INTERNATIONAL STANDARD

ISO 11979-7

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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.

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

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received. www.iso.org/patents

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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).

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 K2_____D Axial length____mm

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 (applanation) _____mm Hg

Medications 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	☐	☐
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	☐	☐

Cont'd: Other pathology and complications	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 ☐

	Operative eye	Fellow eye
Best corrected visual acuity or checkone:	____	____
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/mm²

Cornealthickness (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 dlation	☐	☐	
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 deviceused 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

or check one:	Op. eye	Fellow eye
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	☐	☐

Cont'd: Other pathology and complications

	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 _____

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

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

Adverse event

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

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

8. Severity of adverse event

(check one)

mild ☐

moderate ☐

severe ☐

9. Describe course of adverse event (please print)

10. Diagnosis of adverse event (please print)

11. Treatment of adverse event (please print)

12. Outcome (check one)

Complete recovery ☐

Recovered with sequelae ☐

Not recovered on day of report ☐

Died ☐

Prognosis, if not recovered:

_____

_____

Comments (please print)

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

Comments (please print)

_____

Signature of investigator

Telephone _____

Date: _ _ _ _ _ _
YY MM DD

Annex B
(informative)

Evaluation of post-operative adverse event and visual acuity rates

B.1 General

In order to allow for an uncontrolled investigation, rates of adverse events and visual acuity were taken from data in US studies to derive safety and performance end points (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 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 BCVA, and 3 035 for best-case BCVA.

The data for anterior chamber IOLs were taken from five 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. The terms used in the tables in this annex are defined as follows:

— SPE rate: safety and performance end point (rate derived from analysis of the data from clinical investigations of IOLs approved in the US).

— Maximum number of cases allowed before SPE rate exceeded: this is 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 (see Tables B.1 and B.2).

— Minimum number of cases allowed before less than SPE rate: this is the minimum number of subjects with BCVA 0,3 logMAR or better that can occur in a clinical investigation before the rate in that investigation becomes statistically significantly less than the SPE rate (see Tables B.3 and B.4).

For adverse events not included in Annex B, 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 %	Number of subjects = 100 Max. number of cases allowed before SPE rate exceeded	Number of subjects = 300 Max. number of cases allowed before SPE rate exceeded
Cumulative:			
Cystoid macular oedema	10,0	15	39
Hypopyon	0,2	1	2
Endophthalmitis[a]	0,2	1	2
Lens dislocated from anterior chamber	1,1	3	6
Pupillary block	2,0	5	10
Retinal detachment	1,2	3	7
Secondary surgical intervention[b]	2,6	5	13
Persistent:			
Corneal stroma oedema	0,5	2	4
Cystoid macular oedema	3,8	7	17
Iritis	0,9	3	6
Raised IOP requiring treatment	2,1	5	11

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

[b] Excludes posterior capsulotomies.

Table B.2 — Posterior chamber IOL adverse event rates

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

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

[b] Excludes posterior capsulotomies.

Table B.3 — Overall post-operative BCVA 0,3 logMAR or better

Lens type	SPE rate %	Number of subjects = 100 Min. number of cases allowed before less than SPE rate	Number of subjects = 300 Min. number of cases allowed before less than SPE rate
Anterior chamber IOL	80,4	74	230
Posterior chamber IOL	92,5	88	270

Table B.4 — Best case post-operative BCVA 0,3 logMAR or better

Lens type	SPE rate %	Number of subjects = 100 Min. number of cases allowed before less than SPE rate	Number of subjects = 300 Min. number of cases allowed before less than SPE rate
Anterior chamber IOL	90,1	85	262
Posterior chamber IOL	96,7	94	285

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 0,3 logMAR 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 all tables 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 all the following tables: 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 0,3 logMAR 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 all tables 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.

$$\Pr\{X \geq x / n, p\} = 1 - \sum_{i=0}^{x-1} \binom{n}{i} p^i (1-p)^{n-i} \leq 0{,}05 \tag{B.1}$$

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 0,3 logMAR 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 (see Tables B.3 and B.4), the right-hand side of Formula (B.1) above would be “≥0,95”, p would represent the control rate for BCVA 0,3 logMAR or better and x would be the observed number of success in the investigation.

Annex C
(informative)

Additional elements for toric IOLs

C.1 General

The following additional elements of a toric IOL clinical investigation plan can assist in collecting data for the purpose of determining the safety and performance of this device.

If the toric feature is being applied to a previously approved non-toric parent IOL, then a study of rotational stability of the non-toric IOL model is performed.

If the toric IOL is not associated with any previously approved model, a full clinical investigation as described in Annex A is performed with a substudy of the investigation performed with the zero cylinder power IOLs to assess the rotational stability of the design. This full clinical investigation can include the non-toric IOLs or a combination of the toric and non-toric IOLs, but the first phase of the investigation only includes the non-toric IOLs to confirm the rotational stability of the design prior to the implantation of the toric IOL.

Requirements for rotational stability are given in 6.2.2.

If risk assessment indicates the need additional clinical investigation of the toric IOL model is performed as described in C.3.2 to C.3.8.

C.2 Rotational stability investigation of non-toric IOL

A rotational stability investigation is performed on a non-toric version of proposed toric IOL model to determine if the design is sufficiently stable to be used as a toric IOL, by using a test sample of non-toric IOLs with orientation marks as intended for the toric design.

