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**Ophthalmic implants — Intraocular  
lenses —**

**Part 7:  
Clinical investigations of intraocular  
lenses for the correction of aphakia**

*Implants ophtalmiques — Lentilles intraoculaires —*

*Partie 7: Investigations cliniques de lentilles intraoculaires pour la  
correction de l'aphakie*





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ISO copyright office  
CP 401 • Ch. de Blandonnet 8  
CH-1214 Vernier, Geneva  
Phone: +41 22 749 01 11  
Fax: +41 22 749 09 47  
Email: [copyright@iso.org](mailto:copyright@iso.org)  
Website: [www.iso.org](http://www.iso.org)

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# Contents

Page

<b>Foreword</b>	<b>iv</b>
<b>Introduction</b>	<b>v</b>
<b>1 Scope</b>	<b>1</b>
<b>2 Normative references</b>	<b>1</b>
<b>3 Terms, definitions and abbreviated terms</b>	<b>1</b>
3.1 Terms and definitions	1
3.2 Abbreviated terms	1
<b>4 Justification for a clinical investigation</b>	<b>2</b>
<b>5 Ethical considerations</b>	<b>2</b>
<b>6 General requirements</b>	<b>2</b>
6.1 General	2
6.2 Design of a clinical investigation	2
6.2.1 Requirements for all types of IOLs	2
6.2.2 Additional requirements for toric IOLs (TIOLs)	3
6.2.3 Additional requirements for multifocal IOLs (MIOLs)	3
6.2.4 Additional requirements for accommodating IOLs (AIOLs)	3
6.2.5 Additional requirements for anterior chamber IOLs	3
6.3 Characteristics of clinical investigations	4
6.3.1 General	4
6.3.2 Characteristics to be studied for all types of IOLs	4
6.3.3 Additional characteristics to be studied for TIOLs	4
6.3.4 Additional characteristics to be studied for MIOLs	5
6.3.5 Additional characteristics to be studied for AIOLs	5
6.3.6 Additional characteristics applying to anterior chamber IOLs	5
6.3.7 Additional characteristics	5
6.4 Duration of the investigations	5
6.5 Enrolment	6
6.6 Bilateral implantation	6
6.7 Surgical technique	6
6.8 Examination and treatment of subjects	6
6.9 Adverse events reports	7
6.10 Inclusion and exclusion criteria	7
6.10.1 General	7
6.10.2 Additional inclusion criteria for TIOLs	7
6.10.3 Additional exclusion criteria for MIOLs	7
6.10.4 Additional exclusion criteria for anterior chamber IOLs	8
<b>Annex A (informative) General elements in the clinical investigation of IOLs</b>	<b>9</b>
<b>Annex B (informative) Additional elements for the clinical investigation of TIOLs</b>	<b>14</b>
<b>Annex C (informative) Additional elements for the clinical investigation of multifocal IOLs</b>	<b>19</b>
<b>Annex D (informative) Additional elements in the clinical investigation of accommodating IOLs</b>	<b>22</b>
<b>Annex E (informative) Evaluation of post-operative adverse events and visual acuity rates</b>	<b>27</b>
<b>Annex F (informative) Clinical tests</b>	<b>31</b>
<b>Annex G (informative) Statistical methods and sample size calculations</b>	<b>37</b>
<b>Bibliography</b>	<b>42</b>

## 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 (see [www.iso.org/directives](http://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 (see [www.iso.org/patents](http://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 voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: [www.iso.org/iso/foreword.html](http://www.iso.org/iso/foreword.html).

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

This fourth edition cancels and replaces the third edition (ISO 11979-7:2014). It also cancels and replaces the first edition of ISO 11979-9:2006 and its amendment ISO 11979-9:2006/Amd 1:2014.

The main changes compared to the previous edition are as follows:

- Integration of the multifocal intraocular lens document (ISO 11979-9:2006);
- Technical updates concerning the safety and efficacy of the intraocular lens subtypes monofocal, multifocal, toric and accommodating;
- Recommendations for the clinical investigations of novel lens models; and
- The separation of guidance for intraocular lenses used in cases of aphakia, and intraocular lens used for the correction of ametropia in phakic patients.

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

## Introduction

Intraocular lenses (IOLs) are used to correct residual refractive errors in subjects who have aphakia. Such residual refractive errors typically include sphere and astigmatism, but can also include accommodation. Different designs of IOLs can be used to correct for specific refractive errors. In the case where an IOL is designed to provide more than one type of refractive correction, that IOL will have to satisfy each of the separate requirements of those correction designs.

This document provides requirements and recommendations for intraocular lens investigations of new IOL models. In the case where an IOL model is a modification of a parent IOL model, a risk analysis can be used in order to determine the appropriate level of testing.



# Ophthalmic implants — Intraocular lenses —

## Part 7:

# Clinical investigations of intraocular lenses for the correction of aphakia

## 1 Scope

This document specifies the particular requirements for the clinical investigations of intraocular lenses that are implanted in the eye in order to correct aphakia.

## 2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11979-1, *Ophthalmic implants — Intraocular lenses — Part 1: Vocabulary*

ISO 11979-10:2018, *Ophthalmic implants — Intraocular lenses — Part 10: Clinical investigations of intraocular lenses for correction of ametropia in phakic eyes*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14971, *Medical devices — Application of risk management to medical devices*

## 3 Terms, definitions and abbreviated terms

### 3.1 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

- IEC Electropedia: available at <http://www.electropedia.org/>
- ISO Online browsing platform: available at <https://www.iso.org/obp>

### 3.2 Abbreviated terms

UDVA	uncorrected distance visual acuity
UIVA	uncorrected intermediate visual acuity
UNVA	uncorrected near visual acuity
CDVA	corrected distance visual acuity
CIVA	corrected intermediate visual acuity

CNVA	corrected near visual acuity
DCIVA	distance corrected intermediate visual acuity
DCNVA	distance corrected near visual acuity

## 4 Justification for a clinical investigation

A risk analysis shall be implemented in accordance with ISO 14971. If the risk analysis identifies the need for a clinical investigation, the requirements of ISO 14155 shall apply, with additional requirements given in this document.

If a new IOL model is a modification of a parent IOL for which the safety and performance have already been established through clinical investigation in accordance with this document, then a limited or no additional clinical investigation can suffice. ISO/TR 22979<sup>[1]</sup> provides guidance in determining the need for a clinical investigation.

## 5 Ethical considerations

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

## 6 General requirements

### 6.1 General

There are four main categories of intraocular lenses that are determined by optical design:

- a) monofocal (IOL);
- b) multifocal (MIOL);
- c) toric (TIOL); and
- d) accommodating (AIOL).

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

There is a further subdivision depending on anatomic placement of the IOL:

- posterior chamber; and
- anterior chamber.

Posterior chamber lenses are placed behind (posterior to) the iris. Anterior chamber lenses are placed in front of (anterior to) the iris. Additional requirements apply in the case of anterior chamber lenses.

### 6.2 Design of a clinical investigation

#### 6.2.1 Requirements for all types of IOLs

A clinical investigation shall be designed to compare the rates of adverse events and visual acuities above defined thresholds of the model IOL to the results of historical data. [Annex A](#) provides general guidance for the design of a clinical investigation of IOLs. Historical data can be found in [Annex E](#).



### 6.2.2 Additional requirements for toric IOLs (TIOLs)

Prior to any clinical investigation of a toric intraocular lens, the rotational stability of a mechanically and geometrically equivalent non-toric version of that IOL model shall be demonstrated.

The following performance criteria for rotational stability shall be fulfilled.

The IOL rotation is defined as the difference in postoperative orientation of the meridian defined by the IOL axis indicator between that intended on the day of surgery (Form 0) and that measured at Form 4 and subsequent Forms. (See [A.3](#) for recommendations on reporting periods). The absolute value of the rotation shall be less than 10° in 90 % of the cases and less than 20° in 95 % of the cases.

Subsequently, if found necessary by risk analysis (e.g. to assess the clinical performance of low cylinder power TIOLs), a clinical investigation can be performed using the toric version of the model.

Subjects that undergo a secondary surgery to correct postoperative IOL rotational misalignment shall have their clinical results prior to the secondary surgery carried forward as the final results for that subject, and examinations scheduled later in the clinical investigation shall be performed prior to the secondary surgery, wherever possible. (See [Annex D](#).)

