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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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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO document 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).

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For an explanation of 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 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*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 170, *Ophthalmic optics,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement)

This fifth edition cancels and replaces the fourth edition (ISO 11979-7:2018), which has been technically revised. The changes related herein for updating the document to the fifth edition apply to devices that will enter the marketplace after the date of publication of the fifth edition and are not designed or meant to limit any devices currently approved and marketed, nor those devices in the process of approval.

The main changes are as follows:

— development of definitions of non-accommodative posterior chamber “Simultaneous Vision Range” (SVIOL) lenses that include the subtypes of MIOL (Multifocal), EDF (Extended Depth of Focus) and FVR (Full Visual Range) IOLs, and defining each of these IOL types to allow differentiation among the lens types based on clinical and safety performance measures;

— establishment of guidelines for clinical testing of newly defined IOL types as listed above as well as related novel lens types, with alignment of testing methodologies among the lens types;

— ISO 11979-1, ISO 11979-2, ISO 11979-4 and ISO/TR 22979 are under revision and, when published, will be aligned with this edition of ISO 11979-7.

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

Any feedback or questions on this document should be directed to the user’s national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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 may also correct for a lack of 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, *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 and 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 terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.2 Abbreviated terms

UDVA	uncorrected distance visual acuity
UIVA	uncorrected intermediate visual acuity
UNVA	uncorrected near visual acuity
BSCVA	best spectacle corrected visual acuity
CDVA	corrected distance visual acuity
CS	contrast sensitivity

CNVA corrected near visual acuity

DCIVA distance corrected intermediate visual acuity

DCNVA distance corrected near visual acuity

SE spherical equivalent refraction

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 shall suffice.

ISO/TR 22979[2] provides guidance in determining the need for a clinical investigation. The outcomes of optical evaluation performed according to in ISO 11979-2[1] can be used to include or exclude characteristics to be studied in 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 and/or clinical characteristics or performance:

a) monofocal (IOL);

b) toric (TIOL);

c) simultaneous vision lens (SVIOL): non accommodative lenses of three sub-categories that provide simultaneous vision at multiple distances with EDF and FVR IOLs classified as non-inferior to monofocal lenses at far:

   — multifocal (MIOL); lens implants that emphasize optical and functionally useful acuity levels at far, but when compared to the monofocal control lens, also have improved optical and clinical performances at near focal distances. Multifocal lenses (MIOLs) have additional requirements for near vision;

   — extended depth of focus (EDF IOL); lens implants that emphasize optical and functionally useful acuity levels at far but also from far through intermediate focal distances. Extended depth of focus lenses (EDF IOLs) have additional requirements for intermediate vision;

   — full visual range IOL (FVR IOL) lens implants that emphasize optical and functionally useful acuity levels at far but also from far through intermediate and up to near focal distances. Full visual range lenses (FVR IOLs) have additional requirements at intermediate and near vision;

d) Accommodating (AIOL).

The same basic requirements apply to all of the IOL types. Additional requirements apply to TIOL, SVIOL, AIOL and anterior chamber IOLs.

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 IOL

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. The requirements of Annex A shall apply 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 (TIOL)

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 to be performed 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 Simultaneous Vision IOL (SVIOL) including MIOL, EDF and FVR lenses

6.2.3.1 General

For SVIOL optical designs, a clinical investigation shall evaluate the safety and performance of vision at far as well as any additional intended defined focal distances (e.g., intermediate and/or near). Clinically significant acuity shall be defined as ≤ 0,20 logMAR. All visual acuity items in the table relate to mean monocular photopic visual acuity.

Intermediate visual performance shall be assessed with best distance correction at 66 cm. Near visual performance shall be assessed with best distance correction at 40 cm. Additional testing distances may be used based on the lens design.

In order to minimize pseudo-accommodation, the monofocal IOL used for the control group should be aspheric, commercially available and one for which the selection has been justified.

For all types of SVIOLs, depth of focus testing shall be performed as described in F.3. Specifically for EDF IOLs, such testing is considered a performance requirement and shall meet the criterion listed in Table 1.

Visual acuity performance necessary to meet the requirements in Table 1 shall be obtained using visual acuity charts at distances listed in Table 1, or taken from the depth of focus curve which is generated as

described in F.3. The full depth of focus curve as described in F.3 shall be used to characterize the IOL performance with sufficient precision for inclusion in the labelling of the SVIOL.

The specific effectiveness requirements are related to the type of SVL as listed Table 1 shall be met.

Table 1 — Additional requirements for simultaneous visions IOLs

Category	FAR	INTERMEDIATE (66 cm)	NEAR (40 cm)
SVIOL all types	Δ (mesopic CS) ≤ 0,3 log units at any frequency[a]		
MIOL	CDVA ≤ 0,20 logMAR[b]		DCNVA superior to control
EDF IOL	CDVA non-inferior to control 0,10 logMAR level	DCIVA ≤ 0,20 logMAR	
EDF IOL		DCIVA superior to control	
EDF IOL	Negative defocus range at the 0,20 logMAR threshold is ≥0,5 D greater than control[c]		
EDF IOL	DCVA at 1,0 m ≤ 0,20 logMAR		
FVR IOL	CDVA non-inferior to control 0,10 logMAR level		
FVR IOL		DCIVA ≤ 0,20 logMAR	DCNVA ≤ 0,20 logMAR
FVR IOL		DCIVA superior to control	DCNVA superior to control
FVR IOL	DCVA at 1,0 m and 50 cm ≤ 0,20 logMAR		

a. Δ (mesopic CS) is the difference of the mean contrast sensitivity of the test IOL group minus the mean contrast sensitivity of the control IOL group, each tested under monocular conditions without glare.

b. Visual performance shall meet or exceed 0,20 logMAR in order to prevent performance values to be rounded down to 0,20 logMAR.

c. Refer to Annex F for clinical testing and related references. Visual acuity performance necessary to meet the requirements in Table 1 may be obtained using visual acuity charts at distances listed in Table 1 or taken from the defocus curve which was generated as described in F.3. The full defocus curve as described in F.3 is required to characterize the defocus performance with sufficient precision for inclusion in the labelling for the SVIOL.

