INTERNATIONAL STANDARD

ISO 11979-7

First edition
2001-04-15

Ophthalmic implants — Intraocular lenses —

Part 7: Clinical investigations

Implants ophtalmiques — Lentilles intraoculaires —

Partie 7: Investigations cliniques

Reference number
ISO 11979-7:2001(E)

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Printed in Switzerland

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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 3.

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 part of ISO 11979 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 11979-7 was prepared by Technical Committee ISO/TC 172, *Optics and optical instruments*, 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*

Annex A forms a normative part of this part of ISO 11979. Annexes B, C and D are for information only.

Introduction

This part of ISO 11979 provides fundamental requirements of a general nature for intraocular lenses. It refers to other standards applicable to intraocular lenses for specific methods and requirements.

It always was and still is the intention of Technical Committees ISO/TC 172/SC 7 and CEN/TC 170 to prepare identical ISO and CEN (European Committee for Standardization) standards on intraocular lenses. However, during the preparation of this part of ISO 11979, problems were encountered with normative references to the existing ISO 14155 and EN 540 horizontal standards on clinical investigation of medical devices, which are similar but not identical.

ISO and CEN principles concerning normative references made it impossible to continue the preparation of identical International and European Standards on the clinical investigation of intraocular lenses. As a result, two different standards series have had to be prepared. It is the intention of ISO/TC 172/SC 7 and CEN/TC 170 to revise these standards with the goal to end up with identical ones as soon as identical ISO and CEN horizontal standards become available.

Ophthalmic implants — Intraocular lenses —

Part 7:
Clinical investigations

1 Scope

This part of ISO 11979 specifies particular requirements for clinical investigation protocols for posterior and anterior chamber monofocal intraocular lenses (IOLs) for the correction of aphakia.

NOTE Any other type of IOL not directly covered by ISO 11979 and any IOL for which the sponsor wishes to investigate claims in addition to those defined in ISO 11979 may be clinically evaluated by reference to ISO 14155.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 11979. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 11979 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 14155: 1996, *Clinical investigation of medical devices.*

ISO 11979-1:1999, *Ophthalmic implants — Intraocular lenses — Part 1: Vocabulary.*

ISO 11979-3: 1999, *Ophthalmic implants — Intraocular lenses — Part 3: Mechanical properties and test methods.*

3 Terms and definitions

For the purposes of this part of ISO 11979, the terms and definitions given in ISO 14155 and ISO 11979-1 apply, together with the following.

For the convenience of users of this part of ISO 11979, some definitions from ISO 11979-1 are reproduced in annex A. Terms relating to the design of IOLs are given in ISO 11979-3.

3.1
serious adverse event
event which is potentially sight threatening

NOTE 1 The definition for serious adverse event given in the ICH *Harmonized tripartite guideline for good clinical practice* also applies (see reference [1] in the bibliography).

NOTE 2 Examples of potentially sight-threatening adverse events are included in Tables D.1 and D.2.

4 Ethical considerations

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

5 Requirements

5.1 General requirements

The requirements given in 5.1 to 5.7 of ISO 14155:1996 shall apply.

5.2 Additional requirements

5.2.1 In addition to the requirements given in 5.5 of ISO 14155:1996, the sponsor and the sponsor's investigators shall evaluate the rates of adverse events and visual acuity (VA) for the IOLs under clinical investigation on a continuing basis.

NOTE The published national study of cataract surgery in the United Kingdom may provide useful guidance on clinical performance of IOLs at periods corresponding with the early post-operative case report forms (see references [2] and [3]).

5.2.2 In addition to the requirements given in 5.6 of ISO 14155:1996, the safety and effectiveness of an IOL model shall be established through either:

— a clinical investigation conducted in accordance with this part of ISO 11979; or

— a comparison of the model characteristics that establish the model as a minor modification of a parent model for which the safety and effectiveness have been established through clinical investigation in accordance with this part of ISO 11979.

NOTE Annex B provides guidance in determining if a modification is minor by providing examples of modifications that have historically been considered minor.