For this investigation, at least 100 subjects are enrolled in which all of the following examinations are performed.

a) Photographic documentation of the implanted IOL, on the day of surgery, with visible IOL axis marks and – on the same picture – visible structures of the eye which are stable in time and allow a determination of the rotational angle of the IOL around the optical axis relative to the said structures of the eye. Preferred structures are limbal vessels. The pupil should be dilated. Methods to measure IOL axis mark rotation are given in References [3], [4] and [5].

b) Image analysis methods, either subjectively by an examiner or automatically by image analysis software, is provided to quantitatively document changes in the IOL rotation relative to the eye.

c) The documentation of the IOL rotation relative to the eye is performed on the day of surgery and at the conclusion of the investigation (form 4).

d) The rotation angle differences between each of the follow-up examinations and at the day of surgery are statistically examined. The criteria to assess rotational stability are given in 6.2.2.

If risk analysis indicates that rotational stability may be a function of the angle of implantation, then rotational stability is investigated in several different implanted orientations. This is of particular importance for ciliary sulcus and anterior chamber implantations.

C.3 Clinical investigation of toric IOLs

C.3.1 General

The following clauses describe additional assessments that may be performed if a clinical investigation of the toric IOL is required.

C.3.2 Investigation design

The type of clinical investigation recommended is a controlled investigation when the lowest toric IOL cylindrical power is 1,5 D or below (only for the lowest cylindrical power). The clinical investigation of IOL toric cylindrical power above 1,5 D is uncontrolled. This investigation will assess the performance of the toric IOL to reduce preoperative cylinder.

The control IOL is the same IOL model without cylindrical power. A minimum sample size of 65 subjects is recommended with corneal cylinder within the range indicated for the lowest cylindrical power being investigated. The statistical calculation (see C.3.7.2) demonstrates that a sample size of 65 is often sufficient to demonstrate performance.

C.3.3 Investigation duration

The subjects with phakic or aphakic toric IOLs are followed to form 4.

C.3.4 Investigational group

In the case of the toric surface added to a parent IOL, a Level B study with a minimum sample size of 100 unilateral eyes should be performed. At least 65 should receive the toric IOL with the lowest cylinder power (see C.3.8.1). Enrollment should be adjusted to account for the expected lost-to-follow-up rate.

NOTE For the toric IOL with the lowest cylindrical power, the distribution of subject's astigmatism should support the intended range for that toric IOL as defined in the CIP.

C.3.5 Clinical tests

Use the clinical tests and schedules outlined in Table C.1.

Table C.1 — Recommended examination schedule

Examination	Preop	Op	Form 1	Form 2	Form 3	Form 4
Distance UCVA	a/p		a/p	a/p	a/p	a/p
Distance BSCVA	a/p			a/p	a/p	a/p
Subjective refraction	a/p			a/p	a/p	a/p
Cycloplegic refraction	p					p
Slit lamp examination	a/p		a/p	a/p	a/p	a/p
Fundus exam. with dilated pupil	a/p		a/p	a/p	a/p	a/p
Keratometry	a/p				a/p	a/p
Pachymetry of corneal thickness	p					p
Axial length	a/p					
Anterior chamber depth	a/p					
Gonioscopic exam.	p					
Intraocular pressure	a/p	p[a]	p	p	p	p
IOL axis orientation		a/p	a/p	a/p	a/p	a/p
Status of crystalline lens	p			p	p	p
Specular microscopy[b]	a/p					a/p

[a] Post-surgery operative day IOP measurements are considered if pupillary block is considered a possible complication.

[b] For subjects with aphakic anterior chamber IOLs and phakic IOLs where specular microscopy was not performed for the parent IOL. Evaluation beyond form 4 may be necessary to adequately characterize endothelial cell changes. See E.4 for additional information.

Meaning of a and p:

a = subject with aphakic IOL

p = subject with phakic IOL

C.3.6 Performance outcomes

C.3.6.1 Reduction in cylindrical power of the eye

a) The following are definitions of the reduction in cylindrical power of the eye:

— for studies of aphakic eyes: absolute preoperative magnitude of keratometric or total corneal cylinder minus the absolute postoperative magnitude of subjective refractive cylinder at the corneal plane;

— for studies of phakic eyes: absolute preoperative magnitude of subjective refractive cylinder minus absolute postoperative magnitude of subjective refractive cylinder, both referred to the corneal plane.

b) The following are definitions of the percentage reduction in cylindrical power of the eye:

— for studies of aphakic eyes: absolute preoperative magnitude of keratometric or total corneal cylinder minus the absolute postoperative magnitude of subjective refractive cylinder at the corneal plane expressed as a percentage of the absolute preoperative magnitude of keratometric or total corneal cylinder;

— for studies of phakic eyes: absolute preoperative magnitude of subjective refractive cylinder minus absolute postoperative magnitude of subjective refractive cylinder, both referred to the

corneal plane, expressed as a percentage of the absolute preoperative magnitude of subjective refractive cylinder.

C.3.6.2 IOL axis mark rotation

"IOL axis mark rotation" is defined as the acute angle difference between the measured meridian positions of the axis mark(s) at form 4 minus the measured meridian position of the axis mark(s) at the day of surgery.

IOL axis mark rotation, using a direct measurement method is determined. The method should have sufficient precision (two standard deviations) to detect a five degree change in rotation. Additionally, the method should adjust for head tilt and ocular torsion; for example, by registration to iris details or limbal vasculature (see C.2).

C.3.7 Data analyses

C.3.7.1 General

Use the same accountability, safety and performance analyses as outlined in Annex A for aphakic toric IOLs and in ISO 11979-10 for phakic toric IOLs.

In the event of unanticipated residual or induced astigmatism, the related cause is investigated and reported. If surgical correction of the corneal astigmatism is performed during the investigation period, the refractive error prior to secondary surgery is reported as the final result.

C.3.7.2 Safety analyses

Rate of device related secondary surgical interventions and the 95 % confidence interval on this rate.