Additional elements for investigations of TIOLs are outlined in [Annex B](#).

### 6.2.3 Additional requirements for multifocal IOLs (MIOLs)

For multifocal designs with two or more intended foci, a clinical investigation shall evaluate the safety and performance of vision at far as well as any additional intended focal distances.

The clinical investigation plan shall include a defocus evaluation.

A phased enrolment as outlined in [Annex C](#) shall be considered.

Additional elements for MIOLs are outlined in [Annex C](#).

### 6.2.4 Additional requirements for accommodating IOLs (AIOLs)

A controlled clinical investigation of an AIOL shall evaluate the accommodative amplitude and the additional safety and performance aspects related to the risk assessment. [Annex D](#) identifies safety and performance aspects for consideration. The clinical investigation plan shall include at least one objective method to measure accommodative amplitude.

The investigation enrolment shall consist of two phases (see [Annex D](#)). The second phase shall begin only if the first phase has demonstrated that the IOL design provides an average of at least 1,0 D of objective accommodation. In order for the design to be designated as an AIOL, the overall investigation shall demonstrate objective accommodation of 1,0 D or more at the point of accommodative stability (see [Annex D](#)).

Additional elements for AIOLs are outlined in [Annex D](#).

### 6.2.5 Additional requirements for anterior chamber IOLs

A clinical investigation of an anterior chamber IOL shall evaluate the change in endothelial cell density, hexagonality and coefficient of variation of endothelial cell area, the clearance between the surfaces of the anterior chamber IOL and the posterior surface of the cornea and the iris, the anterior chamber angle (including observations of pigment and synechiae), and any additional safety and performance aspects related to the risk assessment.

## 6.3 Characteristics of clinical investigations

### 6.3.1 General

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

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

If several types of IOLs are combined, the characteristics of each IOL subtype in the combination shall be fully considered.

### 6.3.2 Characteristics to be studied for all types of IOLs

The following characteristics shall be considered:

- a) CDVA;
- b) visual acuity at all intended distances with far correction;
- c) intraocular pressure;
- d) corneal status;
- e) signs of inflammation:
  - anterior chamber cells,
  - anterior chamber flare,
  - cystoid macular oedema,
  - hypopyon, and
  - endophthalmitis.
- f) pupillary block;
- g) retinal detachment;
- h) status of anterior and posterior capsule;
- i) IOL decentration<sup>[2]</sup>;
- j) IOL tilt<sup>[2]</sup>;
- k) IOL discoloration; and
- l) IOL opacity.

### 6.3.3 Additional characteristics to be studied for TIOLs

- a) IOL rotational stability; and
- b) corneal astigmatism:
  - prior to surgery;
  - intended surgical position (Form 0); and
  - post-surgical.

**6.3.4 Additional characteristics to be studied for MIOLs**

- a) uncorrected visual acuity at all intended focal distances;
- b) contrast sensitivity;
- c) defocus evaluation;
- d) pupil size under photopic and mesopic conditions; and
- e) fundus visualization.

**6.3.5 Additional characteristics to be studied for AIOLs**

- a) objective accommodative amplitude;
- b) uncorrected visual acuity at distance, intermediate and near;
- c) visual acuity at near and intermediate using far correction;
- d) additional refraction (over distance correction) required to achieve any improvement in near visual acuity;
- e) contrast sensitivity;
- f) defocus evaluation; and
- g) pupil size.

**6.3.6 Additional characteristics applying to anterior chamber IOLs**

- a) specular microscopy;
- b) anterior chamber depth measurement; and
- c) gonioscopy.

**6.3.7 Additional characteristics**

If justified by the risk analysis, the following additional characteristics shall be considered:

- a) cycloplegic refraction;
- b) specular microscopy;
- c) gonioscopic examination;
- d) pupil size; and
- e) anterior chamber depth measurement.

**6.4 Duration of the investigations**

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

For posterior chamber IOLs that are not modifications of a model for which safety and performance data have been previously established through clinical investigation, the minimum duration of the clinical investigations shall be Form 5 (see [Annex A](#) for recommended visit window tolerances).

For anterior chamber IOLs that are not modifications of a model for which safety and performance data have been previously established through clinical investigation, the minimum duration of the clinical investigations shall be 3 years (see [Annex A](#) for recommended visit window tolerances).

For all TIOLs, a study of the non-toric version of the IOL shall be performed to ensure rotational stability through Form 4. TIOLs that are not a modification of a respective parent IOL shall require a full clinical investigation through Form 5 for posterior chamber IOLs, and 3 years duration for anterior chamber IOLs.

For TIOLs that are a modification of an IOL parent, the rotational stability assessment shall have a duration through Form 4. If a subsequent clinical investigation of the TIOL is performed, it shall also have a duration through Form 4.

For all AIOLs, the minimum clinical study duration shall be Form 5, but can require up to 3 years, based on accommodative stability.

All subjects in a clinical investigation that have not been discontinued shall complete all visits of the investigation. The clinical investigation shall be considered completed when all subjects who have been enrolled in the investigation, including subjects whose IOL was removed repositioned or replaced, have either completed follow up according to protocol or have passed the final visit window.

### 6.5 Enrolment

To minimize the risks associated with the clinical investigation of a new IOL, subject enrolment shall occur in stages. The subject data from each stage shall be evaluated and found acceptable by the sponsor and the coordinating investigator (and by the regulatory body, where applicable) prior to the continuation of the next phase of the clinical investigation. Guidance on phased enrolment is included in [Annex A](#) (monofocal IOLs), [Annex B](#) (TIOLs), [Annex C](#) (MIOLs), and [Annex D](#) (AIOLs).

A risk analysis shall be performed to determine if an earlier additional phase (before Phase 1 listed in the Annexes above) is needed to address specific safety issues associated with the IOL design.

### 6.6 Bilateral implantation

Any plans for fellow eye implantation shall be clearly described in the clinical investigation plan. Only the first eye of each subject shall be included in the primary statistical analysis. When implantation of fellow eyes is permitted, the clinical investigation plan shall specify the time period between implantation of the first eye and the fellow eye. A risk analysis shall be used to guide necessary safety and efficacy data requirements.

Bilateral implantation shall not be implemented until initial safety and performance data have been collected, evaluated and found acceptable by the sponsor and coordinating investigator (and regulatory body, where applicable).

The review of data from at least 50 eyes with six months of follow-up is recommended prior to fellow eye implantation. Risk analysis can allow an earlier implantation in fellow eyes if sufficiently justified by previous clinical experience.

### 6.7 Surgical technique

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

### 6.8 Examination and treatment of subjects

The reporting periods 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

Refer to ISO 14155.

## 6.10 Inclusion and exclusion criteria

### 6.10.1 General

The general inclusion criteria in [6.10.1.1](#) and the general exclusion criteria in [6.10.1.2](#) shall be considered. Additional criteria as given in [6.10.2](#), [6.10.3](#) and [6.10.4](#) shall be considered depending on the risk analysis for the particular IOL model.

#### 6.10.1.1 General inclusion criteria

- a) adult;
- b) cataract;
- c) calculated IOL power is within the range of the investigational IOL;
- d) signed informed consent form; and
- e) clear intraocular media other than cataract.

#### 6.10.1.2 General exclusion criteria

- a) previous intraocular or corneal surgery;
- b) traumatic cataract;
- c) pregnancy or lactation;
- d) concurrent participation in another drug or device investigation;
- e) instability of keratometry or biometry measurements; and
- f) irregular astigmatism.

Subjects shall be discontinued when certain conditions are present at the time of surgery, including:

- zonular instability;
- need for iris manipulation;
- capsular fibrosis or other opacity; and
- inability to fixate IOL in desired position.

In such cases, the subject shall be followed until the condition has stabilized.

#### 6.10.2 Additional inclusion criteria for TIOLs

- a) corneal astigmatism within the range defined in the clinical investigation plan;
- b) stability of the corneal astigmatism (for a minimum of 4 weeks); and
- c) dilated pupil size large enough to visualize TIOL axis markings postoperatively.

#### 6.10.3 Additional exclusion criteria for MIOLs

- a) more than 1 D of pre-operative corneal astigmatism.

