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Ophthalmic implants — Intraocular lenses —

Part 9: Multifocal intraocular lenses

Implants ophtalmiques — Lentilles intraoculaires —

Partie 9: Lentilles intraoculaires multifocales

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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

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

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

ISO 11979-9 was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

ISO 11979 consists of the following parts, under the general title *Ophthalmic implants — Intraocular lenses*:

— *Part 1: Vocabulary*

— *Part 2: Optical properties and test methods*

— *Part 3: Mechanical properties and test methods*

— *Part 4: Labelling and information*

— *Part 5: Biocompatibility*

— *Part 6: Shelf-life and transport stability*

— *Part 7: Clinical investigations*

— *Part 8: Fundamental requirements*

— *Part 9: Multifocal intraocular lenses*

— *Part 10: Phakic intraocular lenses*

Ophthalmic implants — Intraocular lenses —

Part 9:
Multifocal intraocular lenses

1 Scope

This part of ISO 11979 is applicable to any intraocular lens whose optic provides two or more rotationally symmetric powers and whose primary indication is the correction of aphakia with the added benefit of useful vision at more than one distance (e.g. far and near).

NOTE The term “near vision” as used in this part of ISO 11979 includes useful vision at a distance of claimed benefit; e.g. near and/or intermediate distances.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

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

ISO 11979-3, *Ophthalmic implants — Intraocular lenses — Part 3: Mechanical properties and test methods*

ISO 11979-4, *Ophthalmic implants — Intraocular lenses — Part 4: Labelling and information*

ISO 11979-7, *Ophthalmic implants — Intraocular lenses — Part 7: Clinical investigations*

ISO 14155-1, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

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

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

3 Terms and definitions

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

4 Physical requirements

4.1 General

This clause is applicable to the physical properties of multifocal intraocular lenses (MIOLs) in the assembled or final form, as intended for implantation in the human eye.

4.2 Tolerances and dimensions

For tolerances and dimensions, the requirements of ISO 11979-3 apply, together with the following additional requirement that the manufacturer shall establish tolerances with respect to the optical design.

5 Optical requirements

5.1 General

This clause is applicable to the optical properties and performance requirements of MIOLs in their final form, as intended for implantation in the human eye.

5.2 Dioptric power

For dioptric power, ISO 11979-2 applies to the far power of an MIOL and to any distinct near power(s).

Two alternative methods for the determination of dioptric power, given in ISO 11979-2, can be applied to MIOLs. For each near image plane, these methods are modified as follows:

a) for the determination of dioptric power from measured back focal length, once the microscope is focused on the far image plane and the distance from the back vertex of the MIOL to the distant focal point is determined, focus the microscope on the near image plane and determine the distance from the back vertex of the MIOL to the near focal point;

b) for the determination of dioptric power from measured magnification, once the microscope is focused on the far image plane and the linear dimension, h_{image}, in the image is determined, focus the microscope on the near image plane and determine the linear dimension, h_{image}, in the image.

Depending on the MIOL optic design the correction formulas given in ISO 11979-2 could be invalid. In such cases, the manufacturer shall derive and justify corrections that result in dioptric powers that are consistent with power labelling of monofocal IOLs.

If the focusing conditions of ISO 11979-2 are not appropriate for the particular design, another focusing condition shall be developed with justification.

5.3 Imaging quality

The imaging quality shall be evaluated for the far power and any claimed near power(s) or power range. The imaging quality specifications apply in all meridians.

For designs that have no distinct near power, a specification describing the through-focus response performance shall be developed.

The manufacturer shall demonstrate that all available powers meet the imaging quality specifications.