6.2.3.2 Depth of focus testing

Depth of focus evaluations shall be performed on all SVIOL types. See Annex F for additional guidance.

6.2.3.3 Safety requirements

The mean mesopic monocular far contrast sensitivity (without glare) for all SVIOL shall be no worse than 0,3 log units below that of the control at any test spatial frequency. Annex C identifies additional safety and performance requirements for consideration.

NOTE The 0,3 log unit at one spatial frequency is from review of the *Summary of Safety and Effectiveness Documents (SSED's)* of approved MIOL's[3].

6.2.4 Additional requirements for accommodating IOLs (AIOL)

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. Annex F includes depth of focus testing guidance. The clinical investigation plan shall include at least one objective method to measure accommodative amplitude.

The investigation enrollment 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 IOL

The following characteristics shall be considered for all types of IOLs:

a) CDVA;

b) manifest (subjective) refraction;

c) visual acuity at all intended distances with far correction;

d) intraocular pressure;

e) corneal status;

f) signs of intraocular inflammation:

- anterior chamber cells;
- anterior chamber flare;
- cystoid macular oedema;
- hypopyon; and
- endophthalmitis;

g) pupillary block;

h) retinal detachment;

i) status of anterior and posterior capsule;

j) IOL decentration[4];

k) IOL tilt[4];

l) IOL discoloration;

m) IOL opacity;

n) glistenings in IOL;

o) visualization of posterior pole through IOL.

6.3.3 Additional characteristics to be studied for toric IOL

The following additional characteristics shall be considered for toric IOLs:

a) IOL rotational stability, and

b) measured surgical position (Form 0); and pre and post surgical corneal astigmatism.

6.3.4 Additional characteristics to be studied for SVIOLs

The following additional characteristics shall be considered for SVIOLs:

a) depth of focus testing;

b) uncorrected visual acuity at far and intermediate and/or near, as applicable to the type of IOL;

c) intermediate and/or near visual acuity with best distance correction, as applicable to the type of IOL;

d) patient reported outcome (PRO) survey to assess visual symptoms related to the optical properties of the IOL for bilateral implantation of SVIOL;

e) rate of secondary surgical interventions;

f) far contrast sensitivity.

6.3.5 Additional characteristics to be studied for accommodating IOL

The following additional characteristics shall be considered for accomodating IOLs:

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) far contrast sensitivity;

f) pupil size;

g) PRO survey to assess visual symptoms related to the optical properties of the IOL;

h) rate of secondary surgical interventions.

6.3.6 Additional characteristics applying to anterior chamber IOLs

The following additional characteristics shall be considered for anterior chamber IOLs:

a) specular microscopy;

b) anterior chamber depth measurement;

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;

e) anterior chamber depth measurement.

6.4 Duration of the investigations

Consult ISO/TR 22979[2] for guidance on investigation duration for modifications of lens models for which safety and performance have previously been established through clinical investigation.

For all types of 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, an investigation of the non-toric version of the IOL shall be performed to ensure rotational stability through Form 4. Toric IOLs 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 SVIOL that are a modification of an IOL parent, the minimum duration of the clinical investigation shall be through Form 4.

For all AIOLs, the minimum clinical investigation 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 IOL), Annex B (TIOL), Annex C (SVIOL), and Annex D (AIOL).

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 at Form 4 shall be performed 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 shall be as 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

See ISO 14155.

6.10 Inclusion and exclusion criteria

6.10.1 General

The general inclusion criteria in 6.10.2 and the general exclusion criteria in 6.10.4 shall be considered. Additional criteria as given in 6.10.3, 6.10.5 and in 6.10.6 shall be considered depending on the risk analysis for the particular IOL model.

6.10.2 General inclusion criteria

The following general inclusion criteria shall be considered:

a) adult;

b) cataract;

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

d) signed informed consent form;

e) clear intraocular media other than cataract.

6.10.3 Additional inclusion criteria for toric IOL

The following inclusion criteria for toric IOLs shall be considered:

a) corneal astigmatism within the range defined in the clinical investigation plan;

b) stability of the corneal astigmatism (for a minimum of 4 weeks);

c) dilated pupil size large enough to visualize TIOL axis markings postoperatively.

6.10.4 General exclusion criteria

6.10.4.1 General exclusion criteria before surgery

The following general exclusion criteria shall exclude patients prior to surgery:

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;

f) history of intraocular inflammation;

g) Subjects who may be reasonably expected to require a secondary surgical intervention at any time during the investigation (other than YAG capsulotomy);

h) gonioscopic abnormalities;

i) irregular astigmatism.

6.10.4.2 General exclusion criteria at the time of surgery

Subjects who do not meet exclusion criteria describe in 6.10.4.1 and are enrolled in the study may present findings during surgery that preclude inclusion of performance data in the investigation and thus need to be excluded from data collection post operatively. The following general exclusion criteria shall be considered during surgery:

— zonular instability;

— need for iris manipulation;

— capsular fibrosis or other opacity;

— inability to fixate IOL in desired position.

If the IOL has touched the eye, it should be noted if the reason for exclusion is related to the IOL itself and/or any insertion device (e.g. IOL or insertion device defect causing capsular damage, malfunction of insertion device). In cases where the IOL has touched the eye, the subject should be followed, for safety, until completion of the investigation.

6.10.5 Additional exclusion criteria for simultaneous vision IOL

Subjects shall not have more than 1 D of pre-operative corneal astigmatism.

6.10.6 Additional exclusion criteria for anterior chamber IOL

The criteria for the specific AC 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 ≤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
(normative)

General elements in the clinical investigation of IOLs

A.1 Overview

This annex provides elements of a clinical investigation plan (CIP) that 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 uncontrolled and designed 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 should be calculated to be sufficient to detect differences in the safety and performance endpoints in Annex E with similar statistical power to the investigation 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), 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 of a monofocal IOL using historical safety and performance endpoints 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 or more since the prior form evaluation;

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:

— ±0,50 D; and

— ±1,00 D.

k) percentage of eyes that achieve uncorrected visual acuity within:

— 0,0 logMAR or better; and

— 0,2 logMAR or better.

l) percentage of eyes that achieve corrected visual acuity within:

— 0,0 logMAR or better; and

— 0,2 logMAR or better.

m) serious ocular adverse events and adverse device events.