#### 6.10.4 Additional exclusion criteria for anterior chamber IOLs

The criteria for the specific anterior chamber IOL platform shall comply with the specific intended IOL design as described in this subclause, including TIOL, AIOL and MIOL.

- a) angle abnormalities;
- b) glaucoma or ocular hypertension;
- c) angle or anterior chamber anatomy unsuitable to accept IOL design safely;
- d) minimum anterior chamber depth related to design;
- e) endothelial issues:
  - endothelial cell density less than listed in ISO 11979-10:2018, Table 1;
  - percent hexagonality of endothelial cell shape  $\geq 45$  %;
  - coefficient of variation of endothelial cell area  $< 0,45$ ;
  - any endothelial conditions putting the cornea at risk of failure.
- f) corneal oedema.

## Annex A (informative)

### General elements in the clinical investigation of IOLs

#### A.1 General

This Annex provides elements of a clinical investigation plan (CIP) which can assist in collecting data for the purpose of determining the safety and performance of all types of IOLs.

#### A.2 Investigation design and duration

##### A.2.1 General

The suggested clinical investigation design is an uncontrolled study to compare outcomes with the historical safety and performance endpoints in [Annex E](#) at the final follow-up.

NOTE 1 In case of an investigation with a concurrent control group, the number of subjects will have to be calculated to be sufficient to detect differences in the safety and performance endpoints in [Annex E](#) with similar statistical power to the study mentioned above.

NOTE 2 Any additional claims beyond those for safety and performance require separate calculations of an appropriate sample size for each of such claims.

To take into account that some subjects are lost to follow-up during the course of the clinical investigation (including deceased subjects and subjects who have the IOL explanted), enrol as a target (see also [6.4](#)):

- a) 340 subjects in the one-year investigation;
- b) 420 subjects in the three-year investigation.

If risk analysis determines that a limited clinical investigation is sufficient (see ISO/TR 22979[1]), then enrol a target of 115 subjects to achieve a goal of 100 completed subjects.

In order to minimize exposure to the risks of a new IOL, significantly larger numbers of subjects than above should not be enrolled.

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

##### A.2.2 Enrolment

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

- a) Phase 1: A maximum of 100 subjects are included for the initial investigation. 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.

In the case of the limited clinical investigation, the investigation is not phased.

### A.2.3 Standardization of procedures

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.

The minimum number of completed case report forms for each reporting period is the minimum number required for the investigation.

## A.3 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 to 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.

## A.4 Clinical tests

Slit lamp examination is performed at all Forms except Form 0 during surgery.

Uncorrected and corrected visual acuities are measured in logMAR under photopic conditions, and performed at all Forms except for Form 0 during surgery. Methods are outlined in [Annex F](#).

## A.5 Outcomes

The outcomes to be considered are those listed in [Annex E](#) for comparison with historical data.

## A.6 Data analyses

Besides comparisons with the historical data in [Annex E](#), consider the following analyses:

- a) Visual Acuity (VA) stratified by age (<65 and ≥65 years);
- b) best-case VA;
- c) VA stratified by adverse event;
- d) VA stratified by investigator;
- e) subject-by-subject analysis of reasons why subject failed to achieve 0,3 logMAR CDVA;
- f) rates of, and the causes of loss of visual acuity of 0,2 logMAR;
- g) rates of cumulative adverse events stratified by age (<65 and ≥65 years);
- h) rates of persistent adverse events stratified by age (<65 and ≥65 years);



- i) adverse events stratified by investigator;
- j) percentage of eyes that achieve intended vs. achieved SE within:
  - $\pm 0,50$  D, and
  - $\pm 1,00$  D.
- k) percentage of eyes that achieve uncorrected visual acuity within:
  - 0,0 logMAR or better, and
  - 0,3 logMAR or better.
- l) percentage of eyes that achieve corrected visual acuity within:
  - 0,0 logMAR or better, and
  - 0,3 logMAR or better.
- m) serious ocular adverse events and adverse device events.

For the primary analyses of adverse events, the primary statistical analyses is performed using only the first implanted eye for each subject; secondary analyses include all implanted eyes. For performance endpoints, the primary analyses is performed using only the first implanted eye for each subject.

## A.7 Subject accountability

The general requirements for the accountability of subjects are given in ISO 14155. Specific guidance for subject accountability at each of the post-operative visits in IOL clinical investigation designs are provided in [Table A.1](#).

**Table A.1 — Accountability by post-operative visit**

	<b>Total number</b>			
Enrolled <sup>a</sup> (N)				
Implanted <sup>b</sup> (N)				
<b>Subject status</b>		<b>Form 1 (n, %)</b>	<b>Form 2, etc. (n, %)</b>	<b>Final Form (n, %)</b>
Available for analysis <sup>c</sup>				
Discontinued <sup>d</sup>				
Missing at scheduled visit but seen later <sup>e</sup>				
Not seen but accounted for <sup>f</sup>				
Lost to follow-up <sup>g</sup>				
Active <sup>h</sup>				
<p><sup>a</sup> Enrolled — represents the total number of subjects enrolled in the investigation.</p> <p><sup>b</sup> Implanted — represents the total number of subjects implanted with the IOL.</p> <p><sup>c</sup> Available for analysis — represents the total number of subjects for whom data is available at the Form.</p> <p><sup>d</sup> Discontinued — represents the total number of subjects that have discontinued treatment prior to the Form for any reason (e.g. death or device replacement, screen failure, or discontinued following not being implanted), but does not include subjects that are lost to follow-up.</p> <p><sup>e</sup> Missing at scheduled visit but seen later — represents the total number of subjects that were seen outside the time window associated with the Form.</p> <p><sup>f</sup> 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).</p> <p><sup>g</sup> Lost to follow-up — represents the total number of subjects that have missed the Form and there is no information available about them.</p> <p><sup>h</sup> 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.</p>				

The following equation is used to determine the percent accountability for the investigation.

$$\% \text{ Accountability} = (\text{Available for analysis}) / (\text{Enrolled} - \text{Discontinued} - \text{Active})$$

Depending upon the clinical investigation, the total number of subjects might not necessarily represent the total number of eyes. However, 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.

Methods are outlined in [Annex F](#).

## **A.8 Monofocal IOL recommended examination schedule**

Use the tests and schedules outlined in [Table A.2](#) for anterior and posterior monofocal IOLs.

Table A.2 — Monofocal IOL examination schedule

Examination	Form 0		Form 1	Form 2	Form 3	Form 4	Form 5	Form 6 <sup>a</sup>	Form 7 <sup>a</sup>
	Preop	Op							
Distance UCVA	X		X	X	X	X	X	X <sup>a</sup>	X <sup>a</sup>
Distance BSCVA	X			X	X	X	X	X <sup>a</sup>	X <sup>a</sup>
Subjective refraction	X			X	X	X	X	X <sup>a</sup>	X <sup>a</sup>
IOL tilt and decentration			X	X	X	X	X	X <sup>a</sup>	X <sup>a</sup>
Slit lamp examination	X		X	X	X	X	X	X <sup>a</sup>	X <sup>a</sup>
Fundus examination with dilated pupil	X						X	X <sup>a</sup>	X <sup>a</sup>
Keratometry	X								
Pachymetry of corneal thickness	X					X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>
Axial length	X								
Anterior chamber depth	X		X <sup>a</sup>	X <sup>a</sup>					
Gonioscopic exam.	X				X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>
Intraocular pressure	X		X	X	X	X	X	X <sup>a</sup>	X <sup>a</sup>
Specular microscopy	X <sup>a</sup>				X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>
<b>Sub-studies</b>									
Clearance analysis <sup>a,b</sup>	X <sup>a</sup>				X <sup>a</sup>				
<sup>a</sup> For anterior chamber IOLs only. <sup>b</sup> See ISO 11979-10 for guidance.									

## **Annex B** **(informative)**

### **Additional elements for the clinical investigation of TIOLs**

#### **B.1 General**

The following additional elements for a TIOL clinical investigation plan (CIP) 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 TIOL is not associated with any previously approved model, then an initial study of rotational stability of a non-toric version of the new model is performed, followed by a full clinical investigation as described in [Annex A](#). This full clinical investigation may include only non-toric IOLs or a combination of TIOLs and non-toric IOLs.