The imaging quality of a MIOL shall be evaluated by modulation transfer function (MTF) testing in the eye model described in ISO 11979-2 with the following additions:

ISO 11979-2 is modified such that best focus for the power under evaluation is obtained by maximizing the MTF at 50 cycles/mm with a (3 ± 0,25) mm aperture. Using that focus, record the MTF values at the following conditions:

a) small aperture (2 mm to 3 mm), 25 cycles/mm and 100 cycles/mm, for the far power;

b) small aperture (2 mm to 3 mm), 25 cycles/mm and 100 cycles/mm, for the near power(s) or power range;

c) large aperture (4 mm to 5 mm), 25 cycles/mm and 50 cycles/mm, for the far power.

The converging beam from the model cornea described in ISO 11979-2 exposes a central diameter of the MIOL (± 0,1 mm) to, interchangeably, either the small or the large aperture that is chosen to best control the MTF performance.

In order to best control the MTF performance of the MIOL, the small and large apertures used for testing shall be chosen and defined for the lens model over the range of apertures provided above with a tolerance of ± 0,25 mm. The manufacturer shall have the option of setting the minimum MTF specification based on the area under the curve between the two spatial frequencies or on the MTF value for each individual spatial frequency.

The minimum MTF specification shall be set such that it results in acceptable visual outcome, verifiable, or to be verified, by clinical data.

NOTE 1 The minimum MTF specification is typically set as the mean value minus an acceptable level of deviation, e.g. mean value minus two standard deviations.

NOTE 2 The apertures above represent the exposed diameter of the test MIOL and can differ from the aperture stop of the optical bench.

NOTE 3 It can be necessary to have a different imaging quality specification for each combination of test aperture and focus.

5.4 Additional optical characterization

5.4.1 Optical design

Tests that shall be performed to characterize the MIOL optical design are described in Annex A.

5.4.2 Spectral transmittance

For spectral transmittance, ISO 11979-2 applies.

6 Clinical investigation

6.1 General

If clinical evaluation, in accordance with ISO 14155-1, together with risk assessment, in accordance with ISO 14971, identifies the need for a clinical investigation, the requirements of ISO 14155-1, ISO 14155-2 and ISO 11979-7 apply, with additional requirements given in 6.2.

NOTE Considerations for the risk analysis regarding modifications to one or more existing designs are found in ISO/TR 22979 [1].

6.2 Additional requirements for the clinical investigation plan

The requirements for the clinical investigation plan of ISO 11979-7 apply. In addition to the study variables given in ISO 11979-7, the following shall be considered:

a) near visual acuity (VA), with best distance correction;

b) uncorrected near VA;

c) uncorrected distance VA;

d) quality of vision survey;

e) defocus evaluation;

f) fundus visualization;

g) contrast sensitivity;

h) functional performance.

NOTE 1 Information regarding a design of the clinical investigation can be found in Annex B.

NOTE 2 Information regarding determination of sample sizes for the clinical investigation is provided in Annex C.

7 Information supplied by the manufacturer

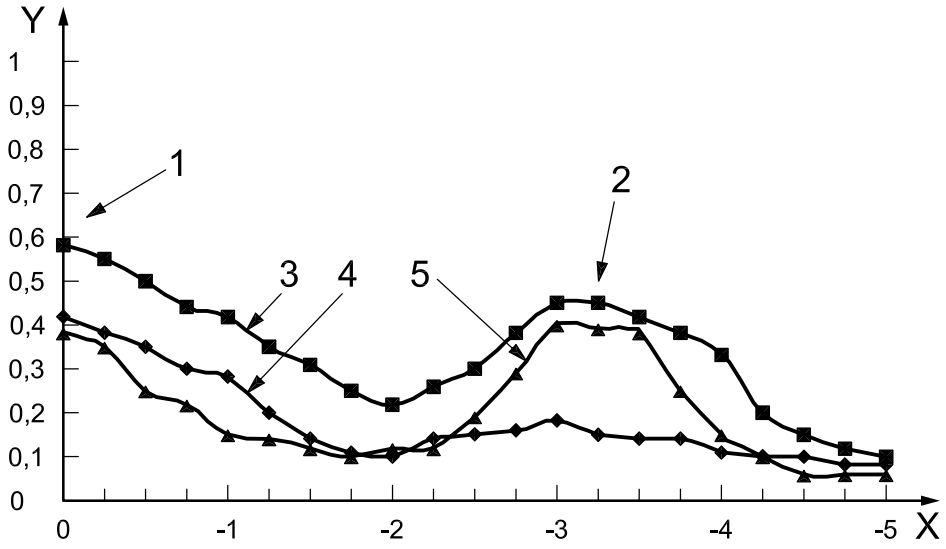
The requirements for the information supplied by the manufacturer given in ISO 11979-4 apply, with the following additional information that shall be made available to the user:

