-year investigation.

Significantly larger numbers of subjects are not to be enrolled in order to minimize exposure to the risks of a new IOL.

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

If the risk analysis determines that a limited clinical investigation is sufficient (see ISO/TR 22979[1]), then enroll 125 subjects.

A.3 Phased enrolment

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

a) phase 1: a maximum of 100 subjects are included. 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.

A.4 Reporting periods

The time frames for the reporting periods are defined below:

a) case report form 0: pre-operative/operative reporting;

b) case report form 1: 1 or 2 days post-operatively;

c) case report form 2: 7 to 14 days post-operatively;

d) case report form 3: 30 to 60 days post-operatively;

e) case report form 4: 120 to 180 days post-operatively;

f) case report form 5: 330 to 420 days post-operatively.

g) case report form 6: 630 to 780 days post-operatively;

h) case report form 7: 990 to 1 140 days post-operatively.

The minimum sample size needs to be achieved at each of the reporting periods.

A.5 Standardization of the clinical evaluation

Define criteria for evaluation of all studied variables. Define testing conditions for all measurements. Before commencing the investigation instruct and train all investigators to use these, in order to obtain data that can be combined for the purpose of statistical analysis.

A.6 Data analysis

Consider the following analyses for both the first eye group and the total eye group:

a) visual acuity (VA) stratified by age;

b) VA for best-case subjects;

c) VA stratified by adverse event;

d) VA stratified by pre-operative ocular pathology;

e) VA stratified by investigator;

f) subject-by-subject analysis of reasons why subject failed to achieve 0,3 logMAR VA;

g) frequency of, and the cause of loss of 10 letters or more on an EDTRS chart (or equivalent) compared to best post-op visual acuity;

h) frequency of cumulative adverse events stratified by age;

i) frequency of persistent adverse events stratified by age;

j) adverse event stratified by investigator;

k) IOL related adverse events (two-sided 95 % confidence interval).

A.7 Subject accountability

The general requirement for accountability of subjects is given in ISO 14155. More specific guidance for subject accountability at each of the post-operative visits in IOL clinical investigations is provided in Table A.1.

Table A.1 — Accountability by post-operative visit

	Total number			
Enrolled (N)		—	—	—
Subject status	—	Form 1 [n, % (n/N)]	Form 2, etc. [n, % (n/N)]	Final form [n, % (n/N)]
Available for analysis	—			
Missing subjects:	—			
Discontinued	—			
Missing at scheduled visit but seen later	—			
Not seen but accounted for	—			
Lost to follow-up	—			
Active	—			
where Enrolled: represents the total number of subjects enrolled in the investigation. Available for analysis: represents the total number of subjects for whom data are available at the form. Discontinued: represents the total number of subjects that have discontinued treatment prior to the form for any reason (e.g. death or device replacement). This category does not include subjects that are lost to follow-up. Missing at scheduled visit but seen later: represents the total number of subjects that were seen outside the time window associated with the form. Not seen but accounted for: represents the total number of subjects that were missing at the scheduled visit but were accounted for by being contacted (e.g. by phone). Lost to follow-up: represents the total number of subjects that have missed the form and there is no information available about them. Active: represents the total number of subjects that have not reached the time associated with the form. The investigation at the form is considered completed when the number of active subjects is zero.				
The following formula is used to determine the percentage of accountability for the investigation: $\%Accountibility = \frac{Available\ for\ Analysis}{(Enrolled - Discontinued - Active)}$				

Depending upon the clinical investigation, the total number of subjects is not necessarily the total number of eyes. For the purposes of this guidance, it is assumed that treatment is unilateral and that the total number of subjects is equivalent to the total number of eyes.

To minimize the uncertainty in the data, the lost to follow-up subjects in the three-year investigation should be less than 30 % and the lost to follow-up in one-year investigation should be less than 10 %.

A.8 Clinical case report forms

The following pages provide examples of case report forms for investigations of monofocal, spherical, non-accommodating IOLs to correct aphakia:

a) pre-operative/operative case report form — posterior chamber lenses (Table A.2);

b) post-operative case report form — posterior chamber lenses (Table A.3);

c) pre-operative/operative case report form — anterior chamber lenses (Table A.4);

d) post-operative case report form — anterior chamber lenses (Table A.5);

e) adverse event case report form (Table A.6).