Requirements for rotational stability are given in [6.2.2](#).

If risk assessment indicates the need, additional clinical investigation of the TIOL model is performed as described in [B.3](#).

#### **B.2 Rotational predictability investigation of non-toric IOLs**

A rotational predictability investigation is performed on a non-toric version of a proposed TIOL model to determine if the design is sufficiently stable to be used as a TIOL by using a test sample of non-toric IOLs with orientation marks as intended for the toric design. The positions of the IOL orientation marks are recorded by viewing the eye from anterior to posterior; negative signed values are used for counter-clockwise rotation and positive signed values are used for clockwise rotation.

The initial IOL orientation is recorded as the intended surgical position at Form 0 during surgery using a registration photograph or other technique in order to document the rotational position of the IOL. Additional orientations are measured and recorded at each Form. (See [A.3](#) for definition of Form durations.) The IOL position differences between Form 0 and Form 4 as well as between Form 0 and later Forms after Form 4 are used to determine the performance criteria.

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

- a) Documentation of the implanted IOL position (with visible IOL axis marks) taken on the day of surgery, with concurrent visible structures of the eye (in the same image) that are fixed and stable in time, and thus allow a determination of the IOL orientation of the IOL around the optical axis relative to the said fixed structures of the eye. Preferred fixed structures are limbal vessels. The pupil is dilated if necessary to visualize the IOL axis marks. Methods to measure IOL axis mark position are given in References [\[3\]](#), [\[4\]](#) and [\[5\]](#).
- b) The image analysis method, either conducted subjectively by an examiner or automatically by image analysis software, is provided to quantitatively document any changes in the IOL axis relative to the fixed eye reference structures.
- c) The rotational angle differences between the day of surgery and each of the appropriate follow-up examinations are statistically examined. The criteria to assess rotational stability are given in [6.2.2](#).

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

## B.3 Clinical investigation of TIOLs

### B.3.1 General

The following clauses describe additional assessments that is performed if deemed necessary by risk analysis (e.g. to assess the clinical performance of low cylinder power TIOLs).

### B.3.2 Investigation design

In the case where the TIOL does not have a parent IOL, a two phase study is performed. In order to evaluate a minimum of 300 implanted subjects at the final form, a summary total of 340 subjects for both phases are enrolled. The first phase enrolls 100 subjects in order to assess TIOL safety and performance. The second phase enrolls the remaining subjects, and all subjects are then followed for a minimum of one year.

In the case where the toric surface is added to a parent IOL, a Level B study with a minimum enrolled sample size of 125 unilateral eyes is performed, with the goal to complete 100 implanted eyes. At least 65 subjects who receive the TIOL with the lowest cylinder power should complete the study. Enrolment is adjusted to account for the expected lost-to-follow-up rate.

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

In the case where IOL toric cylinder powers above 1,5 D are provided, a non-controlled clinical investigation to assess the ability of the TIOL to reduce preoperative cylinder is performed.

In the case where TIOL cylinder powers of 1,5 D or below are provided, a controlled clinical investigation of the lowest cylinder power provided against a zero cylinder power IOL of the same model is performed. A minimum sample size of 65 subjects is recommended for analysis, with corneal cylinder within the range indicated for the lowest cylinder power being investigated. The statistical calculation (see [G.4.1](#)) demonstrates that a sample size of 65 implanted subjects should be sufficient to demonstrate performance.

### B.3.3 Investigation duration

The subjects are followed to Form 4.

### B.3.4 Clinical tests

Use the clinical tests and schedules outlined in [Table B.1](#).

**Table B.1 — Recommended examination schedule**

Examination	Form 0		Form 1	Form 2	Form 3	Form 4
	Preop	Postop				
UDVA	x		x	x	x	x
CDVA	x			x	x	x
SE	x			x	x	x
Slit lamp examination	x		x	x	x	x
<sup>a</sup> For subjects with aphakic anterior chamber IOLs without a parent IOL or where specular microscopy was not performed for the parent IOL. Evaluation beyond Form 4 may be necessary to adequately characterize endothelial cell changes. Refer to <a href="#">Annex F</a> for additional information.						

Table B.1 (continued)

Examination	Form 0		Form 1	Form 2	Form 3	Form 4
	Preop	Postop				
Fundus examination with dilated pupil	x		x	x	x	x
Keratometry	x				x	x
Axial length	x					
Anterior chamber depth	x					
Intraocular pressure	x					
IOL axis orientation		x	x	x	x	x
Specular microscopy <sup>a</sup>	x					x
<sup>a</sup> For subjects with aphakic anterior chamber IOLs without a parent IOL or where specular microscopy was not performed for the parent IOL. Evaluation beyond Form 4 may be necessary to adequately characterize endothelial cell changes. Refer to <a href="#">Annex F</a> for additional information.						

### B.3.5 Performance outcomes

#### B.3.5.1 Reduction in cylindrical power of the eye

“Reduction in cylindrical power of the eye” is defined as the difference between the magnitude of the “preoperative astigmatism” and the magnitude of the subjective (manifest) cylinder at the final Form (referenced to the corneal plane).

The “preoperative astigmatism” is defined as the magnitude of the keratometric cylinder.

The overall cylinder of the cornea may be influenced by the posterior corneal surface as well as the keratometric measurements of the anterior corneal surface.

#### B.3.5.2 IOL axis mark rotation

“IOL axis mark rotation” is defined as the value of the 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.

The IOL axis mark rotation is determined by using a direct measurement method. The method should have sufficient precision (2 standard deviations using signed values) to detect a five degree rotational change. Additionally, the method should adjust for head tilt and ocular torsion; for example, by axis position registration to iris details or limbal vasculature (refer to [B.2](#)).

### B.3.6 Data analyses

#### B.3.6.1 General

Use the same accountability, safety and performance analyses as outlined in [Annex A](#).

In the event of unanticipated residual or induced astigmatism, the 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.

#### B.3.6.2 Safety analyses

Assess the rate of device related secondary surgical interventions and the 95 % confidence interval on this rate (see [Annex G](#) for applicable statistical method).

### B.3.6.3 Performance analyses

#### B.3.6.3.1 Rotational stability of IOL axis mark

The position 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 TIOL axis precision suggested in this clinical annex, every effort should be made to include in the direct method reference to fixed anatomical features, such as the iris, sclera, or conjunctiva.

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

The analysis of IOL axis mark rotation as compared to the intended position at the day of surgery (Form 0) should include:

- a) absolute value of the rotation (median, maximum), and
- b) signed value of the rotation (mean, standard deviation, minimum, maximum).

#### B.3.6.3.2 Reduction in cylindrical power of the eye

Descriptive statistics for the reduction in cylindrical power of the eye (defined in B.3.5.1) at Form 4 are tabulated separately for each cylinder power. These include the mean, standard deviation, median, and maximum and minimum 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 changes are reported in such cases.

For the model with the lowest IOL cylinder power:

- a) If the lowest TIOL cylinder power is  $\leq 1,5$  D (controlled study), statistically compare the mean “reduction in cylindrical power of the eye” to the control group mean “reduction in cylindrical power of the eye”; and
- b) Characterize the “reduction in cylindrical power of the eye” with the mean and a 95 % confidence interval around the mean.

In addition to the statistical comparison in (a) for a controlled study, compare the difference between the means of the test and control arms, and compare the upper confidence limit and the lower confidence limit of the mean change (b) to a minimal clinically significant difference.

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

- c) For each 0,25 D step of preoperative keratometric cylinder, tabulate the following for each arm:
  - the proportion that showed “reduction in cylindrical power of the eye”  $\leq 0,50$  D,
  - the proportion that showed “reduction in cylindrical power of the eye”  $> 0,50$  D,
  - the proportion that showed change in absolute value “reduction in cylindrical power of the eye”  $\leq 0,50$  D,
  - the descriptive statistics for “change in cylindrical power of the eye.” (Mean, standard deviation, median, minimum, maximum), and
  - provide side-by-side comparisons of test and control results.
- d) Scatterplots with regression lines (based on Form 4 and preop data and using separate graphs for each arm of the study): Plot the “Reduction in cylindrical power of the eye” (corneal plane) vs. preoperative keratometric cylinder.