a) a summary of the results of the clinical investigation, if any;

b) a graph of the MTF through focus response performance of the MIOL in the model eye, using the conditions described in Annex A of this part of ISO 11979 (see example in Figure 1); informative text shall accompany the figure explaining that the MTF values in the graph describe the MIOL optical performance in a standardized model eye at 50 cycles/mm as the focus is gradually shifted from that of a far object to increasingly nearer objects and that higher numbers indicate better performance;

c) a graph of the spectral transmittance through the MIOL in the range of 300 nm to 1 100 nm.

The general requirements for information provided by the manufacturer with medical devices specified in EN 1041 [2] should be considered. Symbols can be used instead of text, where appropriate. When symbols are used, the requirements of ISO 15223 [3] and EN 980 [4] should be considered.



Key

X defocus (dioptres)
Y modulation ratio at 50 cycles/mm
1 far object
2 near object
3 3 mm pupil size
4 2 mm pupil size
5 4,5 mm pupil size

Figure 1 — Example of MTF through focus response for multiple pupil sizes

Annex A
(normative)

Optical characterization

A.1 Theoretical evaluation

Make a theoretical evaluation of, or measure, the percentage of light energy going to the images produced by the far power and by each near power (or power range) as a function of aperture from 2,0 mm to 4,5 mm at maximum intervals of 0,5 mm, for the cases when the lens is centred, decentred 0,5 mm, and decentred 1,0 mm. When determining the percentage of light energy going to each of the images, include any unrefracted light, and any other light that does not usefully contribute to the intended image, in the total light energy. Report the results in the form of separate graphs for each case.

A.2 Optical testing

This testing will confirm that the actual performance of the lens is similar to its theoretical performance.

Use ten representative samples each of low, medium and high power manufactured MIOLs for testing in the model eye defined in ISO 11979-2 with the following additions.

a) Modulation transfer function (MTF) testing:

   Generate MTF through-frequency curves at different apertures for the images formed by the far power and by each near power (or power range) with the lens on-axis, decentred 1,0 mm, and tilted 5°. Do this for aperture sizes 2 mm, 3 mm, and 4,5 mm (± 0,25 mm) at the position of the lens. Focus to give maximum modulation ratio for 50 cycles/mm in each case. Report the results in the form of graphs, averaging MTF on-axis curves for each power tested.

   For this MTF testing, ten representative samples each of low, medium and high power manufactured MIOLs are used for the on-axis condition. Each MIOL with the median performance for the on-axis condition from the low, medium and high power groups are used for the subsequent decentred and tilted conditions. Therefore, a total of 30 lenses (10 low, 10 medium, and 10 high power) are used for the on-axis condition, and a total of 3 lenses (1 low, 1 medium, and 1 high power) are used for the decentred and tilted conditions.

   In each case, the performance should be compared to that of a similar monofocal lens.

b) MTF through-focus-response testing:

   Generate the MTF through-focus-response of the MIOL at 50 cycles/mm with 2 mm, 3 mm, and 4,5 mm ± 0,25 mm apertures. Focus to maximum MTF at 50 cycles/mm for an object at infinity and then measure MTF at positions in image space that correspond with increasingly closer object distances down to that corresponding with 20 cm.

c) Recovery of properties following simulated surgical manipulation:

   The testing in this clause applies only to lenses for which the optic is intended to be folded or compressed during implantation. ISO 11979-3 applies with the following additions.