For the IOL intended for correction of aphakia in a general adult population, a clinical investigation shall either be developed using the protocol elements provided in annex C or a sponsor shall develop an equivalent protocol that shall have a similar statistical power to detect differences in adverse event and visual acuity rates between the test population and a concurrent control population. Subjects implanted with a parent IOL that has met the requirements of all parts of ISO 11979 may be used as a control population.

In the case of IOLs designed for either chamber, a separate clinical investigation shall be performed to assess the clinical performance of the IOL in each chamber.

5.2.3 In addition to the requirements given in 5.7 of ISO 14155:1996, all subjects in a clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects that have been enrolled in the investigation, including those whose IOL was removed or replaced, have reached the final reporting period.

6 Methodology

6.1 Documentation

The requirements given in 6.1 of ISO 14155:1996 shall apply.

6.2 Access to information

The requirements given in 6.2 of ISO 14155:1996 shall apply.

6.3 Additional health care

The requirements given in 6.3 of ISO 14155:1996 shall apply.

6.4 Clinical investigation plan

6.4.1 General requirements

The requirements given in 6.4 of ISO 14155:1996 shall apply.

6.4.2 Additional requirements

The following additional requirements shall apply.

The investigational lens shall only be implanted in a single eye of each subject.

At least the minimum sample size required by the study shall be included in the clinical investigation for each reporting period. The sponsor shall ensure a sufficient number of subjects in the clinical investigation so that the minimum number required by the investigation at each reporting period is reached.

NOTE Examples of pre-operative, operative and post-operative case report forms are included in annex C.

6.5 Role of sponsor

The requirements given in 6.5 of ISO 14155:1996 shall apply.

6.6 Role of monitor

The requirements given in 6.6 of ISO 14155:1996 shall apply.

6.7 Role of clinical investigator

6.7.1 General requirements

The requirements given in 6.7 of ISO 14155:1996 shall apply.

6.7.2 Additional requirements

The following additional requirements shall apply.

Clinical investigators shall file adverse event reports of serious adverse events with the sponsor immediately after learning of their occurrence. Other adverse events shall be reported on the case report forms.

7 Presentation of results

The results shall be presented as specified in clause 7 of ISO 14155:1996.

Annex A
(normative)

Selected definitions

To facilitate the understanding of this part of ISO 11979, selected definitions are reproduced in this annex. In the case of discrepancy, the definitions of ISO 11979-1 take precedence over those given here.

A.1
best-case subject
subject with no pre-operative pathology

A.2
cumulative adverse events
total number of adverse events which have occurred at any time up to a specified point in time post-operatively

A.3
intraocular lens model
identification by which the features of an intraocular lens, including those of its body and its loops, and the material(s) used in its construction, have been fully specified

NOTE 1 Examples of body features are body diameter, optic diameter, optic shape factor; examples of loop features are configuration, calibre, angulation.

NOTE 2 Any significant change in the specification of the materials (including their formulation or synthesis procedures) results in it being considered a new model.

A.4
level A modification of a parent intraocular lens model
modifications of a parent model which are considered minor and are not expected to result in any safety hazards or loss in effectiveness when compared to the parent model

A.5
level B modification of a parent intraocular lens model
modifications of a parent model which are greater than level A modifications

NOTE Level B modifications may present a safety hazard or loss of effectiveness concerns which result in a new model that is significantly different from the parent model.

A.6
lost to follow-up
describing a subject for whom the final post-operative case report form is overdue and who cannot be contacted despite extensive written and telephone follow-ups to determine the final clinical outcome

NOTE This category does not include subjects who have died.

A.7
optic shape factor
term describing the curvatures of the refracting surfaces of the optic (e.g. plano-convex, bi-convex)

A.8
parent intraocular lens model
intraocular lens model that a sponsor has qualified based on a clinical investigation of at least 100 subjects and which has met the requirements of all parts of ISO 11979

A.9
persistent adverse event
adverse event which is present at the conclusion of a clinical investigation

Annex B
(informative)

Examples of modifications of a parent IOL model

B.1 Design/material modifications of an IOL model

B.1.1 General

Modifications to an IOL that has previously undergone a clinical investigation by the sponsor have different requirements depending on the magnitude of the modifications. Two levels of modifications have historically been associated with a parent IOL: Level A and Level B. Examples of Level A and Level B modifications are given in B.2.

