INTERNATIONAL STANDARD

ISO 11979-7

Second edition
2006-05-01

Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations

Implants ophtalmiques — Lentilles intraoculaires —

Partie 7: Investigations cliniques

Reference number
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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).

Table A.2 — Pre-operative/ operative case report form for posterior chamber lens clinical investigation

Investigator name: _____ Clinical trial number: _ _ _ _

Patient number: _ _ _ _ Patient initials: _____ Sex: Male: ☐ Female: ☐ Race: Caucasian ☐ Black ☐ Asian ☐ Other ☐ Mixed ☐

Date of birth: _ _ _ _ _ _ (YY MM DD)

Pre-operative report

_ _ _ _ _ _ (YY MM DD)

Operative eye right ☐ left ☐

	Operative eye	Fellow eye
Best corrected visual acuity	_____	_____
or check one:		
Finger count	☐	☐
Hand movement	☐	☐
Light perception	☐	☐
No light perception	☐	☐

IOP (applanation): Op. eye: ___ mmHg Fellow eye: ___ mmHg

Corneal status (check yes or no for each)	yes	no
Normal	☐	☐
Guttata	☐	☐
Other pathology (specify) _____	☐	☐

Cataract

Etiology (check one) senile ☐

other (specify)_____ ☐

Pathology (check yes or no for each)	yes	no	not assessable
Pseudoexfoliation	☐	☐	
Glaucoma	☐	☐	
Previous glaucoma filtering surgery	☐	☐	
Poor pupil dilation	☐	☐	
Previous uveitis	☐	☐	
Previous retinal detachment	☐	☐	
Diabetic retinopathy	☐	☐	☐
Macular degeneration	☐	☐	☐
Amblyopia	☐	☐	
Other (specify) _____	☐	☐	

Biometry K1_____D Axial length_____mm
K2_____D

Target postoperative refraction _____

Signed informed consent obtained: yes ☐ _ _ _ _ _ _ (DD MM YY)

Operative report

Date of surgery _ _ _ _ _ _ (DD MM YY)

Ophthalmic viscosurgical device used yes ☐ no ☐

If yes, specify _____

Intraocular medication (check yes or no for each)	yes	no
Adrenalin	☐	☐
Acetylcholine	☐	☐
Carbachol	☐	☐
Other (specify) _____	☐	☐

Irrigating solution used yes ☐ no ☐

If yes, specify _____

Periocular medication	yes (specify, if appropriate)	no
Anaesthetic	☐ _____	☐
Antibiotic	☐ _____	☐
Corticosteroid	☐ _____	☐
Other (specify)	☐ _____	☐

Incision

Size _____ mm

Type (e.g., corneal, limbal, scleral tunnel) _____

Type of lens extraction (check one)

Phacoemulsification ☐

Other (specify) _____ ☐

Type of capsulotomy (check one)

CCCR (continuous curvilinear capsulorhexis) ☐

Other (specify) _____ ☐

Position of the loops (check one)

in the bag ☐
partly in the bag ☐
in the sulcus ☐
uncertain ☐

	yes	no
Other surgical procedures (check yes or no)	☐	☐

If yes, specify: _____

Problems during surgery (check yes or no for each)	yes	no
Anterior segment bleeding	☐	☐
Iris damage	☐	☐
Posterior capsular opacity remaining	☐	☐
Posterior capsular rupture	☐	☐
Anterior vitrectomy	☐	☐
Other(specify) _____	☐	☐

If investigation lens not implanted indicate reason:

_____

Lens implanted. Place label here:

Time incision to closure _____ min.