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

----------	Total number	----------	----------	----------
Enrolled[a] (N)		----------	----------	----------
Implanted[b] (N)		----------	----------	----------
Subject status	----------	Form 1 (n, %)	Form 2, etc. (n, %)	Final Form (n, %)
Available for analysis[c]	----------			
Discontinued[d]	----------			
Missing at scheduled visit but seen later[e]	----------			

[a] Enrolled — represents the total number of subjects enrolled in the investigation.

[b] Implanted — represents the total number of subjects implanted with the IOL.

[c] Available for analysis — represents the total number of subjects for whom data is available at the Form.

[d] 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.

[e] Missing at scheduled visit but seen later — represents the total number of subjects that were seen outside the time window associated with the Form.

[f] 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).

[g] Lost to follow-up — represents the total number of subjects that have missed the Form and there is no information available about them.

[h] 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.

Table A.1 *(continued)*

Not seen but accounted for[f]	----------			
Lost to follow-up[g]	----------			
Active[h]	----------			

[a] Enrolled — represents the total number of subjects enrolled in the investigation.

[b] Implanted — represents the total number of subjects implanted with the IOL.

[c] Available for analysis — represents the total number of subjects for whom data is available at the Form.

[d] 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.

[e] Missing at scheduled visit but seen later — represents the total number of subjects that were seen outside the time window associated with the Form.

[f] 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).

[g] Lost to follow-up — represents the total number of subjects that have missed the Form and there is no information available about them.

[h] Active — represents the total number of subjects that have not reached the time associated with the Form. The investigation at the Form is considered completed when the number of active subjects is zero.

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

% Accountability = (Available for analysis)/(Enrolled – Discontinued – 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

	Form 0								
Examination	Preop	Op	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6[a]	Form 7[a]
Distance UCVA	X		X	X	X	X	X	X[a]	X[a]
Distance BSCVA	X			X	X	X	X	X[a]	X[a]
Subjective refraction	X			X	X	X	X	X[a]	X[a]
IOL tilt and decentration			X	X	X	X	X	X[a]	X[a]
Slit lamp examination	X		X	X	X	X	X	X[a]	X[a]
Fundus examination with dilated pupil	X						X	X[a]	X[a]
Keratometry	X								
Pachymetry of corneal thickness	X					X[a]	X[a]	X[a]	X[a]
Axial length	X								
Anterior chamber depth	X		X[a]	X[a]					
Gonioscopic exam	X				X[a]	X[a]	X[a]	X[a]	X[a]

[a] For anterior chamber IOLs only.

[b] See ISO 11979–10 for guidance.

Table A.2 *(continued)*

	Form 0								
Examination	Preop	Op	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6[a]	Form 7[a]
Intraocular pressure	X		X	X	X	X	X	X[a]	X[a]
Specular microscopy	X[a]				X[a]	X[a]	X[a]	X[a]	X[a]
Corneal topography/ tomography	X								
Sub-studies									
Clearance analysis[a,b]	X[a]				X[a]				

[a] For anterior chamber IOLs only.

[b] See ISO 11979–10 for guidance.

Annex B
(informative)

Additional elements for the clinical investigation of toric IOLs

B.1 Overview

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 an investigation 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 investigation 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 IOL

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 measured surgical position at Form 0 at the end of 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. 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 final 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 [5], [6] and [7];

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 final 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 toric IOLs

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 investigation 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 enrols 100 subjects in order to assess TIOL safety and performance. The second phase enrols 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 investigation with a minimum enrolled sample size of 115 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 investigation. 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

	Form 0					
Examination	Preop	Postop	Form 1	Form 2	Form 3	Form 4
UDVA	X		X	X	X	X
CDVA	X			X	X	X
SE	X			X	X	X
Slit lamp examination	X		X	X	X	X
Fundus examination with dilated pupil	X		X	X	X	X
Keratometry	X				X	X

[a] 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 Annex F for additional information.

Table B.1 *(continued)*

	Form 0					
Examination	Preop	Postop	Form 1	Form 2	Form 3	Form 4
Axial length	X					
Anterior chamber depth	X					
Intraocular pressure	X					
IOL axis orientation		X	X	X	X	X
Specular microscopy[a]	X					X

[a] 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 Annex F 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 manifest (subjective) 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 related to the optical properties of the lens 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 [5], [6] and [7]. 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 ≤1,5 D (controlled investigation), 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 investigation, 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 percentage of eyes receiving TIOL that showed a "reduction in cylindrical power of the eye" <0,50 D;

   — the percentage of eyes receiving TIOL that showed a "reduction in cylindrical power of the eye" of >0,50 D;

   — the percentage of eyes receiving TIOL that showed a change in absolute value "reduction in cylindrical power of the eye" ≤+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 investigation): 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 investigation.

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 simultaneous vision (SVIOL) IOLs

C.1 Overview

In this annex, guidance is given on the design of the clinical investigation to assess the safety and performance of posterior chamber SVIOL (Simultaneous Vision Lens) IOLs and in analysing the data from that investigation.

In cases where the SVIOL is a modification of a previously approved monofocal IOL, a clinical investigation of 100 bilaterally implanted SVIOL subjects and a minimum of 100 monofocal bilateral control subjects followed to Form 4 can be sufficient to assess the safety and performance of the SVIOL.

In cases where there is no previously approved monofocal parent for the SVIOL, the studies described below should be integrated into clinical design, using 300 subjects in the investigational lens group plus 100 subjects in the control lens group, all followed for 1 year and compared with the results of an aspheric monofocal IOL that is commercially available and for which the selection has been justified.