B.1.2 Level A

Level A modifications of a parent model in almost all cases do not require a clinical investigation. A case where a clinical investigation of a Level A modification of a parent model should be performed is if the modified model poses additional clinical questions which cannot be adequately addressed by preclinical testing, such as potential tissue damage associated with a modification in implantation technique necessitated by the modified design.

A Level A modification of a parent IOL usually does not itself become a parent IOL for subsequent modifications. The only case where it may is described below.

If a model is still under clinical investigation, Level A modified versions of that model may be introduced into the clinical investigation of the model and the data from the original investigational model and the Level A modified model(s) may be combined, except in the case of those Level A changes that involve material substitutions from parent models (i.e. modifications described in B.2.2.12).

A Level A modified IOL which was added to the clinical investigation of the investigational model may only itself be considered a parent IOL at the conclusion of the study if that Level A modified model was investigated in a minimum of 100 subjects at each case report form, if it met the requirements of all parts of ISO 11979 and if the results of a clinical analysis indicate that there is no significant difference between its clinical performance and the clinical performance of the other investigational models in the clinical investigation.

B.1.3 Level B

The clinical investigation of new IOLs that are Level B modifications of a parent model should include a minimum of 100 subjects monitored up to case report form 4 (case report forms are given in annex C).

The minimum number of case report forms for each visit should be 100. The sponsor should anticipate needing to enrol 125 subjects to take into account the subjects that are lost or die in the course of the clinical investigation.

The sample size required for the Level B clinical investigation is the minimum number necessary to detect a clinically significant difference in adverse event and visually acuity rates between the IOL under investigation and the rates associated with the historical control population. If the sponsor chooses to compare the performance of their IOL to a concurrently run control population, the sponsor should enrol sufficient subjects such that the ability of the study to detect changes in visual acuity and adverse event rates are equivalent to the ability associated with the study which compares the IOL to the historical control population.

The loss to follow-up subjects in the Level B investigation should be less than 10 %. Each investigator should have a minimum of 20 subjects, and no more than 25 % of the subjects in the investigation. The Level B clinical investigation should be considered completed when all subjects that have been enrolled in the investigation have reached case report form 4.

A Level B modified IOL may only itself be considered a parent IOL at the conclusion of the study if it was investigated in a minimum of 100 subjects at each case report form (therefore the model could not have been combined with Level A modifications of itself in the clinical study), and if it met the requirements of all parts of ISO 11979.

B.2 Examples of IOL modifications

B.2.1 General

Modifications to an IOL that has undergone a clinical investigation can be classified in one of two categories depending on the level of modification: Level A or Level B. The criteria that are to be used to determine what level of modification has occurred to the parent model are described below.

The applicability column indicates the type of IOL that the modification is allowed with:

P designates polymethylmethacrylate (PMMA) posterior chamber IOLs;

A designates PMMA anterior chamber IOLs;

SP designates posterior chamber IOLs made from soft materials that are of a one-piece, plate design (no loops);

SS designates multi-piece, posterior chamber IOLs with optics made of soft materials and loops made from standard material (PMMA, polypropylene, or polyimide);

SN designates multi-piece, posterior chamber IOLs with optics made of soft materials and loops made from non-standard materials.

A modified model may have various combinations of the modifications listed below, as long as all the required criteria are met (e.g. the modified model may have a larger optic, with a slightly modified loop configuration and a larger overall diameter than the parent model). Modification B.2.2.12 differs from the other modifications in that it involves material/design substitutions of parent models only.

B.2.2 Level A modifications (see B.2.1 for P, A etc.)

B.2.2.1 Mirror-image version of a model

Applicability is P/A/SP/SS/SN.

B.2.2.2 Change in overall diameter

Applicability in the case of the addition of a size specific to patients with a certain anterior chamber width range is A.

B.2.2.3 Changes in loop features

Applicability in the case of changes, such as the addition of notches or the addition of small loops or rounded ends to loops is P/A/SS/SN.