Signature of investigator

_ _ _ _ _ _ (YY MM DD)

Table A.3 — Post-operative case report form for posterior chamber lens clinical investigation

Investigator name: _____ Clinical trial number: _ _ _ _
Patient number: _ _ _ _ Patient initials: _____ Date of birth: YY MM DD

Post-operative report YY MM DD

Eye right ☐ left ☐

Check if the patient is unavailable for this scheduled examination ☐ but continuing in the clinical investigation (sign form with all evaluation in form left blank)

If the patient is discontinued from the investigation, indicate primary reason:

_____

Refraction	Sphere	_____
	Cylinder	_____
	Axis	_____
Keratometry	K1_____D	
	K2_____D	

Best corrected visual acuity		Op. eye	Fellow eye
		_____	_____
or check one	Finger count	☐	☐
	Hand movement	☐	☐
	Light perception	☐	☐
	No light perception	☐	☐

IOP (application) _____ mm Hg

Medications used up to this visit	topical		systemic	
(check yes or no for each)	yes	no	yes	no
Corticosteroids	☐	☐	☐	☐
Antibiotics	☐	☐	☐	☐
NSAIDs	☐	☐	☐	☐
Glaucoma medication	☐	☐	☐	☐

Other (specify) _____

Corneal stromal oedema	wound	central
none	☐	☐
mild/moderate	☐	☐
severe	☐	☐

Iritis (check one)	
none	☐
mild	☐
moderate	☐
severe	☐

Other pathology and complications (check present or absent for each)	present	absent
Wound leak	☐	☐
Flat anterior chamber	☐	☐
Hyphema	☐	☐
Endophthalmitis	☐	☐
if present		
infectious	☐	
sterile	☐	
Vitreous in anterior chamber	☐	☐
Vitreous to wound	☐	☐
Raised IOP requiring treatment	☐	☐
Pupillary block	☐	☐
Anterior synechiae	☐	☐
Posterior synechiae	☐	☐
Deposits on IOL	☐	☐

Other pathology and complications *(Continued)*	present	absent
Fibrin in pupil	☐	☐
Cortical remnants	☐	☐
Nuclear remnants	☐	☐
IOL optic decentration	☐	☐
if present: ____ mm		
IOL optic tilt	☐	☐
if present: _____degrees		
IOL dislocation out of the posterior chamber	☐	☐
IOL optic discoloration	☐	☐
IOL optic opacities	☐	☐
Retinal detachment	☐	☐
Diabetic retinopathy	☐	☐
Cystoid macular oedema	☐	☐
if present diagnosed:		
clinically ☐		
by fluorescein angiography ☐		
Macular degeneration	☐	☐
Optic atrophy	☐	☐
	yes	no
Anterior capsular opacification present?	☐	☐
Is the posterior capsule intact?	☐	☐
if intact:		
posterior capsule fibrosis	☐	☐
Elschnig's pearls	☐	☐
if not intact:		
has the capsule been opened since the last reported visit?	☐	☐
Other pathology?	☐	☐

specify:_____

If visual acuity less than 0,5 (20/40, 6/12) indicate main reason:

_____
_____

Has the operated eye undergone any surgical reintervention since last reported visit?	yes ☐	no ☐

If yes, specify:

_____

Has the patient experienced any adverse event or ophthalmic adverse device effect?	yes ☐	no ☐

If yes, fill in the adverse event/ adverse device effect report form.

If serious, also contact the sponsor in accordance with local regulations.

Signature of investigator

_____ YY MM DD

Table A.4 — Pre-operative/ operative case report form for anterior chamber lens clinical investigation

Investigator name: _____ Clinical trial number: _ _ _ _

Patient number: _ _ _ _ Patient initials: _____ Sex: Male: ☐ Female: ☐ Race: Caucasian ☐ Black ☐ Asian ☐ Other ☐ Mixed ☐

Date of birth: YY MM DD

Pre-operative report

YY MM DD

Operative eye right ☐ left ☐

Best corrected visual acuity or check one:	Operative eye	Fellow eye
Finger count	☐	☐
Hand movement	☐	☐
Light perception	☐	☐
No light perception	☐	☐

IOP (applanation): Op. eye: ___ mmHg Fellow eye: ___ mmHg

Corneal status (check yes or no for each)	yes	no
Normal	☐	☐
Guttata	☐	☐
Other pathology (specify) _____	☐	☐