C.2 Investigation design

C.2.1 General

The objectives of the clinical investigation are to determine the safety and effectiveness of the SVIOL. The recommended primary safety assessments and analysis are provided in C.5.2. In addition to the safety analyses recommended in Annex E, the investigation should characterize the rate of adverse events that may be specifically related to the design features of the SVIOL, and any significant events not listed in Annex E. In addition, key safety endpoints should include contrast sensitivity and corrected distance visual acuity. Key effectiveness endpoints should include visual acuity measurements at various distances and conditions.

The investigation is designed to determine the near and/or intermediate visual performance relative to a functionally useful acuity level (i.e. 0,2 logMAR) for the SVIOL compared to the control monofocal IOL. The SVIOL will qualify for one of three types of IOLs (i.e. MIOL, EDF IOL or FVR IOL) based on its clinical performance at far, intermediate and near distances. The investigation is also designed to assess any decrease in corrected distance visual acuity and contrast sensitivity of the SVIOL as a result of the enhanced visual acuity at intermediate and/or near distances.

The clinical investigative plan should include a description of the methods used to minimize potential for bias (e.g., age-matching, masking, randomization). The protocol should include a thorough description of the methodology used in the depth focus testing, including details of instructions given to technicians and subjects that help to minimize bias of the measurement method.

Investigators should implant the same monofocal IOL (the parent lens if one exists) into all control eyes, using an aspheric monofocal IOL that is commercially available and for which the selection has been justified. Subjects should be masked throughout the study and examiners should be masked for key test procedures such as visual acuity and manifest (subjective) refraction.

The clinical investigation plan (CIP) should describe how subject visits in between reporting periods will be reported and analysed.

The CIP should specify that each investigator should contribute a minimum of 20 test subjects to the total investigation population, but not more than 25 % of the subjects.

The lost to follow-up subjects should comprise less than 10 % of the total investigational population after one year or at the final form, if longer than one year.

C.2.1.1 Design for a simultaneous vision IOL without an approved monofocal parent

For an SVIOL without an approved monofocal parent, there should be an initial Phase 1 to assess the safety and effectiveness of the device with unilateral implantation of the SVIOL. Phase 1 should be randomized in a 3:1 ratio for approximately 72 total test and control subjects. Phase 2 should then proceed with the same 3:1 randomization in order to achieve the balance of 300 bilaterally implanted SVIOL and 100 control subjects. The bilateral implantation should permit appropriate evaluation of visual disturbances. Subjects who were unilaterally implanted with SVIOL in Phase 1 can then in Phase 2 receive the SVIOL in the fellow eye.

C.2.1.2 Design for a simultaneous vision IOL with an approved monofocal parent

For a simultaneous vision IOL with a monofocal parent, a prospective, controlled, randomized, masked (subject and examiner), bilaterally implanted, multi-centre trial of 100 subjects in the SVIOL group and 100 subjects in the control group should be appropriate. The adverse events are compared to the safety and performance endpoints described in Annex E.

C.2.2 Investigation duration

An investigation duration of 1 year (Form 5) should be adequate for SVIOLs without an approved parent. An investigation duration through Form 4 is adequate for SVIOLs that have an approved parent IOL.

C.3 Subjects

The following sections describe the characteristics of the investigation and the control groups.

C.3.1 Test group

For an SVIOL that is a modification of a parent IOL, the existing clinical data from the parent IOL mitigates risk. As such, at least 115 test subjects are enrolled in order to obtain complete follow-up for at least 100 test subjects. Since bilateral implantation is expected in clinical use, all study subjects are implanted bilaterally with the study device.

For an SVIOL that is not a modification of a parent IOL, the study is phased as per C.2.1.1 and a minimum of 340 test subjects are implanted bilaterally in order to obtain complete follow-up on at least 300 test subjects.

C.3.2 Control group

For each of the SVIOL investigations (with and without a parent IOL), at least 115 control subjects are enrolled and bilaterally implanted with a monofocal control IOL (as identified in the CIP), thus providing at least 100 bilaterally implanted control subjects who complete follow-up for each comparison.

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 SVIOL are given in 6.10.5.

C.3.4 Enrolment of subjects

For an SVIOL without an approved parent monofocal lens, enrolment should be in two phases:

Phase 1: Approximately 72 subjects randomized in a 3:1 manner to receive unilateral implantation of the SVIOL and the control IOL.

Subjects should complete the Form 4 visit before phase 2 is entered.

Phase 2: Randomization of subjects in a 3:1 manner for bilateral IOL implantation with 300 subjects receiving SVIOL and 100 subjects receiving control IOL.

For an SVIOL with an approved parent monofocal lens: The investigation is a single-phase investigation through Form 4 with 100 bilaterally implanted subjects in the SVIOL arm and 100 bilaterally implanted subjects in the control arm.

C.4 Clinical tests

C.4.1 General

Characteristics to be considered for evaluation are given in 6.3.2 and 6.3.4. Table C.1 contains a recommended examination schedule for an SVIOL that is a modification of a parent IOL with the illumination level, whether the clinical evaluation is done monocularly or binocularly, and at which visit the clinical evaluation is performed. Reporting periods are listed in Annex A.

C.4.2 Evaluation of variables for all study and control subjects

— UDVA – photopic;

— CDVA – photopic;

— depth of focus testing where indicated – monocular (binocular testing optional);

— manifest (subjective) refraction;

— subject PRO survey;

— IOP;

— slit lamp exam;

— dilated fundus exam (includes evaluation of clarity of fundus image);

— keratometry;

— corneal topography or tomography;

— pupil size – photopic and mesopic;

— axial length measurement;

— lens stability;

— anterior chamber depth;

— gonioscopy if determined by risk analysis;

— contrast sensitivity – mesopic, mesopic with glare (photopic with glare if needed).

C.4.3 Evaluation of Variables if applicable to the SVIOL IOL design

Testing under photopic conditions:

— UIVA;

— UNVA;

— DCIVA;

— DCNVA.

Testing under mesopic conditions:

— CDVA;

— DCIVA;

— DCNVA.

Test methods are given in Annex F.

C.5 Data analysis

C.5.1 General

In addition to the safety and effectiveness analyses described in Annex A, the following additional analyses are recommended.