   To evaluate the combined effects of haptic compression and folding and/or injection, as applicable, first simulate implantation using the maximum recommended time for the MIOL to be held in the folder/injector, and then place the lens in a holder that constrains the haptics to 10 mm diameter (for posterior chamber MIOLs) or the minimum expected constrained diameter (for anterior chamber MIOLs).

Immerse the lens in its holder in aqueous at 35 °C for a minimum of 24 h. Then, while maintaining the constraint, place the lens in the model eye. Thereafter focus to maximum MTF at 50 cycles/mm and measure through-frequency MTF. Do this for apertures of 3 mm and 4,5 mm at the positions of the lens.

Report the results in the form of a graph averaging the through frequency MTF of the lenses measured. The maximum recommended time for the MIOL to be held in the folder/injector is stated in the report.

Annex B
(informative)

Clinical investigation

B.1 Objectives

The objectives of the clinical investigation are to determine the safety and performance of the MIOL. The recommended primary safety endpoint is the evaluation of the secondary surgical reintervention rate related to the optical properties of the MIOL. The null hypothesis is that the study rate minus the control rate is greater than or equal to the minimally detectable difference between the two rates. The alternative hypothesis is that the study rate minus the control rate is less than the minimally detectable difference between the two rates. Annex C of this part of ISO 11979 contains statistical recommendations for determination of the sample size to test this hypothesis.

B.2 Design

The type of clinical investigation recommended is an unmasked, controlled, comparative study. The safety variables that are common to ISO 11979-7 are compared to the safety and performance endpoints described in ISO 11979-7.

A study duration of one year is recommended to adequately evaluate the secondary surgical reintervention rate related to the optical properties of the MIOL.

B.3 Subjects

B.3.1 Study group

Approximately 420 study subjects are enrolled in the study, in order to obtain complete follow-up on at least 300 study subjects.

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

B.3.2 Control group

Approximately 210 control subjects are enrolled in the study, in order to obtain complete follow-up on at least 150 control subjects. Control subjects receive monofocal IOLs. The monofocal IOL is identified in the clinical investigation plan (CIP).

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

B.3.3 Inclusion and exclusion criteria

B.3.3.1 General

Use the same inclusion and exclusion criteria for study and control subjects normally applied for investigations of intraocular lenses. In addition, consider the criteria given in B.3.3.2 and B.3.3.3.

B.3.3.2 Inclusion criteria

Include subjects with clear intraocular media other than cataract.

B.3.3.3 Exclusion criteria

Exclude the following subjects:

a) subjects with ocular disorders, other than cataract, that could potentially cause future acuity losses to a level of 0,66 or worse in either eye;

b) subjects who are expected to require retinal laser treatment;

c) greater than one dioptre of pre-operative corneal astigmatism;

d) inability to achieve secure lens placement in the designated location.

B.3.4 Enrolment of subjects

To minimize the risks associated with the clinical investigation, subject enrolment should occur in stages. The data from each stage are evaluated and found acceptable by the sponsor and the principal investigator(s) prior to proceeding to the next stage.

The following phased enrolment plan is recommended:

a) Phase I: 10 subjects, followed for 30 days to 60 days (Form 3);

b) Phase II: 75 additional subjects, followed for 120 days to 180 days (Form 4);

c) Phase III: remainder of subjects.

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

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

B.4 Variables to be investigated

B.4.1 General

Table B.1 contains a recommended examination schedule, including clinical evaluations to be performed, number of study and control subjects to be tested, whether the clinical evaluation is done monocularly or binocularly, and at which visit the clinical evaluation is performed. For reporting periods, see ISO 11979-7.

In addition to the variables in ISO 11979-7, the following variables are evaluated on all study and control subjects:

a) near visual acuity;

b) pupil size;

c) subject survey.

The following evaluations are done on a smaller sample of best-case study and control subjects (see Table B.1 and Annex C of this part of ISO 11979 for recommended sample sizes):

— defocus curves,

— fundus visualization,

— contrast sensitivity, and

— functional performance.