Endothelial cell count (if done): _____ cells/mm^2

Corneal thickness (if measured): _____ mm

Cataract

Etiology (check one) senile ☐ other (specify)_____ ☐

Pathology (check yes or no for each)	yes	no	not assessable
Pseudoexfoliation	☐	☐	
Glaucoma	☐	☐	
Previous glaucoma filtering surgery	☐	☐	
Poor pupil dilation	☐	☐	
Previous uveitis	☐	☐	
Previous retinal detachment	☐	☐	
Diabetic retinopathy	☐	☐	☐
Macular degeneration	☐	☐	☐
Amblyopia	☐	☐	
Other (specify) _____	☐	☐	

Biometry K1_____D K2_____D Axial length ___mm

Target postoperative refraction _____

Signed informed consent obtained: yes ☐ YY MM DD

Operative report

Date of surgery YY MM DD

Implantation

primary ☐

secondary ☐ if secondary, specify reason _____

Ophthalmic viscosurgical device used yes ☐ no ☐

If yes, specify _____

Intraocular medication (check yes or no for each)	yes	no
Adrenalin	☐	☐
Acetylcholine	☐	☐
Carbachol	☐	☐
Other (specify) _____	☐	☐

Irrigating solution used yes ☐ no ☐

If yes, specify _____

Periocular medication	yes (specify, if appropriate)	no
Anaesthetic	☐ _____	☐
Antibiotic	☐ _____	☐
Corticosteroid	☐ _____	☐
Other (specify)	☐ _____	☐

Incision

Size _____ mm

Type (e.g. corneal, limbal, scleral tunnel) _____

Type of lens extraction (check one)

Phacoemulsification ☐

Other (specify) _____ ☐

Type of capsulotomy (check one)

CCCR (continuous curvilinear capsulorhexis) ☐

Other (specify) _____ ☐

Other surgical procedures (check yes or no)	yes	no
	☐	☐

If yes, specify: _____

Problems during surgery (check yes or no for each)	yes	no
Anterior segment bleeding	☐	☐
Iris damage	☐	☐
Posterior capsular opacity remaining	☐	☐
Posterior capsular rupture	☐	☐
Anterior vitrectomy	☐	☐
Other (specify) _____	☐	☐

If investigation lens not implanted indicate reason:

_____

Lens implanted. Place label here:

Lens orientation _____

Time to incision closure _____ minutes

Signature of investigator

_____ YY MM DD

Table A.5 — Post-operative case report form for anterior chamber lens clinical investigation

Investigator name: _____ Clinical trial number: _ _ _ _

Patient number: _ _ _ _ Patient initials: _____ Date of birth: _ _ _ _ _ _ (YY MM DD)

Post-operative report _ _ _ _ _ _ (YY MM DD)

Eye right ☐ left ☐

Check if the patient is unavailable for this scheduled examination but continuing in the clinical investigation (sign form with all evaluation in form left blank). ☐
If the patient is discontinued from the investigation, indicate primary reason:
_____

Refraction
Sphere _____
Cylinder _____
Axis _____

Keratometry
K1_____D
K2_____D

Best corrected visual acuity	Operative eye	Fellow eye
or check one: Finger count	☐	☐
Hand movement	☐	☐
Light perception	☐	☐
No light perception	☐	☐

IOP (applanation) _____mm Hg

Medication used up to this visit (check yes or no for each)	topical yes	topical no	systemic yes	systemic no
Corticosteroids	☐	☐	☐	☐
Antibiotics	☐	☐	☐	☐
NSAIDs	☐	☐	☐	☐
Glaucoma medication	☐	☐	☐	☐

Other (specify) _____

Corneal stromal oedema	wound	central
none	☐	☐
mild/moderate	☐	☐
severe	☐	☐

Iritis (check one)	
none	☐
mild	☐
moderate	☐
severe	☐

Other pathology and complications (check present or absent for each)	present	absent
Wound leak	☐	☐
Flat anterior chamber	☐	☐
Hyphema	☐	☐
Vitreous in anterior chamber	☐	☐
Vitreous to wound	☐	☐
Hypopyon	☐	☐
Iris atrophy	☐	☐
Eversion of the pupillary margin	☐	☐
Endophthalmitis	☐	☐
if present: infectious ☐ sterile ☐		
Raised IOP requiring treatment	☐	☐
Pupillary block	☐	☐
Anterior synechiae	☐	☐