C.5.2 Safety analyses

Safety analyses should be performed separately for primary eyes for the analyses below and "all eyes" (including fellow eyes) for adverse events and CDVA.

a) For each arm, provide the rate of secondary surgical interventions related to the optical properties of the lens and provide a 1-sided lower 95 % confidence interval. Rates should be provided separately for primary eyes and for "all eyes".

   NOTE A secondary surgical intervention (SSI) related to the optical properties of an SVIOL is defined as an SSI due to subject intolerance of visual symptoms that are not adequately improved by spectacle correction. The investigators should apply this definition to classify each SSI ("related" or "not related" to the optical properties).

b) Report the rates of all types of adverse events and statistically compare rates for ISO SPE event categories to the ISO 11979-7 historical control rates. (For non-SPE types of adverse events, provide rates and 2-sided 95 % confidence intervals.) Rates should be provided separately for primary eyes and for "all eyes".

   NOTE Nd-YAG capsulotomies are considered a non-SPE type of adverse event.

c) Log contrast sensitivity analysis (mesopic without glare) in the "primary eyes":

   — report between-group mean difference in log contrast sensitivity with 90 % non-parametric confidence interval for each spatial frequency;

   — provide descriptive statistics for the log contrast sensitivity for each group (mean; standard deviation; median; 0th, 25th, 50th, 75th, and 100th percentiles) and for each spatial frequency;

   — report the number and frequency of eyes that can and cannot see the reference pattern for each spatial frequency;

   — report the overall number and incidence of eyes for which the mesopic contrast sensitivity at far for the SVIOL is more than 0,3 log units worse than that of the mean contrast sensitivity of the control IOL for a given spatial frequency.

e) Assessment of investigator ability to clinically visualize fundus (and where appropriate, use fundus imaging to assess fundus health).

C.5.3 Effectiveness Analysis

C.5.3.1 General

The primary effectiveness endpoints are related to the type of Simultaneous Vision IOL being investigated. All effectiveness analyses shall be performed using data from the final visit. Inferential statistical analyses

shall be done on primary eyes. Descriptive statistics shall be provided separately for both primary eyes and for "all eyes". The protocol should indicate that all of the endpoints related to the type of SVIOL listed below should be met for success to be claimed for the effectiveness endpoint(s).

C.5.3.2 Multifocal IOLs

The following effectiveness endpoints are related to MIOLs.

a) mean (logMAR) monocular DCNVA under photopic conditions at 40 cm at the final visit demonstrating statistical superiority over the control [one-sided test using level of significance of 0,025]. Additional testing distances may be used depending on the lens design;

b) mean CDVA of ≤ 0,20 logMAR for the Multifocal group.

C.5.3.3 Extended depth of focus IOLs

The following effectiveness endpoints are related to EDF IOLs.

a) Mean (logMAR) monocular DCIVA under photopic conditions at 66 cm at the final visit:

   — DCIVA ≤ 0,20 logMAR;

   — demonstration of statistical superiority over the control [one-sided test using level of significance of 0,025];

b) Mean logMAR ≤ 0,20 for the EDF IOL group on DCVA at 1,0 m;

c) Mean monocular photopic CDVA for the EDF IOL is statistically non-inferior to the control using a non-inferiority margin of 0,10 logMAR [one-sided test using level of significance of 0,05];

d) Negative defocus range at the 0,20 log MAR threshold is > 0,50 D greater than control[8].

C.5.3.4 Full visual range IOLs

The following primary effectiveness endpoints are related to FVR IOLs.

a) Mean (logMAR) monocular DCNVA under photopic conditions at 40 cm at the final visit:

   — demonstrate statistical superiority over the control [one-sided test using level of significance of 0,025];

   — mean DCNVA of ≤ 0,20 logMAR.

b) Mean (logMAR) monocular DCIVA under photopic conditions at 66 cm at the final visit:

   — demonstrate statistical superiority over the control [one-sided test using level of significance of 0,025];

   — DCIVA of ≤ 0,20 logMAR.

c) Mean of ≤ 0,20 logMAR for DCVA at 1,0 m and 50 cm;

d) Mean monocular photopic CDVA for the FVR IOL is statistically non-inferior to the control using a non-inferiority margin of 0,10 logMAR [one-sided test using level of significance of 0,05].

C.5.3.5 Additional Endpoints (Descriptive)

The following should be considered as additional endpoints (as applicable for the type of Simultaneous Vision Lens) analysed with descriptive statistics only:

— defocus curve from +1,0 D through -3,0 D defocus;

— the frequency and proportion of eyes with ocular and visual symptoms (non-directed complaints) collected via open ended questioning;

— the frequency and proportion of eyes with visual symptoms collected via a PRO survey;

— distance-corrected mesopic visual acuity at intermediate distance (66 cm) by group;

— distance-corrected mesopic visual acuity at near distance (40 cm) by group;

— distance corrected mesopic VA at intermediate distance compared to mesopic DCVA (within group paired comparison);

— distance corrected mesopic VA at near distance compared to mesopic DCVA (within group paired comparison);

— UDVA (provide means and compare mean difference between eyes or between groups for bilateral implants);

— residual refractive error: descriptively compare mean error and mean absolute error;

— monocular uncorrected intermediate visual acuity at 66 cm (descriptive statistics);

— monocular uncorrected near visual acuity at the distance of intended near benefit (descriptive statistics);

— actual refractive as compared to predicted refractive outcomes in terms of mean, standard deviation, quartiles and inter-quartile range.

Testing of multiple statistical hypotheses should be conducted in such a manner as to keep the study-wise significance level at 0,05.

All descriptive statistics for the visual acuity outcomes should be provided for both test and control groups. When appropriate, correlations to pupil diameter are to be performed for selected effectiveness measures (e.g. defocus and contrast sensitivity). For binocularly implanted subjects, provide similar descriptive statistics as described above for binocular measures of visual acuity.