B.2.2.4 Change in loop angulation

Applicability in the case of a change from planar to a design with the body angulated posterior to loops resulting in an increase in the sagitta value up to a maximum of 1,6 mm for the 20 D version of the model is P/SS/SN.

B.2.2.5 Change in loop configuration, in loop thickness or width (calibre)

B.2.2.5.1 General

Applicability is P/SS/SN.

To determine if these changes result in modified lenses, which are Level A modifications of the parent lenses, an analysis of the change in mechanical properties that has occurred as a result of the modification is required.

The sponsor should be aware that loop modifications of a model that have satisfied the requirements of this part of ISO 11979 should not be considered as Level A modifications (even if the results of the required mechanical testing qualify them as such) if the modified model poses additional clinical questions that cannot be adequately addressed by preclinical testing (such as potential tissue damage associated with a modification in implantation technique necessitated by the new design).

Two methods of comparing the mechanical properties of a parent model and a modified model are given in this part of ISO 11979 and are described below. A sponsor may use either method. If the sponsor finds that a model is not a Level A with one of the methods, it should be determined whether it might be a Level A by the other method before beginning a clinical evaluation of that modified model.

NOTE A discussion of the methods and data analysis to be used for the testing listed below is given in ISO 11979-3.

B.2.2.5.2 Comparison to a single parent model

Applicability is P/SS/SN.

For comparisons between a modified model and an investigational model which is currently undergoing a clinical investigation, the sponsor should demonstrate that the mechanical properties of the modified lens are not significantly different from the mechanical properties of the investigational model under study.

For comparisons between a modified model and a single parent model, the sponsor should demonstrate that the mechanical properties of the modified lens are not significantly different from the mechanical properties of the parent model.

NOTE A detailed description with examples showing how to apply this method is given in ISO 11979-3.

B.2.2.5.3 Comparison to multiple parent models

Applicability is P/SS/SN.

For comparisons between a modified model and multiple parent models, the sponsor should demonstrate that the mechanical properties of the modified lens are not significantly different from the range of characteristics defined by the parent models.

NOTE A detailed description with examples showing how to apply this method is given in ISO 11979-3.

B.2.2.6 Change in the dioptric power range

Applicability is P/A/SP/SS/SN.

There is no limit to the power range that the sponsor makes available for these types of IOLs, provided each power within the range that a sponsor makes available for a model meets the minimum optical quality level specified in ISO 11979-2.

Sponsors should be advised that, for certain combinations of optic shape factor and material, certain powers may not meet that level because of the affects of spherical aberrations. In such cases, the powers made available shall be restricted to those meeting the requirements of ISO 11979-2.

B.2.2.7 Change in optic or body size and addition of tabs to the periphery of the optic

Applicability is P/SP/SS/SN.

Changes in body circumference design or optic size are allowed if the length is not less than 5,0 mm along any meridian (e.g. going from a circular to an ovoid body) and not greater than 7,5 mm along any meridian.

B.2.2.8 Additions, deletions or moving of positioning holes

Applicability is P/A/SP/SS/SN

Positioning holes, or any other obstruction that interferes with the performance of the optic, should be placed no less than 2,25 mm from the centre of the optic to minimize the possibility of glare or other visual disturbances that may result from these structures.

B.2.2.9 Addition of a ridge to the posterior surface of the body

Applicability is P.

Addition of a ridge to the posterior body is permissible, if the ridge design has been qualified by being a part of a model that has been the subject of a clinical investigation and has satisfied the requirements of this part of ISO 11979, and if the edge of the ridge is not any closer than 2,25 mm to the centre of the optic.

B.2.2.10 Multiple designs in a single clinical investigation

Applicability is P/SS/SN.

A single material may be investigated with more than one design, if all the designs in the clinical investigation have been previously qualified by being associated with parent models. Therefore, the only variable being investigated is the new material. The only restriction is that the mechanical properties of the parent design should not be significantly altered (i.e. not greater than those allowed as a Level A modification) by being manufactured from the new material.