C.3.7.3 Performance analyses

C.3.7.3.1 Rotational stability of IOL axis mark

The rotational stability of the meridian defined by the IOL axis mark is assessed by a direct method. Methods to measure IOL axis mark rotation are given in References [3], [4] and[5]. Given the degree of toric IOL axis accuracy suggested in this clinical annex, every effort should be made to include in the direct method reference to unchanging anatomical features, such as the iris, sclera, or conjunctiva.

The rotation angle differences between each of the follow-up examinations and at the day of surgery are statistically examined (refer to examination schedule). The criteria to assess rotational stability are given in 6.2.2.

Analysis of IOL axis mark rotation from the day of surgery should include:

a) absolute value of the rotation (median, maximum);

b) signed value of the rotation (mean, standard deviation, minimum, maximum).

C.3.7.3.2 Reduction in cylindrical power of the eye

Descriptive statistics for the reduction in cylindrical power of the eye (defined in C.3.6.1) at form 4 should be tabulated separately for each model. These should include the mean, standard deviation, median, maximum and minimum of the change in cylindrical power. Skewed or non-normal data invalidates the use of mean and standard deviation and therefore only the median, maximum and minimum change shall be reported in such a case.

For the model with the lowest IOL cylindrical power:

a) If the lowest toric IOL cylinder power is ≤1,50 D (controlled study), statistically compare the mean "reduction in cylindrical power of the eye" to the control mean "reduction in cylindrical power of the eye";

b) Characterize the "reduction in cylindrical power of the eye" with the mean and a 95 % confidence interval on the mean.

For this outcome, compare the difference between the test and control arm means and the upper confidence limit of the lower confidence limit on the magnitude of the mean change [b), above] to a minimal clinically significant difference. This should be in addition to the statistical comparison in a) for a controlled study.

The following additional analyses should be performed for the lowest cylindrical power model and control (when a control is used):

c) For each 0,25 D step of preoperative cylinder (keratometric for aphakic IOLs, refractive for phakic IOLs), tabulate the following for each arm:

   — the proportion of eyes that showed "reduction in cylindrical power of the eye" <0,50 D

   — the proportion that showed "reduction in cylindrical power of the eye" >0,50 D

   — the proportion that showed change in absolute "reduction in cylindrical power of the eye" ≤ ±0,50 D

   — provide side-by-side comparisons of test and control results.

d) For each 0,25 D bin of preoperative cylinder, tabulate the following for each arm:

   — The descriptive statistics for "change in cylindrical power of the eye" (mean, standard deviation, median, minimum, maximum). Provide side-by-side comparisons of test and control results.

e) Scatterplots with regression lines (based on form 4 and preop data; separate graphs for each arm of the study): "Reduction in cylindrical power of the eye" (corneal plane) vs. preoperative cylinder (keratometric cylinder for aphakic, refractive cylinder for phakic).

Based on the above, a discussion should be provided assessing the device effectiveness across the range of preoperative cylinder that the label indicates is appropriate for implantation with the lowest cylindrical power model. If it appears that meaningful effectiveness is questionable in portions of this treatment region, the labelled range of preoperative astigmatism that is appropriate for IOL implantation is restricted accordingly.

C.3.7.3.3 Change in corneal cylindrical power

The surgically induced change in sphere and cylinder are calculated by analysis of the preoperative and postoperative keratometric readings (power and axis of meridians of highest and lowest power), converted to components in dioptric space. Change is defined as postoperative component values minus preoperative component values.

Analyses should include:

a) analysis of the error in the predicted magnitude of postoperative astigmatism, including the bias, standard deviation, and mean absolute error, and a similar analysis of error in the predicted axis;

b) plot of the absolute error in predicted keratometric axis as a function of preoperative corneal astigmatism, and tabulation of the proportion of eyes with absolute error in axis by 5° wide bins (e.g. 0° to 5°, >5° to 10°).

C.3.7.3.4 Additional performance analyses

Recommended performance analyses specific to characterize the clinical performance of the toric IOLs are described below.

a) Percentage of eyes that achieve UCVA of
   - 0,0 logMAR or better
   - 0,3 logMAR or better

b) Mean UCVA stratified by 0,25 D bin of preoperative cylinder
   - overall
   - for each toric IOL cylindrical power model

C.3.8 Statistical considerations

C.3.8.1 Sample size calculation for the analysis of "reduction in cylindrical power of the eye" (see C.3.6.1) for a study without a control (all toric IOL cylindrical powers >1,50 D)

As the lowest IOL cylindrical power group should show the lowest "reduction in cylindrical power of the eye", the sample size for this group should be sufficient for assessment of "reduction in cylindrical power of the eye".

Calculations have to account for the normality or non-normality of data distribution.

Formula (C.1) may be used to estimate the number of subjects in this "lowest cylinder power" subgroup. The equation provides the sample size necessary to provide 0,20 D precision in the 95 % confidence intervals for the "reduction in cylindrical power of the eye."

$$n = \sigma^2 \left(\frac{Z_{1-\alpha/2}}{\text{precision}} \right)^2 \tag{C.1}$$

where

n is the sample size (number of subjects);

$Z_{1-\alpha/2}$ is the value of standard normal distribution below which exactly the $(1-\alpha/2)$ proportion of the population falls. $(1-\alpha)$ is the confidence (probability) that the parameter being estimated (p) falls within the confidence interval. Here $1-\alpha$ is taken to be 0,95 (for a 95 % confidence interval);

$Z_{1-\alpha/2} = Z_{0,975}$ = 97,5th percentile of the normal distribution = 1,96;

σ is the standard deviation of the "reduction in cylindrical power";

precision is half width of confidence interval estimate = 0,20 D.