Table C.1 — Recommended schedule of procedures

Clinical evaluation	Illumination	Test	Preop	Form 1	Form 2	Form 3	Form 4	Form 5[a]
Uncorrected distance visual acuity (UDVA)	Photopic	Monocular Binocular	X	X	X	X	X X[b]	X X
Best corrected distance visual acuity (CDVA)	Photopic Mesopic	Monocular Binocular Monocular	X		X	X	X X[b] X	X X
Corneal topography or tomography	N/A	N/A	X[c]					
Manifest (subjective) refraction	Photopic	N/A	X		X	X	X	X
Pupil size	Photopic	N/A	X[d]				X	X
Pupil size	Mesopic	N/A				X[e]	X	X[e,f]
Dilated fundus exam	N/A	N/A	X				X	X
Slit lamp exam	N/A	N/A	X	X	X	X	X	X
Intraocular pressure	N/A	N/A	X	X	X	X	X	X
Lens stability (tilt/decentration)[g]	N/A	N/A				X	X	X
Keratometry	N/A	N/A	X					
Non-directed optical/visual symptoms	N/A	N/A		X	X	X	X	X
Subject PRO survey[i]	N/A	N/A				X	X	X
Axial length	N/A	N/A	X					
Anterior chamber depth	N/A	N/A	X					
Gonioscopy	N/A	N/A	X				X[h]	X[h]

a) A minimum investigation duration of 6-months is required. Only SVIOL without approved monofocal parent IOL require 12-months.

b) Binocular visual acuity is required at the last visit, i.e. at 6-months for FVR IOL with monofocal parent.

c) Excludes eyes with irregular astigmatism and other corneal disorders that would influence visual outcomes.

d) Preoperative pupil size should be measured only if needed for inclusion/exclusion criterion for designs that are pupil- size dependent.

e) Mesopic pupil size should be assessed if the subject complains of severe visual symptoms at or greater than Month 1 postoperative visit, as well as the specific visits for contrast sensitivity testing.

f) Testing is repeated at the 12 months (Form 5) visit in the 12-month investigation for those subjects in the contrast sensitivity investigation that had a posterior capsulotomy after the 6 month (Form 4) visit.

g) Lens stability evaluation is performed according to 6.3.2.

h) Gonioscopy should be done at the final visit as determined by risk analysis.

i) Testing to be performed if warranted by risk analysis.

j) PRO Survey performed to assess the visual symptoms related to the optical properties of the lens.

NOTE No clinical observations are required on the day of surgery.

Table C.1 *(continued)*

Clinical evaluation	Illumination	Test	Preop	Form 1	Form 2	Form 3	Form 4	Form 5[a]
Far contrast sensitivity	Mesopic	Monocular					X	X[f]
Far contrast sensitivity	Mesopic with glare	Monocular					X	X[f]
Far contrast sensitivity[i]	Photopic with glare	Monocular					X	X[f]
Depth of focus curve test	Photopic	Monocular Binocular (optional)					X X	
Distance-corrected intermediate visual acuity (DCIVA)	Photopic Mesopic	Monocular Binocular Monocular				X	X X[b] X	X X
Uncorrected intermediate visual acuity (UCIVA)	Photopic	Monocular Binocular				X	X X[b]	X X
Distance-corrected near visual acuity (DCNVA)	Photopic Mesopic	Monocular Binocular Monocular				X	X X[b] X	X X
Uncorrected near visual acuity (UCNVA)	Photopic	Monocular Binocular				X	X X[b]	X X

a) A minimum investigation duration of 6-months is required. Only SVIOL without approved monofocal parent IOL require 12-months.

b) Binocular visual acuity is required at the last visit, i.e. at 6-months for FVR IOL with monofocal parent.

c) Excludes eyes with irregular astigmatism and other corneal disorders that would influence visual outcomes.

d) Preoperative pupil size should be measured only if needed for inclusion/exclusion criterion for designs that are pupil- size dependent.

e) Mesopic pupil size should be assessed if the subject complains of severe visual symptoms at or greater than Month 1 postoperative visit, as well as the specific visits for contrast sensitivity testing.

f) Testing is repeated at the 12 months (Form 5) visit in the 12-month investigation for those subjects in the contrast sensitivity investigation that had a posterior capsulotomy after the 6 month (Form 4) visit.

g) Lens stability evaluation is performed according to 6.3.2.

h) Gonioscopy should be done at the final visit as determined by risk analysis.

i) Testing to be performed if warranted by risk analysis.

j) PRO Survey performed to assess the visual symptoms related to the optical properties of the lens.

NOTE No clinical observations are required on the day of surgery.

Annex D
(informative)

Additional elements for 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 investigation 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[a]
Bilateral[b]	100	50

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

[b] 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 investigation 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 investigation is longer than Form 5 at 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[a]	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	X
UNVA (fixed distance)	Photopic	Monocular	300	122				X	X	X	X	X
		Binocular	100	50					X	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	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					X	X	X	X
		Binocular	100	50						X	X	X
CNVA (record add power required)	Photopic	Monocular	300	122					X	X	X	X
		Binocular	100	50						X	X	X
Accommodative amplitude (objective)	Photopic	Monocular	100[b]	100[b]				X	X	X	X	X
Subjective refraction	Photopic	N/A	300	122	X		X	X	X	X	X	X
Pupil size[c]	Photopic/ mesopic	N/A	300	122	X					X	X	X
Fundus examination with dilated pupil	N/A	N/A	300	122	X			X		X	X	X
Slit lamp examination	N/A	N/A	300	122	X	X	X	X	X	X	X	X
Intraocular pressure	N/A	N/A	300	122	X	X	X	X	X	X	X	X
Lens stability (tilt/decentration)[d]	N/A	N/A	300	122		X	X	X	X	X	X	X
Specular microscopy[e]	N/A	N/A	300	122	X				X	X	X	X

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

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

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

[d] Lens stability is performed according to Reference [4].

[e] This investigation is performed if warranted by risk analysis.

Table D.2 *(continued)*

Examination	Illumination	Testing performed[a]	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
Anterior chamber depth[e]	N/A	N/A	300	122	X			X	X	X	X	X
Gonioscopy[e]	N/A	N/A	300	122	X			X	X	X	X	X
Subject PRO Survey	N/A	N/A	300	122	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

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

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

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

[d] Lens stability is performed according to Reference [4].