B.4.2 Visual acuity

B.4.2.1 General

Best spectacle corrected distance visual acuity (photopic illumination), near visual acuity with distance correction (photopic and mesopic illumination), uncorrected distance visual acuity (photopic illumination), and uncorrected near visual acuity (photopic illumination) are measured. The visual acuity method referenced in ISO 11979-7 (i.e. Snellen) is not recommended. Rather, ETDRS is the preferred method.

Distance and near visual acuity charts, chart illumination, ambient illumination, testing distances and testing procedures are standardized for all investigators. The design of the visual acuity chart and testing procedures with scoring method are described by Ferris [5].

B.4.2.2 Luminance

Use a chart luminance of about 85 cd/m^2 (80 cd/m^2 to 160 cd/m^2 acceptable range) for photopic conditions. Use a chart luminance of about 3 cd/m^2 for mesopic conditions. Try to achieve the same luminance at all testing centres. Ambient illumination is kept from dim to dark. No surface (including reflective surfaces) within the subject's field of view is to exceed the chart background luminance.

B.4.2.3 Chart distance

Near visual acuity with distance correction and uncorrected near visual acuity is tested with the chart at a fixed distance and at the best distance (which is recorded).

Near visual acuity charts should have the angular sizes of the optotypes calibrated for the 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.

For distance visual acuity testing, the best correction to the chart distance should be used after adjusting the chart to optical infinity (e.g. + 0,25 D for a 4 m chart). When determining the best distance refraction for treatment, however, the refraction should be adjusted to the refractive correction at infinity (e.g. −0,25 D for a 4 m chart distance) if the chart is not at optical infinity.

B.4.2.4 Data recording procedures

Record all:

a) testing distances;

b) refractive corrections;

c) measured visual acuities in MAR notation, or other notation convertible to MAR.

B.4.3 Pupil size

Photopic and mesopic pupil diameters are recorded with an accuracy of at least $\pm$ 0,5 mm. For the photopic pupil diameters, eye illumination is identical to that used for photopic visual acuity testing. For the mesopic pupil diameters, eye illumination is identical to that used for mesopic contrast sensitivity testing.

It is recommended that pupil measurements be 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).

B.4.4 Subject survey

Conduct a survey of all subjects to determine their impressions of the quality of their vision. In the survey, perform the following tasks.

a) Ask the subjects to describe the quality of their vision at near and distance in indoor, outdoor (daylight) and night/dark situations. Ask how the vision compares to the vision of their other eye if their other eye has a natural or monofocal lens.

b) Ask the subjects to state whether or not they have observed flare/glare, halo, near or distance distortion, near or distance blurring, diplopia (specify whether monocular or binocular complaint), night vision problems, or colour disturbances. Ask the subjects to describe the conditions under which they experience any problem.

c) Ask the subjects whether, if given the opportunity, they would again elect to be implanted with the same intraocular lens.

At the time of this revision, Javitt *et al*. [6] is the only published questionnaire that has been validated for use in MIOL investigations. A validated questionnaire, such as Vitale *et al*. [7] can also be used, with questions specifically relating to MIOL issues written in the same format added to the questionnaire.

The study subjects' results of the questionnaire are stratified by the other eye status (untreated, implanted with same MIOL, treated with monofocal IOL, etc.).

B.4.5 Fundus visualization

Ask all investigators to rate the clarity of the retinal image through eyes with multifocal intraocular lenses compared to their previous monofocal IOL experience. Investigators should evaluate whether the retinal image has adequate clarity for diagnosis and treatment of potential vitreal/retinal disorders.