B.2.2.11 Multiple materials in a single clinical investigation

Applicability is P/SS/SN.

A single design may be investigated with more than one loop, body or single-piece material if all the materials in the clinical investigation have been previously qualified by being associated with parent models. Therefore, the only variable being investigated is the new design. The only restriction is that, if more than one material is used for the loops, all the models should be Level A modifications of each other in terms of mechanical properties (see B.2.2.5).

B.2.2.12 Interchanging IOL materials and designs

Applicability is P/SS/SN.

Materials and designs from parent models may be interchanged if the use of the material with the new (for that material) design does not result in any significant change in the mechanical properties of the original parent design.

B.2.3 Level B modifications

B.2.3.1 Change in overall diameter

Applicability is P/SS/SN.

This change in overall diameter results in a lens modification displaying mechanical behaviour that does not meet the requirements for a minor modification in B.2.2.5 when compared to a single parent model or when compared to the range of acceptable mechanical behavior of parent models.

B.2.3.2 Change in loop configuration

Applicability is P/SS/SN.

This change in loop configuration results in a lens modification displaying mechanical behaviour that does not meet the requirements in B.2.2.5 when compared to a single parent model or when compared to the range of acceptable mechanical behaviour of parent models. If the change in loop configuration of the modified lens (e.g. a single piece disc lens) appears to have the potential to cause different or greatly increased safety concerns as compared to the parent model(s), the new model should undergo the 300 subject clinical investigation required for new models.

B.2.3.3 Change in loop material or calibre

Applicability is P/SS/SN.

This change in loop material (to another material that has been qualified by being part of a parent model) or calibre results in a lens modification that does not meet the requirements in B.2.2.5 when compared to a single parent model or when compared to the range of acceptable mechanical behaviour of parent models.

B.2.3.4 Change to new loop material for sponsor

Applicability is P/SS/SN.

This is a change in loop material to a material that is new to the sponsor, but is a material whose long-term safety as a loop material can be supported by the ophthalmic literature. The articles must provide the identity of the material used, and the sponsor must be using the identical material.

B.2.3.5 Change in body material

Applicability is P/SS/SN.

This is a change in body material to a material that is new to the sponsor, but is a material whose long-term safety as a body material can be supported by the ophthalmic literature. The articles shall provide the identity of the material used, and the sponsor shall use the identical material.

B.2.3.6 Change in body or optic diameter

Applicability is P/SS/SN.

This is a change in body or optic diameter outside the range from 5,0 mm to 7,5 mm. The sponsor should be aware that the evaluations of models that incorporate optics less than 5,0 mm in diameter should include clinical testing to evaluate the effects of glare on the subject's visual acuity that may result from the small optic.

B.2.3.7 Initial addition of a model with a ridge

Applicability is P.

This is an initial addition of a model with a ridge on the posterior surface of the body.

Annex C
(informative)

Elements of an IOL clinical protocol

C.1 IOL clinical protocol elements

C.1.1 General

The following are important elements of a clinical protocol which will assist the sponsor in collecting sufficient, relevant and appropriate data to determine the safety and effectiveness of IOLs which are within the scope of this part of ISO 11979. These elements were derived from the historical data on the long clinical experience associated with these types of IOLs.

C.1.2 Control population

The clinical results of a historical control population are provided in annex D. The clinical performance of the IOL under investigation may either be compared to these data or to the results of a concurrently run control population using an appropriate control.

C.1.3 Number of subjects

The clinical investigation should include a minimum of 300 subjects when the performance of the IOL will be compared to the performance of the historical control population. The comparison of the performance of the IOL to an appropriate, concurrently studied control population should require the sponsor to enrol sufficient subjects such that the ability of the study to detect changes in visual acuity and adverse event rates is equivalent to the ability associated with the 300 subject study which compares the IOL performance to the performance of the historical control population. The sponsor should be aware that any additional claims beyond the safety and effectiveness of the IOL will require the sponsor to calculate an appropriate sample size in all cases.

To take into account the subjects that are lost during the course of the clinical investigation, the sponsor should anticipate needing to enrol about:

— 390 subjects in the one-year investigation;

— 500 subjects in the three-year investigation.