[e] 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);

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 are 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 are 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 PRO Survey;

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 4 210 for adverse events and overall CDVA, and 3 035 for best-case CDVA.

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 CDVA, and 635 for best-case CDVA.

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

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

[b] Excludes posterior capsulotomies.

Table E.2 — Posterior chamber IOL adverse event rates

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

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

[b] Excludes posterior capsulotomies.

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

Lens type		Number of subjects = 100		Number of subjects = 300	
	SPE rate %	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 CDVA 0,3 logMAR or better

Lens type		Number of subjects = 100		Number of subjects = 300	
	SPE rate %	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:

a) for cumulative events: the number of eyes with event/ the number of eyes for which the IOL touched the eye;

b) 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.

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

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 DCVA 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 "≥0,95", *p* would represent the control rate for DCVA 0,3 logMAR or better and *x* would be the observed number of successes 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/(testing distance in metres). For example, if distance testing is done at 4 m and the measured subjective refraction is −0,25 − 0,75 × 090, then the infinity-adjusted subjective refraction would be −0,50 − 0,75 × 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[8].

F.1.3 Luminance

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

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

No surface (including reflective surfaces) within the subject's field of view should exceed the chart background in luminance. In addition, ambient lighting should be dim and not affect the background luminance of the chart (incident on the chart) or be directed at the patient (providing an additional glare source). No light source should detract from the appearance of the chart to the patient (i.e, glare and distracting reflections should be avoided) and no light source should be visible to patients other than the chart illumination.

Luminance is standardized among all testing centres. Additional guidance concerning luminance testing is given by the AAO[9].

F.1.4 Data recording procedures

The following are recorded:

a) all physical and optical testing distances;

b) all refractions;

c) all acuity measurements should use logMAR notation.

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 Depth of focus evaluation

Depth of focus testing is used to demonstrate the clinical subjective depth of focus performance in accordance with the theoretical lens design. This test measures the range of useful vision provided by the SVIOL through the measurement of visual acuity for various vergence (defocus) ranges by using trial lenses of different fixed powers. Visual acuity is assessed under standardized test conditions (with CDVA in place) for each trial lens and a using distance visual acuity chart. Alternatively, such testing may instead be performed with chart testing at the appropriate focal distances instead of using minus lenses.

The clinical depth of focus should be determined by using data from all subjects and utilize the mean visual acuity at each defocus level; mean acuities are then plotted by connecting the associated data points with lines. The data should be stratified, when possible, to determine the depth of focus for each pupil size group of small (≤3,0 mm) medium (>3,0 mm and <4,0 mm) and large (≥4,0 mm) pupil size groups.

Depth of focus evaluation is conducted for all SVIOLs for characterization. However, EDF IOLs have a defined performance requirement at intermediate distance (Table 1).

F.3.1 Sample size

In cases where the SVIOL is a modification of a previously approved monofocal IOL, testing is performed with a minimum of 100 SVIOL subjects and 100 monofocal control subjects. In the case where the SVIOL is not a modification of an approved monofocal IOL and requires a full 300 subject investigation, a defocus evaluation sub-investigation should be performed with at least 100 subjects.

For monocular assessments, the eye to be tested should be the first eye that had implantation performed.

F.3.2 Test conditions and equipment

Defocus curve testing should be performed using the phoropter or trial frame and the 100 % contrast ETDRS chart at ≥4 m. Due to numerous visual acuity measurements in a defocus curve test, it is recommended that whenever possible, acuity testing be done using computerized charts with random presentation of letters. If the use of computerized charts is not possible, the sponsor should rationalize in the investigation protocol how bias due to memorization of letters will be minimized.

F.3.3 Test procedures

F.3.3.1 General

The best distance correction/manifest (subjective) refraction should be used to ensure the subject's vision is optimally corrected for the testing distance. Testing should be performed monocularly and the untested eye should be fully occluded. The pupil sizes for all the subjects in the investigation should be measured at the time of testing. When testing using trial frame or phoropter, the subject should be carefully observed for squinting and should be frequently reminded not to squint.

Subject fatigue can have a slight impact on a subject's visual acuity performance during the defocus curve testing. The sponsor should take measures to minimize this effect by proper scheduling of the test. To prevent testing bias, the sequence of letters presented used should be randomized.

F.3.3.2 Procedures for EDF IOL

To obtain the defocus curve for EDF IOLs, visual acuity should be measured first with the best distance correction (0,0 D) and then subsequently in 0,5 diopter defocus steps between +1,00 D and -2,00 D, except for the region from +0,50 D through -0,50 D, which should be done in 0,25 D steps. Letters should be randomly presented to avoid memorization. The defocus range of +1,00 D to -2,00 D may be modified as applicable based upon lens design and expected depth of focus. The protocol should specify range of lens powers used.

F.3.3.3 Procedures for MIOL and FVR IOLs

To obtain the defocus curve for MIOLs and FVR IOLs, visual acuity should be measured first with the best distance correction and then subsequently in 0,5 diopter defocus steps between +1,00 D and -3,00 D, except for the region from +0,50 D through -0,50 D, which should be done in 0,25 D steps. Letters should be randomly presented to avoid memorization. The defocus range of +1,00 D to -3,00 D may be modified as applicable based upon lens design and expected depth of focus. The protocol should specify range of lens powers.

F.3.4 Data analysis and presentation

For the SVIOL and the control IOL, the individual visual acuity data at each defocus level should be averaged and the mean visual acuity is plotted as a line plot with visual acuity (on Y axis) as a function of defocus (X axis). This data should also be stratified, when possible, to determine the clinical depth of focus for small (≤3,0 mm), medium (>3,0 mm and <4,0 mm) and large (≥4,0 mm) pupil size groups.

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 (~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 chinrest 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 [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;

   2) direct the subject's attention to the near fixation target and repeat the last 2 steps;

   3) repeat near measurements with the fixation target at, 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 Subjective accommodation measurement methods

F.4.2.1 General

Subjective accommodative testing can be used to further characterize the AIOL.