B.4.6 Defocus evaluation

The purpose of the defocus evaluation is to compare binocular clinical performance to the theoretical lens design. This testing is performed under photopic conditions.

a) The number of subjects should be at least ten bilaterally-implanted study subjects and ten bilaterally-implanted control subjects for each of the following pupil size groups: small ($\leqslant$ 2,5 mm), medium ($>$ 2,5 mm and $<$ 4,0 mm) and large ($\geqslant$ 4,0 mm). If ten subjects are not available in any pupil size category, then the maximum number available is used. Only include subjects when both of their pupils fall in a single size range.

b) A binocular defocus evaluation that measures visual acuity is obtained by using the best corrected distance refraction and then defocusing the image in 0,5 D increments to $-$5 D.

c) Three best-fit defocus curves are generated, at small, medium and large pupil sizes. The best-fit curves are determined from the mean visual acuity of the study group at each defocus level.

B.4.7 Far contrast sensitivity

Measure sinusoidal grating contrast sensitivity at far. For this purpose, gratings produced on either charts or monitors can be used, provided that they are validated. Use the same test system at all sites.

The sine-wave gratings are accurately produced on a chart (reflective or transmissive) or a high-resolution monitor.

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

Let the subject 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 against spatial frequency.

a) Subjects

The number of subjects to be tested is determined as described in Annex C. All subjects should be best case.

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

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

b) Lighting conditions

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

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

If the maximum glare produced with the test equipment does not result in 0,10 log unit contrast sensitivity loss at 6 cycles/degree under photopic conditions, then the maximum glare that the equipment can produce should be used as the photopic glare level.

c) Spatial frequencies

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

d) Indeterminate data

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

B.4.8 Functional performance

B.4.8.1 General

The purpose of a functional performance test is to determine whether there is a significant difference between the study and control groups.

An example of such a test is a driving study assessing visual performance while driving under low visibility environmental conditions such as inclement weather, night driving, and headlight glare conditions. The subparts in this section provide information for a driving study example.

B.4.8.2 Subjects

The study group subjects are bilaterally implanted with the MIOL. The control group subjects are bilaterally implanted with the monofocal IOL.

Study and control groups are best-case subjects, having similar age, gender, and driving experience demographics. Contrast sensitivity testing is performed on all subjects and potential correlations with response parameters are assessed.

Include enough subjects to statistically detect performance differences between study and control groups. Data for the variability estimates are obtained from published sources or from a preliminary validation study.

B.4.8.3 Study design

The study is designed to portray relevant visual aspects of the driving conditions. Two types of visual tasks are included in the protocol: recognition of traffic signs and detection of road hazards. In both cases, the luminance, contrast and angular size of traffic signs and road hazards are replicated, simulating representative and realistic examples of typical road signs and hazards.

The response measures for sign recognition and hazard detection include the recognition/detection distance, and percentage of correct responses. To reduce variability, response reaction times should be measured for each subject, and used to compensate for the response delays in the detection and recognition data. Multiple trials of signs of the same lettering height with different information and multiple trials of hazards should also be performed to reduce variability.

The environmental conditions include clear roadway lighting, reduced visibility (e.g. fog or windshield condensation), and glare from approaching headlights. The lighting replicates night time driving such as headlights only in a rural environment and/or a combination of headlight and streetlights in a city environment. If using a projection system, the signs presented in the simulation should be illuminated.

The testing for the driving study is performed at the Form 4 timeframe, or thereafter, counted from the time of implantation of the second eye.

B.4.8.4 Apparatus validation

B.4.8.4.1 Simulation validation

Devise a set of tests to demonstrate that the visual resolution, contrast and luminance of the simulation projections are sufficient to allow for sign recognition and hazard detection at simulated distances similar to real-world signs / objects in the real-world environments.

B.4.8.4.2 Pilot study of subjects in validated simulator

Using elements of the simulation study design, conduct a pilot study to obtain baseline measures of variability that are used to estimate the minimum numbers of subjects needed for the control and test groups of the main study.

B.5 Data analyses

B.5.1 General

An accountability of subjects in the study is provided as described in ISO 11979-7.

An analysis of the primary safety and performance endpoints by demographic variables (e.g. age, gender, race) should be provided.