Experience indicates that for a low cylindrical power toric of about 1,75 D, it is reasonable to assume that the standard deviation for "reduction in cylindrical power" is 0,82 D. Therefore:

$$n = \left(0{,}82^2\right)\left(\frac{1{,}96}{0{,}20}\right)^2 = 64{,}6 \tag{C.2}$$

Thus, for the "lowest toric cylindrical power" subgroup, the minimum recommended sample size should be 65 subjects.

C.3.8.2 Sample size calculation for statistical comparison of "reduction in cylindrical power of the eye" in controlled study (aphakic and phakic toric IOLs)

For aphakic and phakic toric IOLs, the "reduction in cylindrical power of the eye" (see C.3.6.1) in the toric IOL investigation group and the control (spherical IOL) group is compared at the final visit. This should be done for the "lowest cylindrical power" subgroup. The selection criteria for the control group are the same as for the lowest cylindrical power investigation group. The goal is to demonstrate superiority in "reduction in cylindrical power" in the toric group.

The null hypothesis is:

H_0: reduction in $\text{cylinder}_{\text{toric}} \leq \text{reduction in cylinder}_{\text{control}}$

The alternative hypothesis is:

H_1: reduction in $\text{cylinder}_{\text{toric}} > \text{reduction in cylinder}_{\text{control}}$

Below is an example of a sample size calculation (two-sample *t*-test). Using the following assumptions:

— $\alpha = 0{,}025$ [type I error rate] (This is equivalent to 0,05 for a 2-sided test);

— $\beta = 0{,}10$ [type II error rate];

— The minimum difference in "reduction in cylinder" between the two arms that one is attempting to detect (with 90 % power) is 0,38 D;

— the standard deviation for the "reduction in cylinder" for each arm is 0,66 D;

— use the two-sample *t*-test with equal variances and sample sizes.

Standard statistical software yields a minimum sample size of 65 subjects in each arm.

Annex D
(informative)

Additional elements for accommodating IOLs

D.1 General

The following additional elements of an accommodating IOL (AIOL) clinical investigation plan can assist in collecting data for the purpose of determining the safety and performance of this device.

D.2 Investigation design

The investigation consists of two phases:

a) randomized, comparative investigation to assess objective accommodation. If at least 1 D of accommodation can be demonstrated the second phase can commence.

b) randomized, comparative investigation to assess the safety and to further study the magnitude and consistency of the accommodative performance.

The study also uses the historical data in Annex B to investigate the general safety and performance of the accommodating IOL.

The objective accommodative amplitude testing of the control group should be used to verify the test method used in the clinical investigation, and should demonstrate minimal accommodative amplitude for the control group.

The CIP should include a description of the selection of subjects for objective measurement of accommodation and include description of methods used to minimize potential for bias (e.g. age-matching and masking).

D.2.1 Enrolment of subjects

Enrolment occurs in the following two phases.

a) Phase I: enrol 50 subjects, follow to form 4. Assess the objective accommodative amplitudes. If sufficient amplitude is demonstrated, phase II may be initiated.

b) Phase II: all additional subjects.

D.3 Investigation duration

The first phase of the investigation has duration according to form 4.

The total study duration depends on when accommodative amplitude stability is demonstrated, with a minimum duration to form 5 and a maximum duration to form 7. Stability is demonstrated by a less than 25 % decrease or a not statistically significant decrease in the mean of the within eye percentage change in accommodative amplitude measurements taken six months apart. If the pilot data analysis and risk analysis raise long-term safety concerns, longer follow-up may be needed.

The investigational plan should include a statement that a long-term follow-up (e.g. up to three years) may be necessary. It is recommended that an informed consent for a three-year follow-up is obtained.

D.4 Investigation and control groups

See Table D.1.

Table D.1 — Sample size requirements for the investigation and control group

Implantation	Sample size	
	Investigation group	Control group
Unilateral – Phase I	50	50
Unilateral – Phase II	250	72[a]
Bilateral[b]	100	50

[a] Total number of unilateral control subjects set by number needed for contrast sensitivity subinvestigation.

[b] This is an optional subset of the total number of subjects.

D.5 Clinical tests

Use the clinical tests and schedules outlined in Table D.2.

D.6 Outcomes

D.6.1 General

This clause outlines elements considered in the design of a clinical investigation of an accommodating IOL.

D.6.2 Performance outcomes — Accommodative amplitude

Clinical investigation includes objective assessment of accommodation on investigation eyes and control eyes. A test may be selected from those described in E.3.2.2. The recommended primary effectiveness end point is the amplitude of accommodation. A sample size calculation should be performed to ensure that the proposed number of subjects for the objectively measured amplitude of accommodation testing are sufficient to demonstrate superiority over the control for the outcome at the time point of stability (or final visit, if study is longer than 12 months). In any case, no fewer than 100 eyes in the investigational arm and 50 eyes in the control arm should have objective amplitude testing at the final visit.

Subjective accommodative testing and biometric testing is optional and may be performed to characterize the AIOL performance.

D.6.3 Safety outcomes

D.6.3.1 Specular microscopy

Specular microscopy is performed in investigation and control patients if warranted by risk analysis. In that case, it is performed preoperatively and at form 4, form 5, form 6 and form 7. Specular microscopy images are taken of the central cornea. In addition, peripheral measurements are taken if warranted by the design or placement of the AIOL. The peripheral locations to be photographed should be specified based on the design and/or placement of the AIOL. See E.4 for additional information.

D.6.3.2 Subject questionnaire

Subjects may be given a questionnaire to assess symptoms and quality of life issues related to the accommodating IOL. It is recommended that a self-administered questionnaire be used to avoid bias. At the time of the publication of this part of ISO 11979, there are no published questionnaires that have been specifically validated for use in accommodating IOL investigations. The questionnaire should

include questions regarding glare, halos, double vision, spectacle/contact lens use, night driving and intermediate distance tasks and spectacle independence for defined activities. The time of onset of visual symptoms should also be addressed.