The above analysis is provided to assess the device effectiveness across the entire range of preoperative keratometric cylinder used in the study.

#### **B.3.6.3.3 Change in corneal cylindrical power**

The surgically induced change in cylinder is 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; and
- 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°).

#### **B.3.6.3.4 Additional performance analyses**

Recommended performance analyses specific to characterize the clinical performance of the TIOLs are described below:

- a) percentage of eyes that achieve UDVA within:
  - 0,0 logMAR or better, and
  - 0,3 logMAR or better.
- b) mean UDVA stratified by 0,25 D of preoperative keratometric cylinder:
  - overall, and
  - for each TIOL cylindrical power model.



## Annex C (informative)

### Additional elements for the clinical investigation of multifocal IOLs

#### C.1 General

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

#### C.2 Investigation design

The type of clinical investigation recommended is an unmasked, controlled, comparative study. Safety and performance endpoints are compared to those in [Annex E](#).

The recommended primary safety endpoint is the evaluation of the secondary surgical intervention rate related to the optical properties of the MIOL. The null hypothesis is that the study rate minus the control rate is greater than or equal to the minimally detectable difference between the two rates. The alternative hypothesis is that the study rate minus the control rate is less than the minimally detectable difference between the two rates. [Annex G](#) contains statistical recommendations for determination of the sample size to test these hypotheses.

#### C.3 Subjects

##### C.3.1 Study group

In order to obtain complete follow-up on at least 300 study subjects, approximately 340 study subjects are enrolled.

Since many of the clinical evaluations for study subjects are performed binocularly, a minimum of 150 study subjects are implanted bilaterally with the study device.

##### C.3.2 Control group

In order to obtain complete follow-up on at least 150 implanted control subjects, approximately 170 control subjects are enrolled in the study. Control subjects receive monofocal IOLs as identified in the CIP.

All the control subjects are implanted bilaterally with the control device.

##### C.3.3 Inclusion and exclusion criteria

General inclusion and exclusion criteria for an IOL investigation are given in [6.10.1](#), with additional criteria for MIOL given in [6.10.3](#).

##### C.3.4 Enrolment of subjects

To minimize the risks associated with the clinical investigation, subject enrolment occurs in stages. The data from each stage are evaluated and should be found acceptable by the sponsor, the principal investigators (and regulatory body, where appropriate) prior to proceeding to the next stage.

The following phased enrolment plan is recommended:

- a) Phase I — 10 subjects, followed for 30 d to 60 d (Form 3);

- b) Phase II — 75 additional subjects, followed for 120 d to 180 d (Form 4);
- c) Phase III — remainder of subjects.

NOTE 1 Previous clinical experience, i.e. well-documented results from clinical studies, can be used to justify faster enrolment.

NOTE 2 In cases where the MIOL design depends upon bilateral implantation, and if the monofocal analogue of the MIOL has previously been demonstrated to have performed adequately, bilateral implantation of the MIOL may begin in the initial phase of the study.

## C.4 Clinical tests

Characteristics to be considered for evaluation are given in [6.3.1](#) and [6.3.3](#). [Table C.1](#) contains a recommended examination schedule with the number of study and control subjects to be tested, whether the clinical evaluation is done monocularly or binocularly, and at which visit the clinical evaluation is performed. For reporting periods, see [Annex A](#).

The following variables are evaluated on all study and control subjects:

- a) UNVA;
- b) pupil size;
- c) subject survey; and
- d) fundus visualization.

The following evaluations are done on a smaller sample of best-case study and control subjects:

- e) defocus curves; and
- f) contrast sensitivity.

Test methods are given in [Annex F](#).

**Table C.1 — Recommended postoperative examination schedule**

					Form 0						
Study	Illumi- nation	Number of study subjects	Number of control subjects	Testing performed <sup>a</sup>	Pre- op	Post- op	Form 1	Form 2	Form 3	Form 4	Form 5
CDVA	Photopic	300	150	Monocularly Binocularly				X	X	X X	X X
DCNVA	Photopic Mesopic	300	150	Monocularly Binocularly					X	X X	X X
UDVA	Photopic	300	150	Monocularly Binocularly				X	X	X X	X X
UNVA	Photopic	300	150	Monocularly Binocularly					X	X X	X X
Pupil size	Photopic Mesopic	300	150	Monocularly	X <sup>b</sup>					X X	
Lens decen- tration and tilt	N/A	300	150	Monocularly					X	X	X
Subject survey	N/A	All available bilaterally implanted	All available bilaterally implanted	Binocularly						X	X
Fundus vis- ualization	N/A	300	None	Monocularly					X		
Sub-studies											
Defocus evaluation	Photopic	30 <sup>c</sup>	30 <sup>c</sup>	Binocularly						X	
Far contrast sensitivity <sup>d</sup>	Photopic with glare	Open <sup>e</sup>	Open <sup>e</sup>	Binocularly						X	X <sup>f</sup>
	Mesopic										
	Mesopic with glare									X	X <sup>f</sup>
<p><sup>a</sup> The testing is to be performed monocularly or binocularly as specified. If the testing is monocular, the first eye implanted should be reported in the primary analysis. Binocular testing is performed on the study group subjects who are implanted bilaterally with the MIOL and on the control group subjects who are implanted bilaterally with the control IOL.</p> <p><sup>b</sup> Preoperative pupil size only needs to be measured if needed to meet an inclusion or exclusion criterion for designs that are pupil-size dependent.</p> <p><sup>c</sup> Subjects in the defocus study should come from the 3 pupil size categories defined in the standard. If 10 subjects are not available in some pupil size categories, then the maximum number available is used.</p> <p><sup>d</sup> For each of the test conditions, the pupil sizes of the study and control subjects in the far contrast sensitivity sub-study should be representative of the pupil sizes associated with the subjects enrolled in the clinical investigation.</p> <p><sup>e</sup> A recommended sample size is not defined and is determined by the sponsor. <a href="#">Annex C</a> provides considerations for determination of the sample size.</p> <p><sup>f</sup> The testing is repeated at Form 5 for those subjects in the contrast sensitivity study that had a posterior capsulotomy after the Form 4 visit. If the subject is scheduled for a posterior capsulotomy at the Form 4 visit, contrast sensitivity testing is deferred to the Form 5 visit.</p>											

## Annex D (informative)

### Additional elements in the clinical investigation of accommodating IOLs

#### D.1 Investigation design

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

The investigation consists of two phases:

- a) Phase I: Enrol 100 subjects in a randomized, comparative investigation to assess accommodative amplitudes, followed through Form 4. If at least 1,0 D of objective accommodation is demonstrated, then the second phase may commence.
- b) Phase II: Enrol all additional randomized subjects to assess safety and to further evaluate the magnitude and consistency of the accommodative performance.

The study uses the historical data in [Annex E](#) to investigate the far visual performance and safety characteristics of the AIOL.

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

The CIP includes 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 Investigation and control groups

[Table D.1](#) lists the recommended sample sizes for investigation and control groups.

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

Implantation	Sample size	
	Investigation group	Control group
Unilateral — Phase I	50	50
Unilateral — Phase II	250	72 <sup>a</sup>
Bilateral <sup>b</sup>	100	50
<sup>a</sup> Total number of unilateral control subjects set by number needed for contrast sensitivity sub-investigation.		
<sup>b</sup> This is an optional subset of the total number of subjects.		

#### D.3 Investigation duration

The first phase of the investigation has duration to Form 4.

The total study duration should depend 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 measuring the mean change in the objective accommodative amplitude determined by within-eye analysis taken 6 months apart and demonstrating a less than 25 % decrease.

If the Phase I data analysis and risk analysis raise long-term safety concerns, longer follow-up may be needed.

The CIP should include a statement that a long-term follow-up (e.g. up to 3 years) may be necessary. It is recommended that informed consent for a three-year follow-up is obtained.

## **D.4 Clinical tests**

Use the clinical tests and schedules outlined in [Table D.2](#).

## **D.5 Outcomes**

### **D.5.1 General**

This clause outlines performance outcomes (see [D.5.2](#)) and safety outcomes (see [D.5.3](#)) considered in a clinical investigation of an AIOL.