The sponsor should further refrain from enrolling significantly larger numbers of subjects than are listed above to minimize the number of subjects exposed to the risks associated with the implantation of an IOL model which has not yet been determined to be safe and effective.

To assist in achieving a balance in the number of subjects from each investigator, the sponsor's clinical protocol should require that each investigator have a minimum of 20 subjects, and no more than 25 % of the subjects in the investigation.

To minimize the uncertainty in the data, the lost to follow-up subjects in the three-year investigation should be less than 30 % and the lost to follow-up in one-year investigation should be less than 10 %.

C.1.4 Duration of the clinical investigation

Extensive clinical experience indicates that the following study durations are necessary to make an adequate assessment of the adverse event rates associated with the following types of IOLs:

— one year (case report form 5): for all posterior chamber IOLs;

— three years (case report form 7): for all anterior chamber IOLs.

The above is relevant whether the IOLs are surface modified or not by a coating or by chemical treatment designed to alter the surface chemistry to enhance the biocompatibility of the IOL.

To minimize the risks associated with the clinical investigation of a new IOL, the clinical investigation of a new IOL model should consist of two phases:

— Phase 1: The first phase of the clinical investigation consists of the implantation of the IOL model in no more than 100 subjects. After at least 50 of those subjects have reached case report form 4, their data are clinically evaluated by the sponsor and the investigator. If the IOL model's performance in these first 50 subjects is acceptable, the sponsor may begin the next phase of the investigation.

— Phase 2: The second phase of the clinical investigation consists of the implantation of the remainder of the subjects necessary for the clinical investigation.

C.1.5 Reporting periods

As a minimum, the clinical data for the subjects should include the post-operative case report forms up to case report form 5 for the one-year clinical investigation. These forms are defined below:

— Case Report Form 0: Pre-operative/Operative reporting;

— Case Report Form 1: Post-operative reporting 1 or 2 days post-operatively;

— Case Report Form 2: Post-operative reporting 7 to 14 days post-operatively;

— Case Report Form 3: Post-operative reporting 30 to 60 days post-operatively;

— Case Report Form 4: Post-operative reporting 120 to 180 days post-operatively;

— Case Report Form 5: Post-operative reporting 330 to 420 days post-operatively.

As a minimum, the three-year clinical investigations should include all the case report forms listed above and both case report forms defined below:

— Case Report Form 6: Post-operative reporting 630 to 780 days post-operatively;

— Case Report Form 7: Post-operative reporting 990 to 1140 days post-operatively.

Clinical evaluations during these reporting periods are necessary to capture the data associated with the potential adverse events of the types of IOLs which are within the scope of ISO 11979.

Unscheduled visits and the procedures to capture adverse events that may occur between case report forms should be addressed in the clinical investigation plan.

For the one-year and three-year clinical investigations, the minimum number of case report forms for each reporting period should be 300.

C.2 Additional clinical guidance

C.2.1 General

Additional clinical guidance which will assist the sponsors in designing their IOL clinical investigation protocol and in analysing the data from that investigation is provided below.

C.2.2 Standardization of the clinical evaluation

The sponsors should ensure as far as is possible that the criteria used by all investigators for evaluation of adverse events and the parameters associated with the visual acuity evaluation (e.g. chart design, light levels, uniformity of chart illumination, chart reflectivity, minimization of glare, test distance, general methodology) are sufficiently similar to allow for the combining of data from the investigators.

If the sponsors determine that it is necessary to correlate the optotypes used in their clinical investigation to a standard optotype, they should use the method described in ISO 8597 (see reference [3] in the Bibliography).

C.2.3 Guidance on data analysis

The sponsors should consider evaluating the clinical data in terms of the following to look for trends which may suggest that a problem does or does not exist with the lens design, which may not be apparent from an overall analysis of the adverse event and visual acuity (VA) rates:

— VA by age;

— best-case VA;

— VA by adverse event;

— VA by pre-operative ocular pathology;

— patient-by-patient analysis of reasons why patient failed to achieve 0,5 (6/12; 20/40) VA;

— rates of cumulative adverse events by age;

— rates of persistent adverse events by age;

— rates of other adverse events;

— VA by investigator;

— adverse event by investigator.