The questionnaire items should have previously been referenced in the peer-reviewed literature and their reliability and validity undergone some degree of evaluation. Alternatively, their reliability and validity can be evaluated in a pilot study. The results of the subject questionnaire are stratified by fellow eye status (untreated, implanted with same accommodating IOL, etc.).

See Reference [6] or Reference [7] for examples of questionnaires that can be used as a starting point.

Table D.2 — Recommended examination schedule (1 of 2 pages)

Examination	Illumination	Testing performed[a]	Number of AIOL subjects	Number of controls subjects	Reporting period							
					Pre-op	Op	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 7
Uncorrected distance visual acuity	Photopic	Monocular	300	122	X		X	X	X	X	X	X	X
		Binocular	100	50						X	X	X	X
Best spectacle corrected distance visual acuity	Photopic	Monocular	300	122	X			X	X	X	X	X	X
		Binocular	100	50						X	X	X	X
Uncorrected near visual acuity (fixed distance)	Photopic	Monocular	300	122					X	X	X	X	X
		Binocular	100	50						X	X	X	X
Near visual acuity with distance correction (fixed distance)	Photopic	Monocular	300	122					X	X	X	X	X
		Binocular	100	50						X	X	X	X
Uncorrected intermediate visual acuity (fixed distance)	Photopic	Monocular	300	122						X	X	X	X
		Binocular	100	50							X	X	X
Intermediate visual acuity with distance correction (fixed distance)	Photopic	Monocular	300	122						X	X	X	X
		Binocular	100	50							X	X	X
Best spectacle corrected near visual acuity (record add power required)	Photopic	Monocular	300	122						X	X	X	X
		Binocular	100	50							X	X	X
Accommodative amplitude (objective)	Photopic	Monocular	TBD[b]	TBD[b]					X	X	X	X	X
Subjective refraction	Photopic	N/A	300	122	X			X	X	X	X	X	X
Pupil size[c]	Photopic/ mesopic	N/A	300	122	X						X	X	X
Fundus examination with dilated pupil	N/A	N/A	300	122	X						X	X	X
Slit lamp examination	N/A	N/A	300	122	X		X	X	X	X	X	X	X

Table D.2 — Recommended examination schedule (2 of 2 pages)

Examination	Illumination	Testing performed[a]	Number of AIOL subjects	Number of controls subjects	Reporting period								
					Pre-op	Op	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 7
Intraocular pressure	N/A	N/A	300	122	X		X	X	X	X	X	X	X
Lens stability (tilt/decentration)[d]	N/A	N/A	300	122			X	X	X	X	X	X	X
Subject questionnaire[e]	N/A	N/A	300	122	X						X	X	X
Specular microscopy[f]	N/A	N/A	300	122	X					X	X	X	X
Anterior chamber depth[f]	N/A	N/A	300	122	X				X	X	X	X	X
Gonioscopy[f]	N/A	N/A	300	122	X				X	X	X	X	X
Substudies													
Far contrast sensitivity	Mesopic	Monocular	122	122							X	X	X
		Binocular	optional	optional							X	X	X
Far contrast sensitivity	Mesopic with glare	Monocular	122	122							X	X	X
		Binocular	optional	optional							X	X	X

[a] The testing is to be performed monocularly or binocularly as specified. If the testing is monocular, the first eye implanted is reported in the primary analysis. Binocular testing is performed on the investigation group subjects who are implanted bilaterally with the AIOL and on the control group subjects who are implanted bilaterally with the control IOL.

[b] Sample size is determined from a statistical analysis with the minimum number of AIOL subjects being 100.

[c] Pupil size is assessed for all tests influenced by pupil size at the post-op visits specified in the pupil size row.

[d] Lens stability is performed according to Reference [2].

[e] Questionaire should include subject grading of visual/optical symptoms, ability to perform specific sustained reading tasks, and satisfaction/functioning questions (e.g. need glasses for near tasks).

[f] This investigation is performed if warrented by risk analysis.

D.7 Data analyses

D.7.1 General

Based on the risk analysis, safety and performance analyses appropriate to the specific AIOL and intended population are selected from the following subclauses.

D.7.2 Safety analyses

Consider the following safety analyses:

a) frequency of optical and visual symptoms assessed in a questionnaire;

b) endothelial cell count analysis (if applicable);

c) rate of device-related secondary surgical interventions and the 95 % confidence interval on this rate.

D.7.3 Performance analyses

Consider the following performance analyses:

a) accommodative amplitude (objective assessment);

b) percentage of eyes that achieve a change of less than or equal to 1,00 D of spherical equivalent between two refractions performed at least three months apart;

c) mean change in spherical equivalent between visits as determined by a paired analysis;

d) mean change in accommodative amplitude between visits at least six months apart as determined by paired analysis;

e) percentage of eyes that achieve best spectacle corrected distance VA for each line of VA (0,1 log units);

f) distribution of eyes that achieve near VA with distance correction (fixed distance) between 0,0 logMAR and 0,7 logMAR;

g) distribution of eyes that achieve best spectacle corrected near VA between 0,0 logMAR and 0,7 logMAR;

h) post-operative spectacle independence as assessed by the questionnaire;

i) intermediate VA with distance correction;

j) percentage that achieve combined uncorrected distance VA and uncorrected near VA of 0,7 logMAR or lower to 0,0 logMAR or lower in 0,1 logMAR decrements;

k) descriptive comparisons (means and standard deviations) between the AIOL and control groups, for the six-month postoperative distance refraction.