### **D.5.2 Accommodative amplitude**

Clinical investigation includes an objective assessment of accommodation on both investigation and control eyes. A test may be selected from those described in [Annex F](#). The recommended primary effectiveness endpoint is the amplitude of accommodation. A sample size calculation is performed to ensure that the proposed number of subjects for the objectively measured amplitude of accommodation testing is 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 are optional and can be performed to further characterize the AIOL performance.

### **D.5.3 Specular microscopy**

If indicated by risk analysis, specular microscopy is performed in both investigation and control subjects. In such cases, it is performed preoperatively and at Form 4, Form 5, and if applicable, Form 6 and Form 7. Specular microscopy images are taken of the central cornea. In addition, peripheral measurements are taken if indicated by the design or placement of the AIOL. The peripheral locations to be photographed are specified based on the design and/or placement of the AIOL. Refer to [Annex F](#) for additional information.

Table D.2 — Recommended examination schedule

Examination	Illumination	Testing performed <sup>a</sup>	Number of AIOL subjects	Number of controls subjects	Reporting period							
					Pre-op	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 7
UDVA	Photopic	Monocular	300	122	X	X	X	X	X	X	X	X
		Binocular	100	50					X	X	X	X
CDVA	Photopic	Monocular	300	122	X		X	X	X	X	X	X
		Binocular	100	50						X	X	X
UNVA (fixed distance)	Photopic	Monocular	300	122				X	X	X	X	X
		Binocular	100	50						X	X	X
DCNVA (fixed distance)	Photopic	Monocular	300	122				X	X	X	X	X
		Binocular	100	50					X	X	X	X
UIVA (fixed distance)	Photopic	Monocular	300	122					X	X	X	X
		Binocular	100	50							X	X
DCIVA (fixed distance)	Photopic	Monocular	300	122					X	X	X	X
		Binocular	100	50						X	X	X
CNVA over far correction (record add power required and any improvement in resultant VA)	Photopic	Monocular	300	122								
		Binocular	100	50						X	X	X
CNVA (record add power required)	Photopic	Monocular	300	122								
		Binocular	100	50						X	X	X
Accommodative amplitude (objective)	Photopic	Monocular	100 <sup>b</sup>	100 <sup>b</sup>						X	X	X
		N/A	300	122	X		X	X	X	X	X	X
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.												
Sample size is determined from a statistical analysis with the minimum number of AIOL subjects being 100.												
Pupil size is assessed for all tests influenced by pupil size at the post-op visits specified in the pupil size row.												
Lens stability is performed according to Reference [2].												
This investigation is performed if warranted by risk analysis.												

Table D.2 (continued)

Examination	Illumination	Testing performed <sup>a</sup>	Number of AIOL subjects	Number of controls subjects	Reporting period								
					Pre-op	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 7	
Pupil size <sup>c</sup>	Photopic/mesopic	N/A	300	122	X						X		X
Fundus examination with dilated pupil	N/A	N/A	300	122	X						X		X
Slit lamp examination	N/A	N/A	300	122	X	X	X	X	X	X	X	X	X
Intraocular pressure	N/A	N/A	300	122	X	X	X	X	X	X	X	X	X
Lens stability (tilt/decentration) <sup>d</sup>	N/A	N/A	300	122		X	X	X	X	X	X	X	X
Specular microscopy <sup>e</sup>	N/A	N/A	300	122	X				X	X	X	X	X
Anterior chamber depth <sup>e</sup>	N/A	N/A	300	122	X			X	X	X	X	X	X
Gonioscopy <sup>e</sup>	N/A	N/A	300	122	X			X	X	X	X	X	X
Subject survey	N/A	N/A	300	122	X				X	X	X	X	X
Sub-studies													
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

<sup>a</sup> 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.

<sup>b</sup> Sample size is determined from a statistical analysis with the minimum number of AIOL subjects being 100.

<sup>c</sup> Pupil size is assessed for all tests influenced by pupil size at the post-op visits specified in the pupil size row.

<sup>d</sup> Lens stability is performed according to Reference [2].

This investigation is performed if warranted by risk analysis.

## D.6 Data analyses

### D.6.1 General

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

### D.6.2 Safety analyses

The following safety analyses are performed, and additional safety considerations are included based on risk analysis:

- a) endothelial cell count analysis (if applicable); and
- b) the rate of device-related secondary surgical interventions and the 95 % confidence interval on this rate.

Both the first and the second eye of each subject are included in an analysis of endothelial cell loss, adjusted for the correlation between eyes. For the primary analyses of other adverse events, the primary statistical analyses is performed using only the first implanted eye for each subject; secondary analyses includes all implanted eyes.

### D.6.3 Performance analyses

The objectively measured amplitudes of accommodation are characterized by descriptive statistics. These include, for both test and control groups the mean, standard deviation and 95 % confidence intervals, as well as detailed descriptions of the distributions. Additional statistical comparisons may be performed. In order to be considered effective, the investigational AIOL should, at the final form, demonstrate stable mean objective amplitudes of accommodation that are statistically superior to that of the control IOL. For performance endpoints, the primary analyses is performed using only the first implanted eye for each subject.

- a) accommodative amplitude (objective assessment);
- b) percentage of eyes that achieve a change of less than or equal to 1,0 D of spherical equivalent between two refractions performed at least 3 months apart;
- c) mean change in spherical equivalent between visits as determined by paired analysis;
- d) mean change in accommodative amplitude between visits at least 6 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) percent that achieve combined UDVA and UNVA of 0,7 logMAR or better to 0,0 logMAR or better in 0,1 logMAR increments; and
- k) descriptive comparisons (means and standard deviations) between the AIOL and control groups, for the 6-month postoperative distance refraction.



## Annex E (informative)

### Evaluation of post-operative adverse events and visual acuity rates

#### E.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 endpoints (SPE).

#### E.2 Background

The historical 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 4210 for adverse events and overall BCVA, and 3035 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.

#### E.3 Adverse event and visual acuity rates

The adverse event and rates of subjects with visual acuity achieving defined thresholds are provided in [Tables E.1, E.2, E.3, and E.4](#). The terms used in the tables in this annex are defined as follows:

- SPE rate: safety and performance endpoint (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 E.1 and E.2](#)).
- Minimum number of cases allowed before less than SPE rate: this is the minimum number of subjects with CDVA 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 E.3 and E.4](#)).

For example, in the case of “pupillary block” in [Table E.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 CDVA 0,3 logMAR or better in [Table E.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.

**NOTE** For adverse events not included in [Annex E](#), comparison with published literature, previous clinical experience and the investigators’ clinical judgement will be used to determine acceptability.

Table E.1 — Anterior chamber IOL adverse event rates

Adverse event		Number of subjects = 100		Number of subjects = 300	
	SPE rate %	Thresh- old rate %	Max. number of cases allowed before SPE rate exceeded	Thresh- old rate %	Max. number of cases allowed before SPE rate exceeded
<u>Cumulative:</u>					
Cystoid macular oedema	10,0	18,8	15	14,9	39
Hypopyon	0,2	3,0	1	1,4	2
Endophthalmitis <sup>a</sup>	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 <sup>b</sup>	2,6	8,5	5	5,6	13
<u>Persistent:</u>					
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
<sup>a</sup> Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.					
<sup>b</sup> Excludes posterior capsulotomies.					

Table E.2 — Posterior chamber IOL adverse event rates

Adverse event		Number of subjects = 100		Number of subjects = 300	
	SPE rate %	Thresh- old rate %	Max. number of cases allowed before SPE rate exceeded	Threshold rate %	Max. number of cases allowed before SPE rate exceeded
<u>Cumulative:</u>					
Cystoid macular oedema	3,0	8,9	6	6,0	14
Hypopyon	0,3	3,0	1	1,8	3
Endophthalmitis <sup>a</sup>	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 <sup>b</sup>	0,8	4,2	2	2,6	5
<u>Persistent:</u>					
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
<sup>a</sup> Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.					
<sup>b</sup> Excludes posterior capsulotomies.					

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

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

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

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

## E.4 Additional guidance

For the calculation of cumulative and persistent adverse event rates, the following calculations should be followed, using the primary eyes for the main analysis in each case:

- For cumulative events: The number of eyes with event/ the number of eyes enrolled;
- For persistent events: The number of eyes with event/ the number of eyes present at the final visit

For [Tables E.1](#) and [E.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 E.3](#) and [E.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 the above tables: type I error = 0,05; 80 % power; one-sided alternative. The calculated results for the adverse events ([Tables E.1](#) and [E.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 E.3](#) and [E.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.