B.5.2 Refractive results and adverse events

Since the need to achieve an accurate refractive result (usually emmetropia) is imperative, clinical data is evaluated at intervals during the study to validate the accuracy of, and to refine, the power calculation procedure, if necessary.

This annex assumes one near power for the MIOL. If multiple powers are included in the study, additional considerations are necessary. For example, the optimum distance associated with each power is provided by the sponsor.

Consider the following analyses in addition to those in ISO 11979-7:

a) posterior capsulotomy rate by post-operative visit;

b) analysis of visual acuity and adverse events for lost to follow-up subjects.

The effects of patients lost to follow-up should be explored as comprehensively as possible. If methods other than extrapolating the results of a lost to follow-up subject's clinical results to the final post-operative visit are used (last visit carried forward), detailed explanations of the procedures employed for dealing with missing data should be described and the potential implications of such analyses on the overall study outcomes should be provided.

B.5.3 Functional performance

Sponsors should employ standard statistical analyses to determine the size and statistical significance of any differences between study and control group data in terms of detection and recognition distances.

Sponsors should provide analyses wherever possible to determine if the detection and recognition distances determined by their studies are adequate for safe and effective vehicle control.

Table B.1 — Recommended postoperative examination schedule

Study	Illumination	Number of study subjects	Number of control subjects	Testing performed[a]	Pre-operative	Form 0	Form 1	Form 2	Form 3	Form 4	Form 5
Best spectacle corrected distance visual acuity	Photopic	300	150	Monocularly				X	X	X	X
				Binocularly						X	X
Near visual acuity with distance correction	Photopic and mesopic	300	150	Monocularly					X	X	X
				Binocularly							X
Uncorrected distance visual acuity	Photopic	300	150	Monocularly				X	X	X	X
				Binocularly						X	X
Uncorrected near visual acuity	Photopic	300	150	Monocularly					X	X	X
				Binocularly						X	X
Pupil size	Photopic and mesopic	300	150	Monocularly	X[b]					X	
Lens decentration and tilt	N/A	300	150	Monocularly					X	X	X
Subject survey	N/A	All available bilaterally implanted	All available bilaterally implanted	Binocularly						X	X
Fundus visualization	N/A	300	None	Monocularly					X		
Sub-studies											
Defocus evaluation	Photopic	30[c]	30[c]	Binocularly						X	
Far contrast sensitivity[d]	Photopic with glare	Open[e]	Open[e]	Binocularly						X	X[f]
	Mesopic									X	X[f]
	Mesopic with glare									X	X[f]
Functional performance		Open[e]	Open[e]	Binocularly						X	

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

[b] Preoperative pupil size only needs to be measured if needed to meet an inclusion or exclusion criterion for designs that are pupil-size dependent.

[c] Subjects in the defocus study should come from the three pupil size categories defined in this International Standard. If ten subjects are not available in some pupil size categories, then the maximum number available is used.

[d] For each of the test conditions, the pupil sizes of the study and control subjects in the far contrast sensitivity sub-study should be representative of the pupil sizes associated with the subjects enrolled in the clinical investigation.

[e] A recommended sample size is not defined and is determined by the sponsor. Annex C provides considerations for determination of the sample size.

[f] The testing is repeated at the Form 5 visit for those subjects in the contrast sensitivity study that had a posterior capsulotomy after the Form 4 visit. If the patient is scheduled for a posterior capsulotomy during the Form 4 visit, contrast sensitivity testing is deferred to the Form 5 visit.

Annex C
(informative)

Determination of sample sizes for the clinical investigation

C.1 Symbols

The following symbols are defined here for use within this annex.

a) Confidence interval parameters:

- $1-\alpha$ confidence interval level
- $1-\beta$ power
- δ non-inferiority margin, assumed to be positive
- p_c control proportion
- p_t test proportion
- $z_{1-\alpha}$ standard normal quantile for confidence level
- $z_{1-\beta}$ standard normal quantile for power (coverage probability)
- L_{lcl} lower confidence limit, i.e. lower limit of the confidence interval

b) Normal distribution statistics and parameters:

- μ population mean
- σ population standard deviation
- n sample size
- $\bar{x}$ sample mean

c) Hypothesis testing parameters:

- α Type 1 error rate for the hypothesis
- β Type 2 error rate for the hypothesis

C.2 Sample size guidance for safety and performance evaluation

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

The null hypothesis (H_0) is that the test rate (p_t) minus the control rate (p_c) is greater than or equal to the minimally detectable difference (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.

