INTERNATIONAL STANDARD

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Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations

Implants ophtalmiques — Lentilles intraoculaires —
Partie 7: Investigations cliniques

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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 11979-7 was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This second edition cancels and replaces the first edition (ISO 11979-7:2001), which has been technically revised.

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*

— *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 monofocal intraocular lenses (IOLs) for the correction of aphakia.

2 Normative references

The following referenced documents are indispensable for the application 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 14155-1, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14155-2, *Clinical investigation of medical devices for human subjects — Part 2: Clinical investigation plans*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11979-1, ISO 14155-1 and ISO 14155-2 apply.

4 Justification for a clinical investigation

The requirements given in ISO 14155-1 shall apply.

If a new model is a minor 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 provides guidance in determining if a modification is minor.

5 Ethical considerations

For clinical investigations of medical devices for human subjects, the requirements in ISO 14155-1 shall apply.

6 General requirements

6.1 General

The general requirements for a clinical investigation given in ISO 14155-1 and the clinical investigation plan requirements in ISO 14155-2 shall apply, with additional requirements given below.

6.2 Additional requirements

6.2.1 Design

A clinical investigation of an IOL model shall be designed in one of two ways:

a) as an uncontrolled study, in which case the results are compared to the adverse events and visual acuity rates given in Annex B.

b) as a controlled study, with the provision that the statistical power to detect differences in the adverse event rates and visual acuity is similar to the uncontrolled study. The control lens shall conform with applicable parts of ISO 11979.

NOTE Annex A provides guidance for the design of a clinical investigation.

6.2.2 Variables

The following variables shall be considered:

— best spectacle corrected visual acuity (BSCVA);

— refraction;

— intraocular pressure;

— corneal status;

— iritis;

— IOL decentration;

— IOL tilt;

— IOL discoloration;

— IOL opacity;

— cystoid macular oedema;

— hypopyon;

— endophthalmitis;

— pupillary block;

— retinal detachment;

— status of anterior and posterior capsule.

Additional variables can be studied in the clinical investigation to support specific claims.

6.2.3 Other considerations

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 prior to the continuation of the clinical investigation. Guidance on phased enrolment is included in Annex A.

Only the first eye of each subject shall be included in the primary statistical analysis.

Any plans for fellow eye implantation shall be described in the clinical investigation plan. Bilateral implantation shall not be implemented until initial safety and effectiveness data have been collected, evaluated and confirmed by the sponsor and principal investigators.

The review of data from at least 50 eyes with six months of follow-up is recommended. Previous clinical experience, i.e. results from well-documented clinical investigations, may be adequate justification to begin bilateral implantation earlier in the study.

The duration of the clinical investigation shall be one year for all posterior chamber IOLs, and 3 years for all anterior chamber IOLs.

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

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

All subjects in a clinical investigation shall be monitored for the duration 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.

Serious ophthalmic 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 the standard visit case report forms and are collected during monitoring.

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.

NOTE This annex reflects the experience with clinical investigations of IOLs in the USA.

A.2 Number of subjects

The clinical investigation includes a minimum of 300 subjects when the results are compared to the safety and performance endpoints in Annex B. In the case of a study with a concurrent control group, calculate the number of subjects sufficient to detect differences in the safety and performance endpoints in Annex B with similar statistical power to the study 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), then enrol 125 subjects.

A.3 Phased enrolment

To minimize the potential risks, the clinical investigation consists of two phases as follows.

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: post-operative reporting 1 d or 2 d post-operatively;

c) Case report Form 2: post-operative reporting 7 d to 14 d post-operatively;

d) Case report Form 3: post-operative reporting 30 d to 60 d post-operatively;

e) Case report Form 4: post-operative reporting 120 d to 180 d post-operatively;

f) Case report Form 5: post-operative reporting 330 d to 420 d post-operatively;

g) Case report Form 6: post-operative reporting 630 d to 780 d post-operatively;

h) Case report Form 7: post-operative reporting 990 d to 1 140 d post-operatively.

The minimum number of completed case report forms for each reporting period is 300.

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:

a) VA stratified by age;

b) best-case VA;

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 0,5 (6/12; 20/40) VA;

g) rate of visual acuity decrease of 10 letters or more on an early treatment of diabetic retinopathy study (EDTRS) chart (or equivalent) between a form evaluation and a later form evaluation with the cause of the visual acuity decrease described in each case;

h) rates of cumulative adverse events stratified by age;

i) rates of persistent adverse events stratified by age;

j) adverse event stratified by investigator.

A.7 Subject accountability

The general requirement for accountability of subjects is given in ISO 14155-1. 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

Subject status	Total number			
	Enrolled [a]	Form 1	Form 2, etc.	Final form
	N_{tot}			
Available for analysis [b], n_{aa}		n_{aa}, (n_{aa}/N_{tot}) %	n_{aa}, (n_{aa}/N_{tot}) %	n_{aa}, (n_{aa}/N_{tot}) %
Missing subjects:				
Discontinued [c], n_d		n_d, (n_d/N_{tot}) %	n_d, (n_d/N_{tot}) %	n_d, (n_d/N_{tot}) %
Missing at scheduled visit but seen later [d], n_{sl}		n_{sl}, (n_{sl}/N_{tot}) %	n_{sl}, (n_{sl}/N_{tot}) %	n_{sl}, (n_{sl}/N_{tot}) %
Not seen but accounted for [e], n_{ns}		n_{ns}, (n_{ns}/N_{tot}) %	n_{ns}, (n_{ns}/N_{tot}) %	n_{ns}, (n_{ns}/N_{tot}) %
Lost to follow-up [f], n_{lf}		n_{lf}, (n_{lf}/N_{tot}) %	n_{lf}, (n_{lf}/N_{tot}) %	n_{lf}, (n_{lf}/N_{tot}) %
Active [g], n_a		n_a, (n_a/N_{tot}) %	n_a, (n_a/N_{tot}) %	n_a, (n_a/N_{tot}) %

Explanation of symbols:

n represents the number of subjects associated with the form for that type of information.

(n/N_{tot}) % represents the percentage of subjects associated with the form of that type of information with respect to the total number of subjects enrolled in the study.

[a] "Enrolled" or N_{tot} represents the total number of subjects enrolled in the investigation.

[b] "Available for analysis" or n_{aa} represents the total number of subjects for whom data is available at the form.

[c] "Discontinued" or n_d 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 doesn't include subjects that are lost to follow-up.

[d] "Missing at final scheduled visit but seen later" or n_{sl} represents the total number of subjects that were seen outside the time window associated with the form.

[e] "Not seen but accounted for" or n_{ns} represents the total number of subjects that were missing at the scheduled visit but were accounted for by being contacted (e.g. by phone).

[f] "Lost to follow-up" or n_{lf} represents the total number of subjects that have missed the form and there is no information available about them.

[g] "Active" or n_a 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 equation is used to determine the percent accountability, % $N_{account}$, for the investigation.

$$\%\ N_{account} = \frac{n_{aa}}{N_{tot} - n_d - n_a}$$

where n_{aa}, N_{tot}, n_d and n_a are as defined in Table A.1.

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 next pages provide examples of the following case report forms:

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).