The objectively measured amplitude of accommodation are characterized by descriptive statistics. These include, for both test and control groups mean, standard deviation, 95 % confidence interval, and detailed description of the distribution. Additionally, statistical comparisons can be performed. In order to be considered effective, the investigational AIOL should be statistically superior to the control IOL at the final form for mean objective amplitude of accommodation.

D.8 Statistical considerations

D.8.1 Statistical symbols and definitions

Table D.3 lists the statistical symbols used throughout the following statistical analysis methods and gives their definitions.

Table D.3 — Meaning of symbols

Parameters and statistics in normal distribution	
Symbol	**Description**
z	standard normal variable (units of standard deviations)
μ	population mean
σ	population standard deviation
n	sample size
$\bar{x}$	sample mean
π	population proportion
p	sample proportion
Hypothesis testing symbols	
Symbol	**Description**
H_0	null hypothesis
H_0: $\mu \leq 0$	a logical statement to be read "The null hypothesis is that the mean, μ, is less than or equal to zero"
H_1	alternative hypothesis
α	the probability of falsely rejecting the null hypothesis. This is also referred to as the "significance level" for the hypothesis test.
β	the probability of falsely accepting the null hypothesis
$1-\beta$	the statistical "power" of the hypothesis test.
δ	non-inferiority margin - The difference between two population means (e.g. before/after; Treatment A/Treatment B) that can be allowed before this difference is believed to be of clinical significance.
$z_{1-\alpha}$	standard normal quantile. The value of the standard normal variable Z, below which $(1-\alpha)$ of the distribution lies.
$z_{1-\beta}$	standard normal quantile for power
Pr	probability - generally given numerically as a fraction between 0 and 1 or as a percentage between 0 % and 100 %
$Pr\{X > x/n\}$	a logical probability statement to be read "the probability that X is greater than x for the condition of sample size n"

Table D.4 provides a convenient list of standard normal quantiles that are used throughout.

Table D.4 — Normal quantiles to use in formulae/equations

α	(1-α)	$z_{1-\alpha}$
0,025	0,975	1,960
0,050	0,950	1,645
0,100	0,900	1,282
0,150	0,850	1,036
0,200	0,800	0,842
0,500	0,500	0,000

D.8.2 Calculation of necessary sample sizes

D.8.2.1 Sample size of the AIOL arm, based on safety considerations

The sample size for the investigation is based on the adverse event analyses provided in Annex B.

D.8.2.2 Sample size for a contrast sensitivity subinvestigation

Contrast sensitivity differences are determined by comparing a group of investigational subjects with a group of control subjects.

For non-inferiority hypothesis testing for studies that compare investigation and control eyes of different subjects, the sample size required for two means from a normal sample can be determined from Formula (D.1):[8]

$$n = 2\sigma^2 \left[\frac{(z_{1-\alpha} + z_{1-\beta})}{\delta + (\mu_t - \mu_c)} \right]^2 \quad \text{for } \mu_t > \mu_c - \delta \tag{D.1}$$

The subscript "t" refers to treatment and the subscript "c" refers to the control. Usually the population means for the two groups are assumed equal for power and sample size calculations. If they are not assumed equal, the denominator is constrained to be positive in non-inferiority problems. This assumption increases the sample size as the differences between population means approaches the non-inferiority margin. The assumptions also avoid the extreme condition of having smaller sample size requirements when the denominator becomes more negative.

In order to calculate sample size using the above equations, the non-inferiority margin (δ), the standard deviation, the power (1 – β) and the significance level (α) have to be chosen. Values for these parameters should be chosen based on experience or published literature.

As an example, consider an investigation comparing a group of investigational subjects with a group of control subjects. Assume a power (1 – β) of 90 % with a significance level (α) of 5 %. The non-inferiority margin (δ) has been set at one half the contrast sensitivity loss that is typically considered to be clinically significant. Typically, losses of 0,3 log units are considered to be clinically significant, when they occur at two or more spatial frequencies. This example then allows for a detectable difference of 0,15 log units. Other values can be used if appropriate. Standard deviation chosen for the example is 0,4 log units, which is based on published literature and experience. Standard deviation values can vary based upon investigation conditions (e.g. testing equipment, lighting conditions). The sponsor should choose the expected standard deviation based on literature and/or experience.

Solving for this equation:

$$n = 2\left[\frac{0,4(1,645+1,282)}{0,15}\right]^2 = 121,84 \cong 122 \qquad \text{(D.2)}$$

Therefore, 122 investigation eyes and 122 control eyes are required for the contrast sensitivity subinvestigation. With 122 subjects per group, there is a power of 90 % to detect a difference in group means of 0,15 log units (with α = 0,05).

Annex E
(informative)

Clinical tests

E.1 Visual acuity: distance, intermediate and near

Distance and near acuity charts, chart illumination, ambient illumination, testing distances and testing procedures are standardized for all investigators. Reporting of refractions are standardized across investigational sites.

All near and intermediate testing that is carried out through the "distance correction" should be carried out through the infinity-adjusted subjective refraction (rounded to the nearest 0,25 D). Distance subjective VA and testing distance are recorded on the case report forms. If the distance subjective refraction is done at a testing distance of less than 6 m, an infinity-adjusted subjective refraction is reported in the final report. In order to adjust subjective refraction to infinity, adjust the measured spherical power by subtracting 1/(testing distance in metres). (For example, if distance testing is done at 4 m and the measured subjective refraction is −0,25−0,75X090, then the infinity-adjusted subjective refraction would be −0,50−0,75X090.).

Intermediate visual acuity testing is performed at 66 cm.

Near visual acuity testing is performed at 40 cm.

The design of the visual acuity chart and testing procedures with scoring methods are described in Reference [9].