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

where

$p$  is the rate for the SPE;

$n$  is the sample size; and

$x$  is the number of observations in 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 E.3](#) and [E.4](#)), the right-hand side of [Formula \(E.1\)](#) above would be “ $\geq 0,95$ ”,  $p$  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 F (informative)

### Clinical tests

#### F.1 Visual acuity: distance, intermediate and near

##### F.1.1 General

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

##### F.1.2 Chart distance

Distance acuity testing is done at a specified far distance, and adjusted to infinity. In order to adjust subjective refraction to infinity, adjust the measured spherical power by subtracting  $1/(\text{testing distance in metres})$ . For example, if distance testing is done at 4 m and the measured subjective refraction is  $-0,25 - 0,75 \times 090$ , then the infinity-adjusted subjective refraction would be  $-0,50 - 0,75 \times 090$ .

Near and intermediate distance acuity charts should have the angular sizes of the optotypes calibrated for the specific distance used.

For testing at a fixed distance, the chart distance is precisely defined, i.e. no head movements relative to the charts are allowed.

Intermediate visual acuity testing is performed at a distance specified in the clinical investigation plan.

The design of the visual acuity chart and testing procedures with scoring methods are described in Ferris[6].

##### F.1.3 Luminance

For photopic testing, a specific chart background luminance should be selected from 85 cd/m<sup>2</sup> to 100 cd/m<sup>2</sup>.

For mesopic conditions, a specific chart luminance of approximately 2,5 cd/m<sup>2</sup> to 3,2 cd/m<sup>2</sup> is used.

No surface (including reflective surfaces) within the subject's field of view should exceed the chart background in luminance.

Luminance is standardized among all testing centres. Additional guidance concerning luminance testing is given by the AAO[7].

##### F.1.4 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 acceptable notation include:
  - logMAR (common logarithm of MAR);

- decimal notation (reciprocal of MAR); and
- standard Snellen notation (actual test distance/test distance that would render MAR = 1).

Other forms of notation are not acceptable.

## F.2 Pupil size

Pupil size is measured at the illumination levels associated with all tests that may be influenced by pupil size. For pupil size testing at low light conditions, measurements are made with an infrared camera or light amplification equipment to increase precision and reliability, to avoid shielding the pupil from light, and to provide good pupil visibility with dark irises. Pupil measurements are made 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.

## F.3 Defocus evaluation

The purpose of defocus evaluation is to assess the useful depth of visual field with any type of IOL intended to enhance depth of field. This testing is typically performed under photopic conditions.

A defocus curve that measures visual acuity is obtained by using the CDVA, and then defocusing the image by  $-4,0$  D of sphere or greater, depending on the IOL optical design. Measure the visual acuity and then proceed to decrease the defocus in 0,5 D steps up to  $+2,0$  D, measuring the acuity at each level of defocus. Record the pupil size(s) and measurement conditions. The subjective accommodative amplitude is defined as the range of myopic spherical defocus power (in D, starting at 0,0) where the visual acuity in logMAR is less than (better than) the CDVA (zero defocus) plus 0,1 logMAR (one line). Subjective accommodation can be assessed for a monocular or a binocular condition. Testing procedures should be utilized that minimize subject fatigue as well as possible memorization of letters.

- a) Number of subjects: At least 10 bilaterally-implanted study subjects and 10 bilaterally-implanted control subjects for each of the following pupil size groups are evaluated: small ( $\leq 2,5$  mm), medium ( $> 2,5$  mm and  $< 4,0$  mm) and large ( $\geq 4,0$  mm). If 10 subjects are not available in any pupil size category, then the maximum number available is used. Only include subjects when the size of both of their pupils falls within a single range.
- b) Three best-fit defocus curves are generated, at small, medium and large pupil sizes. The best-fit curves are determined from the mean visual acuity of the study group at each defocus level.

## F.4 Accommodation measurements

### F.4.1 Objective accommodation measurement methods

#### F.4.1.1 General

At least one objective measure of accommodation by refractive change is used to compare investigation and control subjects.

A compelling accommodative stimulus is critical for eliciting the maximum amplitude of accommodative response. This is ideally high contrast letter charts or targets that are presented at real distances (as opposed to being presented optically). Visual targets should be randomized to prevent bias, fatigue and learning. 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 acuity.

### F.4.1.2 Objective refractive changes

#### F.4.1.2.1 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 ( $\sim 0$  D 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.

#### F.4.1.2.2 Autorefractors

Autorefractors provide an objective refraction (sphere, cylinder and axis) measurement. These perform optical measurements of the refractive state of the eye. The measurement is normally done with infrared light. Several measurements are 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 subject 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. Report the principle of the instrument.

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

##### a) Preparations:

- 1) Extinguish the room lights.
- 2) Align and focus instrument in accordance with manufacturer's instructions.
- 3) Sit the subject at instrument with chin on the chin-rest and head against the forehead rest.

##### b) Distance refractive measurement:

- 1) Ensure distance correction is in place by means of a spectacle or a contact lens and measure refraction [With this correction, the instrument should indicate distance spherical equivalent (or defocus converted to dioptres in the case of aberrometry) in the interval  $-0,25$  D to  $+0,25$  D].
- 2) Place fixation target at its distance calibrated position (i.e. 0 D) and ensure target illumination is switched on.

##### c) Near refractive measurement:

- 1) While keeping the subject in position at the headrest, move the fixation target to the 1 D (100 cm) position and measure refraction.
- 2) Repeat near measurements with the fixation target at, for example, the 2 D (50 cm) and 3 D (33 cm) positions.

##### d) Treatment of data:



Record the distance spherical equivalent and the near spherical equivalent for each distance assessed in the appropriate case report form (CRF), and retain the autorefractor records with the source documentation.

#### **F.4.1.2.3 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 at the time of the publication of this document 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.

#### **F.4.1.3 Objective biometric/biomechanical changes**

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 should 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 monocular responses.

### **F.4.2 Contrast sensitivity**

#### **F.4.2.1 General**

Gratings produced on either charts or monitors can be used. Charts that have been studied in the literature and have repeatability and reproducibility assessments and normative data are preferred. Use the same test system at all sites.

**NOTE** Methods to minimize high-frequency artefacts that could affect the data are to blur the outer edges of the grating and to surround all edges by a uniform field equal to the grating in space-averaged luminance. Further information about the effects of sharp edges on gratings are provided in Thornl[8].

The subject should practice the test once at photopic conditions for all spatial frequencies.

Testing is performed twice for each subject at each test condition (lighting and spatial frequency). The duplicate measures are then averaged to obtain a single measure for each subject at each test condition.

Report the results as graphs of contrast sensitivity vs. spatial frequency.

#### **F.4.2.2 Subjects**

The number of subjects to be tested is determined as described in [Annex G](#). All subjects should be best case.



Include in the CIP a description of how subjects are selected for the contrast sensitivity evaluation. For example, testing sequentially enrolled subjects that meet the best case criteria is one way to minimize selection bias.

Stratify the test results by pupil size on each 0,5 mm.

#### **F.4.2.3 Lighting conditions**

Standardize photopic and mesopic light levels, ambient illumination, chart luminance and glare source luminance across all investigators and sites. Testing is conducted at the same photopic and mesopic chart luminance levels specified for the standard acuity testing. However in addition to mesopic contrast sensitivity, photopic and mesopic contrast sensitivity testing can additionally be performed in the presence of a glare source.

Pilot studies to validate the proposed testing conditions are recommended. The minimum level of glare is the amount necessary to significantly reduce the contrast sensitivity of young adults with normal corneas and normal vision, but not so great as to completely wash out the target in these young, normal adults. A small pilot study of normal adults may be necessary to determine appropriate glare levels. The reduction in contrast sensitivity due to glare in normal adults should be a loss of about 0,10 log units at 6 cycles/degree. Subjects in this pilot study that show an increase in contrast sensitivity performance should be excluded from the analysis.