Other pathology and complications *(Continued)*

	present	absent
Posterior synechiae	☐	☐
Incorrect lens size	☐	☐
Iris tuck	☐	☐
Deposits on IOL	☐	☐
Fibrin in pupil	☐	☐
Cortical remnants	☐	☐
Nuclear remnants	☐	☐
IOL optic decentration	☐	☐
if present: _____ mm		
IOL tilt	☐	☐
if present: _____ degrees		
IOL optic discoloration	☐	☐
IOL optic opacities	☐	☐
IOL dislocation out of the anterior chamber	☐	☐
Retinal detachment	☐	☐
Diabetic retinopathy	☐	☐
Cystoid macular oedema	☐	☐
if present diagnosed:		
clinically ☐		
by fluorescein angiography ☐		
Macular degeneration	☐	☐
Optic atrophy	☐	☐

	yes	no
Is the posterior capsule intact?	☐	☐
if intact:		
posterior capsular fibrosis	☐	☐
Elschnig's pearls	☐	☐
If not intact:		
has the capsule been opened since last reported visit?	☐	☐
Other pathology?	☐	☐

Specify:_____

If visual acuity less than 0,5 (20/40, 6/12) indicate main reason:
_____

Lens orientation _____

Has the operated eye undergone any surgical reintervention since last reported visit?	yes ☐	no ☐

If yes, specify: _____

Has the patient experienced any adverse event or ophthalmic adverse device effect?	☐	☐

If yes, fill in the adverse event/adverse device effect report form.

If serious, also contact the sponsor in accordance with local regulations.

Signature of investigator

_____ _ _ _ _ _ _ (YY MM DD)

Table A.6 — Adverse event/ adverse device effect report form

Investigator name: _____ Clinical trial number: _ _ _ _

Patient number: _ _ _ _ Patient initials: _____ Date of birth: _ _ _ _ _ _ (YY MM DD)

1. Operative eye right ☐ left ☐

2. Date of implant _ _ _ _ _ _ (YY MM DD)

3. Lens model number _____

4. Lens serial number _____

5. Power of IOL _____ D

11. Treatment of adverse event (please print)

Adverse event

6. Date of onset _ _ _ _ _ _ (DD MM YY)

7. Duration (hours, days, etc.) _____

8. Severity of adverse event

(check one)

mild ☐

moderate ☐

severe ☐

12. Outcome (check one)

Complete recovery ☐

Recovered with sequelae ☐

Not recovered on day of report ☐

Died ☐

Prognosis, if not recovered:

_____

_____

9. Describe course of adverse event (please print)

Comments (please print)

13. Does reporting physician believe adverse event is lens related? yes ☐ no ☐

Comments (please print)

10. Diagnosis of adverse event (please print)

_____ Date: _ _ _ _ _ _ (YY MM DD)

Signature of investigator

Telephone _____

Annex B
(informative)

Evaluation of post-operative adverse event and visual acuity rates

B.1 General

In order to allow for an uncontrolled study, rates of adverse events and visual acuity were taken from data in USA studies to derive safety and performance endpoints (SPE).

B.2 Background

The data for the SPE rates were derived from weighted averages of the data from large clinical investigations of anterior and posterior chamber IOLs.

The data for posterior chamber IOLs were taken from eight recent clinical investigations of posterior chamber IOLs that were approved in the US (December 1989 to December 1997). The pooled sample size for these clinical investigations was 4 210 for adverse events and overall best corrected visual acuity (BCVA), and 3 035 for best case BCVA.

The data for anterior chamber IOLs were taken from five recent clinical investigations for anterior chamber IOLs that were approved in the US (March 1988 to June 1991). The pooled sample size for these clinical investigations was 952 for adverse events and overall BCVA, and 635 for best case BCVA.

B.3 Adverse event and visual acuity rates

The adverse event and visual acuity rates are provided in Tables B.1, B.2, B.3 and B.4.

For adverse events not included in this annex, comparison with published literature, previous clinical experience and the investigators' clinical judgement, will determine acceptability.