The following conditions, materials and procedures for acuity testing are recommended.

E.1.1 Luminance

A specific chart background luminance is selected from 80 cd/m^2 to 160 cd/m^2 (85 cd/m^2 recommended) for photopic testing. Luminance is as close as possible to a common luminance for all testing centres.

Ambient illumination should be from dim to dark, to maximize pupil size. No surface (including reflective surfaces) within the subject's field of view should exceed the chart background in luminance.

E.1.2 Data recording procedures

The following are recorded:

a) All physical and optical testing distances.

b) All refractions.

c) All acuity measurements using MAR notation (minimum angle of resolution in minutes of arc) or other notation convertible to MAR. Examples of notation include:

   — logMAR (common logarithm of MAR) is acceptable.

   — decimal notation (reciprocal of MAR) is acceptable.

   — standard Snellen notation (actual test distance/test distance that would render MAR = 1) is acceptable.

NOTE Jaeger notation is not acceptable.

E.2 Pupil size

Pupil size is measured at the illumination levels associated with all tests that can be influenced by pupil size. For mesopic pupil size testing, the measurements should be made with an infrared or light amplification pupilometer/camera or any other objective method and is initiated only after the eye has had time to fully adapt to the testing conditions (approximately 10 min). In all cases, the pupil size is measured at the corneal plane to the nearest 0,5 mm.

E.3 Accommodation measurements

E.3.1 Subjective accommodation measurements: Defocus curves

A defocus curve that measures visual acuity is obtained by using the best corrected distance refraction and then defocusing the image by −5 D of sphere. Measure the visual acuity and then proceed to decrease the defocus in 0,5 D steps up to +2 D, measuring the acuity at each level of defocus. Record the pupil size(s) and measurement conditions. The subjective accommodative amplitude is defined by the range of accommodation where the visual acuity is above BCDVA plus one line (plus 0,1 logMAR).

E.3.2 Objective accommodation measurement methods

E.3.2.1 General

At least one objective measure of accommodation by refractive change is used to compare investigation and control subjects. Examples of suitable methods are summarized in E.3.2.2.

A compelling accommodative stimulus is critical for eliciting the maximum amplitude of accommodative response. This is ideally a high contrast letter chart or target that is presented at real distances (as opposed to optically). The target size can be adjusted to match the subject's distance corrected near visual acuity. In the ideal case, the subject would view the targets binocularly, although this is often not practical or possible. Many instruments will only permit monocular measurement, with the accommodation stimulus being presented to the measured eye by means of viewing an internal target presented in a Badal optical system, or by presenting the stimulus to the fellow eye. Monocular measurements should not be compared to binocular measurements because binocular acuity is normally better than monocular.

E.3.2.2 Objective refractive changes

E.3.2.2.1 General

Objective refractive methods measure the change in refracting power of the eye. This is an optical measurement of the vergence power of the eye. The refraction is normally referred to a certain vertex distance in front of the eyes (normally 12 mm: the spectacle plane). The vertex distance can be adjusted in the various instruments via software setting (0 mm, 15 mm, etc). For low refractive powers (~0 to 4 D, for example) vertex distance has little effect on the power, but vertex distance will have an increasing effect for higher refractive powers. The objective refractive methods provide a standard refraction (sphere, cylinder and axis), which can be converted to spherical equivalent refraction (SE), which is used to express the overall refractive power of the eye. Measurements are made at two different days per viewing distance. These should preferably be repeated at approximately the same time each day with the time documented.

E.3.2.2.2 Autorefractors

Autorefractors provide an objective refraction (sphere, cylinder and axis) measurement. This is an optical measurement of the refractive state of the eye. The measurement is normally done with infrared light. Several measurements are usually taken and recorded in succession. Pupil diameter is measured before and after testing.

Some autorefractors have an open field of view. In other words, the patient can see through the instrument past a beam splitter. This open field of view allows targets to be viewed at real distances monocularly or binocularly. Many autorefractors measure at a fixed pupil diameter, but some measure over the entire ocular pupil. The principle of the instrument is reported.

An open-field autorefractor can use the following procedure. If necessary to obtain a reading in subjects with small pupils, mydriatic drops such as phenylephrine or other sympathomimetic agent can be used for pupil dilation. Under no circumstances should antimuscarinic agents such as atropine or tropicamide be used.

a) Distance refractive measurement

   1) Ensure distance correction is in place by means of a spectacle or a contact lens. (With this correction, the instrument should indicate distance sphere in the interval –0,25 D to +0,25 D.)

   2) Sit subject at instrument with chin on the chin-rest and head against the forehead rest. Cover the non-investigation eye.

   3) Place fixation target at its distance calibrated position (i.e. 0 D) and ensure target illumination is switched on.

   4) Extinguish room lights.

   5) Align and focus instrument in accordance with manufacturer's instructions.

   6) Take at least 3 reasonable readings and record the results.

b) Near refractive measurement

   1) While keeping the subject in position at the headrest, move the fixation target to the 1 D (100 cm) position.

   2) Direct the subject's attention to the near fixation target and repeat the last 2 steps.

   3) Repeat near measurements with the fixation target at the 2 D (50 cm) and 3 D (33 cm) positions.

   4) Record a minimum of 3 reasonable readings at each test distance.

   5) Record the distance sphere and the near sphere for each distance assessed in the appropriate case report form (CRF).

   6) Retain the autorefractor records with the source documentation.