F.4.2.2 Subjective accommodative testing

For AIOLs, the subjective accommodative amplitude is obtained by starting with the CDVA, and then defocusing the image until accommodative failure, depending on the IOL optical design and performance. Measure the visual acuity and then proceed add minus power in 0,5 D steps, 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.

F.4.3 Contrast sensitivity

F.4.3.1 General

Standardize photopic and mesopic light levels, ambient illumination, chart luminance and glare source luminance across all investigators and sites. Testing should be conducted at the same photopic and mesopic chart luminance levels specified for the standard acuity testing. In addition, photopic and mesopic contrast sensitivities may 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 investigation 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 investigation that show an increase in contrast sensitivity performance should be excluded from the analysis.

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 artifacts that could affect the data may include blurring the outer edges of the grating and surrounding 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 Thorn[10].

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.4.3.2 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.(photopic/mesopic as applicable) for small (≤3,0 mm), medium (>3,0 mm and <4,0 mm) and large (≥4,0 mm) pupil size groups.

F.4.3.3 Spatial frequencies

Measure contrast sensitivity under mesopic conditions at spatial frequencies as close as possible to 1,5 cycles/degree, along with 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.4.3.4 Indeterminate data

Use the instructions for the test system chosen to clarify in the CIP how indeterminate data are treated in the analysis. The scoring instructions provided by the manufacturer of the equipment are to be followed with the following exception: If a subject is unable to see a targeted spatial frequency at any available contrast (including the contrast of the reference patch), the highest contrast or, equivalently, the lowest contrast score should be given, preceded by the appropriate inequality symbol (< or >) to indicate that the actual sensitivity is below the given value. Prior to any averaging or other statistical calculations, all contrast threshold values should be converted to log contrast sensitivity values (i.e., log10(1/CT), where CT is the threshold contrast value). The number and percentage of subjects who cannot see any contrast should be recorded and tabulated for each spatial frequency to provide a qualitative extent of the bias. Descriptive tables should include a note that the corresponding mean values are biased upward and variability values are biased downward (using < and > symbols). The percentage of subjects who cannot see any contrast level gives a qualitative indication of the extent of the bias. In such cases, statistical comparisons between test and control are not warranted.

Testing used by the Sponsor should employ contrast test patterns that provide sufficient maximum contrast to minimize the proportion of subjects who are unable to see any of the patterns (including the test patch). Utilizing test patterns without a full range of contrast will increase the proportion of subjects unable to see any of the test patterns (including the demonstration patch).

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 investigation. 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 investigation, 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 investigation. 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 investigation 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

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

Table G.2 — Normal quantiles to use in formulae

α or β	$(1-\alpha)$ 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 MIOL 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 test 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 (δ) 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 (δ) 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 (δ) of 0,014, α = 0,05, 80 % power, and a one-sided alternative. Sample size can be calculated using the method of Farrington and Manning[11].

NOTE 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 test 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[12]:

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

The subscript "t" refers to treatment (test eyes) 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:

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

for the sample size. For example, non-inferiority in a two-sample comparison of means solves this formula for the sample size (Lin[11]):

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

$$= \Pr\left[(\bar{x}_{\text{t}} - \bar{x}_{\text{c}}) - z_{1-\alpha}\sqrt{2\sigma^2/n} > -\delta\right]$$

where L_{lcl} 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 test 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 an investigation comparing a group of test subjects with a group of control subjects. Assume a power of 90 % (β = 0,100) with a 95 % confidence interval (α = 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 (δ) 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. 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 investigational 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 test eyes and 122 control eyes would be required for the contrast sensitivity sub-investigation. 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 TIOL

G.4.1 Sample size calculation for the analysis of "Reduction in cylindrical power of the eye" (see B.3.5.1) for an investigation 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;

σ 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:

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

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

The alternative hypothesis is:

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

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);

— β = 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.

Bibliography

[1] ISO 11979-2, *Ophthalmic implants — Intraocular lenses — Part 2: Optical properties and test methods*

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

[3] SSED's of approved MIOL's can be found through https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

[4] Holladay JT, Calogero D, Hilmantel G, Glasser A, MacRae S, Masket S, Stark W, Tarver ME, Nguyen T, Eydelman M, Special Report: American Academy of Ophthalmology task force summary statement for measurement of tilt, decentration and chord length. Ophthalmology 2017, **124** (1) pp. 144–146

[5] Patel CK, Ormonde S, Rosen PH, Bron AJ, Postoperative intraocular lens rotation: a randomized comparison of plate and loop haptic implants. Ophthalmology 1999, **106** (11) pp. 2190-2195

[6] Weinand F, Jung A, Stein A, Pfutzner A, Becker R, Pablovic S, Rotational stability of a single-piece hydrophobic acrylic intraocular lens: New method for high-precision rotation control. J Cataract Refract Surg 2007, **33** pp. 800-803

[7] Shah GD, Praveen MR, Vasavada AR, Rampal NV, Vasavada VA, Asnani PK, Pandita T, Software-based assessment of postoperative rotation of toric intraocular lens. J Cataract Refract Surg 2009, **35** pp. 413-418

[8] Ferris FL, Kassoff A, Bresnick GH, Bailey I, New visual acuity chart for clinical research. Am J Ophthalmol 1982, **94** pp. 91-96

[9] MacRae S., Holliday J.T., Glasser A. et al., Special Report: American Academy of Ophthalmology Task Force Consensus Statement for Extended Depth of Focus Intraocular Lenses. Ophthalmology 2017, **124** (1) pp. 139-141

[10] Thorn F., Effects of dioptric blur on the Vistech contrast sensitivity test. Optom Vis Sci. 1990, **57** pp. 8-12

[11] Farrington CP, Manning G, Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity of relative risk. Statistics in Medicine 1990, **9** pp. 1447-1454

[12] Lin SC, Sample size for therapeutic equivalence based on confidence interval. Drug Information Journal 1995, **29** pp. 45-50

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