#### **F.4.2.4 Spatial frequencies**

Measure contrast sensitivity under mesopic conditions at spatial frequencies as close as possible to 1, 5, 3, 6, and 12 cycles/degree. Under photopic conditions, measure contrast sensitivity at spatial frequencies as close as possible to 3, 6, 12 and 18 cycles/degree.

#### **F.4.2.5 Indeterminate data**

Use the instructions for the test system chosen to clarify in the CIP how indeterminate data are treated in the analysis. It should be confirmed that the percentage of subjects with indeterminate data is consistent with the equipment manufacturer's population norms at the photopic and mesopic conditions.

### **F.5 Specular microscopy**

#### **F.5.1 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.

### F.5.2 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; and
- 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, at least three acceptable images are taken at each visit. At the pre-operative and the Form 4 specular microscopy visits, there should be six images taken of the given area of the cornea, and the mean density from three of the six 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.

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, then the sponsor should include in the CIP a method 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. Have a back-up technician who is trained 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.

## Annex G (informative)

### Statistical methods and sample size calculations

#### G.1 Definition of symbols

[Table G.1](#) lists symbols used in sample size and other calculations.

**Table G.1 — Symbol definitions**

<b>Parameters and statistics in normal distribution</b>	
<b>Symbol</b>	<b>Description</b>
$Z$	standard normal variable (units of standard deviations)
$\mu$	population mean
$\sigma$	population standard deviation
$N$	sample size
$\bar{x}$	sample mean
$\pi$	population proportion
$P$	sample proportion
<b>Hypothesis testing symbols</b>	
<b>Symbol</b>	<b>Description</b>
$H_0$	null hypothesis
$H_0: \mu \leq 0$	a logical statement to be read “The null hypothesis is that the mean, $\mu$ , is less than or equal to zero”
$H_1$	alternative hypothesis
$\alpha$	the probability of falsely rejecting the null hypothesis. This is also referred to as the “significance level” for the hypothesis test.
$\beta$	the probability of falsely accepting the null hypothesis
$1-\beta$	the statistical “power” of the hypothesis test
$\delta$	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 %
$Pr\{X > x \mid n\}$	a logical probability statement to be read “the probability that $X$ is greater than $x$ for the condition of sample size $n$ ”

**Table G.2 — Normal quantiles to use in formulae**

$\alpha$ or $\beta$	$(1-\alpha)$ or $(1-\beta)$	$z_{1-\alpha}$ or $z_{1-\beta}$
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

## G.2 Sample size calculations

### G.2.1 General

A sample size should be adequate to evaluate the primary endpoint selected based on risk analysis.

### G.2.2 Example: Sample size calculation for rate of secondary surgical re-intervention

As an example, the recommended primary safety endpoint for MIOLs is the evaluation of the secondary surgical re-intervention rate related to the optical properties of the MIOL. Since the rate of this adverse event in the control population is expected to be low (about 0,1 %), sample sizes of at least 300 study subjects (300 first implanted eyes) and 150 prospective control subjects are anticipated to allow adequate precision (minimal detectable difference equal to 1,4 %.)

The null hypothesis ( $H_0$ ) is that the test rate ( $p_t$ ) minus the control rate ( $p_c$ ) is greater than or equal to the minimally detectable difference ( $\delta$ ) between the two rates. The alternative hypothesis ( $H_1$ ) is that the test rate ( $p_t$ ) minus the control rate ( $p_c$ ) is less than the minimally detectable difference ( $\delta$ ) between the two rates.

$$H_0: p_t - p_c \geq \delta$$

$$H_1: p_t - p_c < \delta$$

The following assumptions are recommended for the sample size calculation: an assumed control rate ( $p_c$ ) and test rate ( $p_t$ ) of 0,001, a minimally detectable difference ( $\delta$ ) of 0,014,  $\alpha = 0,05$ , 80 % power, and a one-sided alternative. Sample size can be calculated using the method of Farrington and Manning<sup>[9]</sup>. Note that this sample size calculation assumes that Formula 3 and method 3 of Farrington and Manning will be used to test for non-inferiority.

## G.3 Sample size guidance for sub-studies

### G.3.1 General

For non-inferiority hypothesis testing for studies that compare study and control eyes of different subjects, the sample size required for two means from a normal sample can be determined from the following formula from Lin<sup>[10]</sup>:

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

The subscript “t” refers to treatment (study) and the subscript “c” refers to the control. Usually the population means for the two groups are assumed equal (i.e.  $\mu_t - \mu_c = 0$ ). 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.

The sample size formulae for treatment differences are based on solving the probability statement:

$$1 - \beta = \Pr[L_{\text{icl}} > -\delta]$$

for the sample size. For example, non-inferiority in a two-sample comparison of means solves this formula for the sample size (Lin<sup>[10]</sup>):

$$\begin{aligned} 1 - \beta &= \Pr[L_{\text{icl}} > -\delta] \\ &= \Pr\left[\left(\bar{x}_t - \bar{x}_c\right) - z_{1-\alpha} \sqrt{2\sigma^2/n} > -\delta\right] \end{aligned}$$

where  $L_{\text{icl}}$  is the lower confidence limit.

The resulting sample size formulae have boundary conditions for the expected values and non-inferiority margins. If the boundary conditions are not met, then the probability statement above should be analysed directly by numerical methods.

Also note that if the non-inferiority margin is set to zero, then these sample size formulae simplify into usual sample size formulae for one-sided hypothesis tests. In all cases, the sample size should be rounded up to the next largest integer.

[Table G.2](#) provides a convenient list of standard normal quantiles that are used in the examples.

## G.3.2 Contrast sensitivity

### G.3.2.1 General

Contrast sensitivity losses should be determined by comparing a group of study subjects with a group of control subjects.

In order to calculate sample size using the above formulae, the acceptable difference between means (non-inferiority margin), the standard deviation, it is necessary to choose the power level and the confidence interval. Values for these parameters should be chosen based on experience or published literature.

### G.3.2.2 Example

Consider a study comparing a group of study subjects with a group of control subjects. Assume a power of 90 % ( $\beta = 0,100$ ) with a 95 % confidence interval ( $\alpha = 0,050$ ). The detectable difference has been selected at one half the contrast sensitivity loss that is typically considered to be clinically significant. The non-inferiority margin ( $\delta$ ) has been set at one half of the contrast sensitivity loss that is typically considered to be clinically significant for an individual subject. Typically, losses of 0,3 log units are considered to be clinically significant when they occur at two or more spatial frequencies. Therefore, this example for sample size estimation allows for a detectable difference of 0,15 log units in the mean values between the multifocal and control groups. The 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 study conditions (e.g. testing equipment, lighting conditions). The manufacturer should choose the expected standard deviation based on literature and/or experience.

Solving for this formula:

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

Therefore, 122 study eyes and 122 control eyes would be required for the contrast sensitivity sub-study. With 122 subjects per group, there is a 90 % probability that a one-sided 95 % confidence interval between the group means would be less than 0,15 log units.

## G.4 Sample calculations specific for TIOLs

**G.4.1** Sample size calculation for the analysis of “Reduction in cylindrical power of the eye” (see [B.3.5.1](#)) for a study without a control (all TIOL 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 must account for the normality or non-normality of data distribution.

The following formula can be used to estimate the number of subjects in this “lowest cylinder power” sub-group. The formula 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.”

$$n = \sigma^2 \left( \frac{Z_{1-\alpha/2}}{w} \right)^2$$

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), and  $Z_{1-\alpha/2} = Z_{0,975} = 97,5\text{th percentile of the normal distribution} = 1,96$ ;
- $\sigma$  is the standard deviation of the “reduction in cylindrical power”;
- $w$  is the desired half-width of 95% confidence interval estimate, and it is assumed that  $w = 0,20$  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:

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

Thus, for the “lowest toric cylindrical power” sub-group, the minimum recommended sample size should be 65 subjects.

**G.4.2** Sample size calculation for statistical comparison of “reduction in cylindrical power of the eye” in controlled study TIOLs.

For TIOLs, the “reduction in cylindrical power of the eye” (see [B.3.5.1](#)) in the TIOL investigation group and the control (non-TIOL) group is compared at the final visit. This should be done for the “lowest cylindrical power” sub-group. 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:

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

The alternative hypothesis is:

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

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 2 arms that you are 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.

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