Table B.1 — Anterior chamber IOL adverse event rates

Adverse event	SPE rate [c]	Number of subjects = 100		Number of subjects = 300	
		Threshold rate [d]	Max. number of cases allowed before SPE rate exceeded [e]	Threshold rate [d]	Max. number of cases allowed before SPE rate exceeded [e]
	%	%		%	
Cumulative:					
Cystoid macular oedema	10,0	18,8	15	14,9	39
Hypopyon	0,2	3,0	1	1,4	2
Endophthalmitis [a]	0,2	3,0	1	1,4	2
Lens dislocated from anterior chamber	1,1	5,4	3	3,2	6
Pupillary block	2,0	7,8	5	4,5	10
Retinal detachment	1,2	5,4	3	3,4	7
Secondary surgical intervention [b]	2,6	8,5	5	5,6	13
Persistent:					
Corneal stroma oedema	0,5	4,2	2	2,2	4
Cystoid macular oedema	3,8	10,1	7	7,1	17
Iritis	0,9	5,4	3	3,0	6
Raised IOP requiring treatment	2,1	7,8	5	4,9	11

[a] Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.

[b] Excludes posterior capsulotomies.

[c] The SPE rate is the safety and performance endpoint.

[d] The threshold rate is the minimum rate detectable as statistically significantly different from the SPE rate (greater than the SPE rate in the case of adverse events; less than the SPE rate in the case of BCVA).

[e] The maximum number of cases allowed before SPE rate exceeded are the maximum number of subjects with that adverse event that can occur in a clinical investigation before the rate in that investigation becomes statistically significantly greater than the SPE rate.

Table B.2 — Posterior chamber IOL adverse event rates

Adverse event	SPE rate [c]	Number of subjects = 100		Number of subjects = 300	
		Threshold rate [d]	Max. number of cases allowed before SPE rate exceeded [e]	Threshold rate [d]	Max. number of cases allowed before SPE rate exceeded [e]
	%	%		%	
Cumulative:					
Cystoid macular oedema	3,0	8,9	6	6,0	14
Hypopyon	0,3	3,0	1	1,8	3
Endophthalmitis [a]	0,1	3,0	1	1,0	1
Lens dislocated from posterior chamber	0,1	3,0	1	1,0	1
Pupillary block	0,1	3,0	1	1,0	1
Retinal detachment	0,3	3,0	1	1,8	3
Secondary surgical intervention [b]	0,8	4,2	2	2,6	5
Persistent:					
Corneal stroma oedema	0,3	3,0	1	1,8	3
Cystoid macular oedema	0,5	4,2	2	2,2	4
Iritis	0,3	3,0	1	1,8	3
Raised IOP requiring treatment	0,4	4,2	2	1,8	3

[a] Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.

[b] Excludes posterior capsulotomies.

[c] The SPE rate is the safety and performance endpoint.

[d] The threshold rate is the minimum rate detectable as statistically significantly different from the SPE rate (greater than the SPE rate in the case of adverse events; less than the SPE rate in the case of BCVA).

[e] The maximum number of cases allowed before SPE rate exceeded are the maximum number of subjects with that adverse event that can occur in a clinical investigation before the rate in that investigation becomes statistically significantly greater than the SPE rate.

Table B.3 — Overall post-operative BCVA 0,5 (6/12, 20/40) or better

Lens type	SPE rate [a]	Number of subjects = 100		Number of subjects = 300	
		Threshold rate [b]	Min. number of cases allowed before less than SPE rate [c]	Threshold rate [b]	Min. number of cases allowed before less than SPE rate [c]
	%	%		%	
Anterior chamber IOL	80,4	69,6	74	74,3	230
Posterior chamber IOL	92,5	84,4	88	88,3	270

[a] The SPE rate is the safety and performance endpoint.

[b] The threshold rate is the minimum rate detectable as statistically significantly different from the SPE rate (greater than the SPE rate in the case of adverse events; less than the SPE rate in the case of BCVA).

[c] The minimum number of cases allowed before less than SPE rate are the minimum number of subjects with BCVA 0,5 or better that can occur in a clinical investigation before the rate in that investigation becomes statistically significantly less than the SPE rate.