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

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

The following assumptions are recommended for the sample size calculation: an assumed control rate (p_c) of 0,001, a minimally detectable difference (δ) of 0,014, $\alpha = 0{,}05$, 90 % power, and a one-sided alternative. Sample size can be calculated using the method of Farrington and Manning [9]. Note that this sample size calculation assumes that Equation 3 and Method 3 of Farrington and Manning will be used to test for non-inferiority.

C.3 Sample size guidance for substudies

C.3.1 General

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

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

The subscript “t” refers to treatment (study) and the subscript “c” refers to the control. Usually the population means for the two groups are assumed equal (i.e. $\mu_t - \mu_c = 0$). If they are not assumed equal, the denominator is constrained to be positive in non-inferiority problems. This assumption increases the sample size as the differences between population means approaches the non-inferiority margin. The assumptions also avoid the extreme condition of having smaller sample size requirements when the denominator becomes more negative.

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

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

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

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

where L_{lcl} is the lower confidence limit.

The resulting sample size equations 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 C.1 provides a convenient list of standard normal quantiles that are used in the examples.

Table C.1 — Normal quantiles to use in equations

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

C.3.2 Contrast sensitivity substudy

C.3.2.1 General

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

In order to calculate sample size using the above equations, 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.

C.3.2.2 Example

Consider a study comparing a group of study subjects with a group of control subjects. Assume a power of 90 % ($\beta = 0{,}100$) with a 95 % confidence interval ($\alpha = 0{,}050$). The detectable difference has been selected at one half the contrast sensitivity loss that is typically considered to be clinically significant. Typically, losses of 0,3 log units are considered to be clinically significant, when they occur at 2 or more spatial frequencies. This example then allows for a detectable difference of 0,15 log units. Other values can be used if appropriate. The standard deviation chosen for the example is 0,4 log units, which is based on published literature and experience. Standard deviation values can vary based upon study conditions (e.g. testing equipment, lighting conditions). The manufacturer should choose the expected standard deviation based on literature and/or experience.

Solving for this equation:

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

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

C.3.3 Functional performance substudy

C.3.3.1 General

Functional performance losses should be determined by comparing measurements from a subset of binocular MIOL subjects with binocular monofocal IOL subjects in a simulated driving performance study.

C.3.3.2 Example

Consider a study comparing a group of bilaterally implanted study subjects with a group of bilaterally implanted control subjects. Assume a power of 90 % ($\beta = 0{,}100$) with a 95 % confidence interval ($\alpha = 0{,}050$). The non-inferiority margin is selected at 25 % of the detection/recognition distance found in the driving simulation study as recommended in the functional performance section of this International Standard (see Annex B).

The standard deviation used in the actual sample size determination should be chosen based on the results of the preliminary validation studies. Typically the standard deviations are greatest for identification distances under the city lighting with glare lighting condition and may be approximately 30 % of the mean identification distance of about 62 m.

Assume a standard deviation of 18,6 m (30 % of the mean) and solve for this equation:

$$n = 2(18{,}6)^2 \left[\frac{(1{,}645 + 1{,}282)}{0{,}25(62) + (0)} \right]^2 = 24{,}67 \cong 25$$

For a driving simulation study of binocular MIOL subjects and binocular monofocal control subjects, the sample size for each group would be 25. Therefore, with 25 subjects there is a 90 % probability that a one-sided upper 95 % confidence interval level on the mean group difference will fall below 15,5 m (25 % of the mean identification distance).

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