E.3.2.2.3 Wavefront aberrometry

This class of instruments is used primarily to measure the total wavefront aberration of the eye, including higher order aberrations as well as defocus and astigmatism. Although most aberrometers on the market the time of the publication of this part of ISO 11979 are designed to measure the refractive state of the eye relative to optical infinity, some are also equipped to measure accommodative amplitude. Several different implementations are used to characterize the refractive performance of the eye. Aberrometers generally provide a traditional refraction (sphere, cylinder, and axis), which is calculated by considering the wavefront aberrations over a specified pupil diameter, from which the spherical equivalent can be obtained as a measure of the accommodative response.

E.3.2.3 Objective biometric/biomechanical changes

E.3.2.3.1 General

Biometry methods measure changes in the biometric distances in the eye (anterior chamber depth and lens thickness, for example). One or more biometric measures may be useful in characterizing an AIOL. Natural accommodation is always associated with a biometric change. A measurement of a biometric

change with an AIOL does not directly provide an indication of the extent of the accommodative refractive change, but may be useful to validate the intended mode of action:

a) forward movement of an optic;

b) movement of two optics;

c) an increase in axial thickness of a lens; or

d) changes in surface curvature of an optic.

For biometry methods accommodation stimulus can be given naturally to the fellow eye, or by means of a target viewed through a Badal system in the measured eye. Care has to be taken in evaluating responses induced by pharmacologic agents because they may be extreme compared to the response from a natural accommodating stimulus, such as a near target. The biometry methods can only measure monocularly.

The sponsor may consider using one or more of the biometry methods listed below.

E.3.2.3.2 Partial coherence interferometry (PCI)

This technique has been widely used in research applications for investigating ocular accommodative biometric changes. This is a high resolution optical technique for measuring axial distances. A bundle of infrared light is split into two bundles separated by an optical path difference generated by an interferometer. At refractive index boundaries normal to the incidence of the light, light packages are reflected back into a detection arm of the instrument. Reflected light reaching the detection arm from two boundaries separated by the same optical path difference undergo positive interference, which generates a signal. The measured optical distances have to be converted to physical distances by means of the group refractive indices of the ocular media. PCI is a non-contact optical technique with an internal fixation target for alignment. The fixation target can also be defocused to present an accommodation stimulus. If the accommodative effort of the subject results in an axial shift of internal ocular boundaries, these can be recorded.

E.3.2.3.3 Optical coherence tomography (OCT)

OCT also uses partial coherence interferometry to measure optical distances in the eye. However, with OCT, a three dimensional image of the anterior segment is reconstructed. This is accomplished by scanning the PCI beam with respect to the eye. As with PCI, the optical distances are measured and have to be converted to physical distance by dividing by the ocular media group refractive indices. This is also a non-contact procedure. Biometric distances of anterior chamber depth and lens thickness, as well as lens surface curvatures can be measured from the reconstructed image.

E.3.2.3.4 Scheimpflug photography

Scheimpflug photography can also be used to measure distances in the anterior segment of the eye. To obtain reliable distances, it is of importance that the images are properly corrected for the geometry of the Scheimpflug camera, and for refraction at any preceding interfaces.[10] There are commercial instruments available with this capability.

E.4 Specular microscopy

E.4.1 General

The main safety concern to be addressed by specular microscopy is the possibility of a progressive decrease in endothelial cell density, which could lead to corneal decompensation.

Specular microscopy images are taken of the central cornea. Peripheral measurements are taken if warranted by the design or placement of the IOL. The peripheral locations to be photographed are specified based on the design and/or placement of the implant.

To determine endothelial cell density decrease, specular microscopy is performed preoperatively and every six months for the duration of the study. Decreases due to surgical trauma can be determined by evaluating the cell counts at month 6 in comparison to the preoperative measurements. To determine decreases over time, measurements from the six-month examination and later time points are analysed.

Operated fellow eyes with the experimental IOL can be used in the endothelial cell density analysis after correcting for the correlation between eyes. This can be accomplished in many statistical packages using the general estimating equations method. The net effect of this technique is to adjust the standard errors (and thus the confidence intervals) for the slope estimates to account for the observed correlation between fellow eyes.

E.4.2 Collection of data

The methods used for the collection and analysis of specular microscopy data are critically important to minimize the variability associated with these measurements. Common sources of variability in specular microscopy are:

a) not returning to same location;

b) poor image quality (less than 100 countable cells);

c) technician error;

d) improper reader analysis;

e) not maintaining equipment calibration/alignment.

There are several ways to reduce this variability. Sponsors should implement as many of these recommendations as possible.

To address differences in location of the image within a given area of the cornea, three acceptable images are taken at each visit. The mean density from the three images is used.

Non-contact specular microscopes are strongly recommended. The same model of specular microscope is used at each site.

Prior to the beginning of the study, each site takes an initial set of images for evaluation of image quality. Training (or retraining) is performed as necessary and includes the following important points:

A preferred image has distinct cells, with at least 100 countable cells (150 cells preferred) that can be grouped in a uniform area.

The use of a reading centre is strongly recommended. If the use of a reading centre is not possible, the sponsor has to establish a protocol for the collection and analysis of images to be used by each participating site. The person responsible for taking and accepting the images is adequately trained in both specular photography and in the evaluation of the images. If possible, the same trained and certified technician/photographer is used at each site throughout the study. A back-up technician who is trained is also available.

The reading centre or technician performing the image analysis is advised of the following recommendations.

a) A minimum of 100 cells (ideally 150 cells) in a contiguous area are counted.

b) The centre method for counting cells is recommended.

c) When selecting cells to count, use the area with the fewest distortions (not in shadow, washed-out, or blurred).

NOTE The quality of cells in an image is critical. Be aware that increased variability in the data can be seen in some subjects (e.g. polymegethism/pleomorphism post-contact lens wear).

A calibration grid can be obtained from the specular microscope manufacturer. The study monitor should check the calibration at each site on a yearly basis.

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