Table B.4 — Best case post-operative BCVA 0,5 (6/12; 20/40) or better

Lens type	SPE rate [a]	Number of subjects = 100		Number of subjects = 300	
		Threshold rate [b]	Min. number of cases allowed before less than SPE rate [c]	Threshold rate [b]	Min. number of cases allowed before less than SPE rate [c]
	%	%		%	
Anterior chamber IOL	90,1	81,2	85	85,4	262
Posterior chamber IOL	96,7	91,1	94	93,6	285

[a] The SPE rate is the safety and performance endpoint.

[b] The threshold rate is the minimum rate detectable as statistically significantly different from the SPE rate (greater than the SPE rate in the case of adverse events; less than the SPE rate in the case of BCVA).

[c] The minimum number of cases allowed before less than SPE rate are the minimum number of subjects with BCVA 0,5 or better that can occur in a clinical investigation before the rate in that investigation becomes statistically significantly less than the SPE rate.

For example, in the case of “pupillary block” in Table B.1 for a 300-subject investigation, the SPE rate is 2,0 % and the minimum rates detectable as statistically significantly greater is 4,5 % with 10 as the maximum number of subjects allowed before the rate is significantly greater than the SPE rate.

For example, in the case of BCVA 0,5 or better in Table B.3 for a 300-subject investigation, the anterior chamber SPE rate is 80,4 % and the maximum rate detectable as statistically significantly less is 74,3 %, with 230 subjects as the minimum number of subjects necessary for the rate to be not statistically significantly less than the SPE rate.

B.4 Additional guidance

For Tables B.1 and B.2, observed clinical investigation rates will be slightly less than the rates detectable as significantly higher than the SPE rates because any statistical comparison has a margin of sampling error built into it. Similarly, the required success rates in Tables B.3 and B.4 will be slightly higher than the rates detectable as significantly lower because of the allowance for sampling error. The power in Tables B.1 to B.4 is only 80 % to detect differences as far from the SPE rate as the listed threshold rate. If a threshold rate closer to the SPE rate is felt to be clinically different, the power for the given sample sizes will be less than 80 %, hence resulting in a possibly large type II error, if the null hypothesis is not rejected.

The following assumptions were used for Tables B.1 to B.4:

— Type I error = 0,05;

— 80 % power;

— one-sided alternative.

The calculated results for the adverse events (Tables B.1 and B.2) are based on using the binomial distribution, as mathematically described below, to test the null hypothesis that the true adverse event rate is less than or equal to the SPE rate. The alternative hypothesis would be that an adverse event rate is greater than the SPE rate. Similarly, for the best corrected visual acuity (Tables B.3 and B.4), the null hypothesis is that the true rate of cases with visual acuity 0,5 or better is greater than or equal to the SPE rate. The alternative hypothesis is that the “success” rate is less than the SPE rate. The “threshold rate” (i.e. alternative hypothesis value) in Tables B.1 to B.4 represents the minimum or maximum theoretical rate that would be considered statistically significantly lower or higher than the SPE rate. This “threshold” rate is a function of the sample size and power.

$$\Pr\left\{X \geqslant x / n, p\right\} = 1 - \sum_{i=0}^{x-1} \binom{n}{i} p^i \left(1 - p\right)^{n-i} \leqslant 0{,}05$$

where

p is the rate for the SPE;

n is the sample size;

x is the observed number from the investigation.

The maximum of allowable events, "x", can be obtained using an inverse-input binomial probability calculator, by setting the left-tail probability value equal to 0,95, for the given sample size (n) and control rate (p). Similarly, the minimum number required with BCVA 0,5 or better can be obtained using an inverse-input binomial calculator, by setting the left-tail probability value equal to 0,05, for the given sample size (n) and control rate (p). In this case (Tables B.3 and B.4), the right-hand side of the above equation would be "$\geqslant$ 0,95", p would represent the control rate for BCVA 0,5 or better and x would be the observed number of success in the investigation.

Bibliography

[1] ISO/TR 22979, *Ophthalmic implants — Intraocular lenses — Guidance on assessment of the need for clinical investigation of intraocular lens design modifications*

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