This clinical data evaluation should provide insight into whether an IOL's failure to meet the clinical performance levels associated with the historical or concurrent control populations is device related.

The sponsors should be aware that clinical performance levels for a large historical control population have never been established for adverse events other than those listed in the tables in annex D. The sponsors should use their investigators' clinical assessments, values from published literature and/or values from previous clinical investigations, if any, that the sponsors have undertaken to determine the minimum acceptable clinical performance levels for these other adverse events.

C.2.4 Clinical case report forms

The next pages provide examples of the following case report forms:

— pre-operative/operative case report form — posterior chamber lenses (Table C.1);

— post-operative case report form — posterior chamber lenses (Table C.2);

— pre-operative/operative case report form — anterior chamber lenses (Table C.3);

— post-operative case report form — anterior chamber lenses (Table C.4);

— adverse event case report form (Table C.5).

Table C.1 — Pre-operative case report form for posterior chamber lens study

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

Patient number: _ _ _ _ Patient Initials: _____ Sex: Male: ☐ Race: Caucasian ☐

Female: ☐ Black ☐

Asian ☐

Other ☐

Mixed ☐

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

Pre-operative report

_ _ _ _ _ _ (DD MM YY)

Operative eye	right ☐	left ☐
	Operative eye	Fellow eye
Best corrected visual acuity	_____	_____
or check one:		
finger count	☐	☐
hand movement	☐	☐
light perception	☐	☐
no light perception	☐	☐

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

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

Cataract

etiology (check one) senile ☐

other (specify)_____ ☐

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

Biometry K1_____D Axial length_____mm

K2_____D

Target postoperative refraction _____

Signed informed consent obtained: yes ☐

_ _ _ _ _ _ (DD MM YY)

Operative report

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

Viscoelastic used yes ☐ no ☐

If yes, specify _____

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

Irrigating solution used yes ☐ no ☐

If yes, specify _____

Periocular medication (check yes or no for each)	yes (specify)	no
Antibiotic	☐ _____	☐
Corticosteroid	☐ _____	☐
Other (specify)	☐ _____	☐

Incision

Incision size _____

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

Type of lens extraction (check one)

Planned ECCE ☐

Phacoemulsification ☐

Other (specify) _____ ☐

Type of capsulotomy (check one)

CCCR (continuous curvilinear capsulorhexis) ☐

Can Opener ☐

Other (specify) _____ ☐

Position of the loops (check one)

in the bag ☐

partly in the bag ☐

In the sulcus ☐

uncertain ☐

Other surgical procedures (check yes or no for each)	yes	no
Peripheral iridotomy/iridectomy	☐	☐
Sphincterotomy	☐	☐
Other (specify) _____	☐	☐

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

If study lens not implanted indicate reason:

Lens implanted. Place label here:

Time incision to closure _____ min. _____

Signature of investigator

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

Table C.2 — Post-operative case report form for posterior chamber lens study

Investigator name: _____ Clinical Trial No: _ _ _ _

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

Post-operative Report

_ _ _ _ _ _ (DD MM YY)

Eye right ☐ left ☐

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

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

Refraction
Sphere _____
Cylinder _____
Axis _____

Keratometry
K1_____D
K2_____D

Best corrected visual acuity

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

IOP (Applanation) _____mmHg

Medications used up to this visit

(check yes or no for each)	topical yes	topical no	systemic yes	systemic no
Corticosteroids	☐	☐	☐	☐
Antibiotics	☐	☐	☐	☐
NSAIDs	☐	☐	☐	☐
Glaucoma medication	☐	☐	☐	☐

Other (specify) _____

Corneal stromal oedema

	wound	central
none	☐	☐
mild/moderate	☐	☐
severe	☐	☐

Iritis (check one)

none	☐
mild	☐
moderate	☐
severe	☐

Other pathology and complications

(check present or absent for each)	present	absent
Wound leak	☐	☐
Flat anterior chamber	☐	☐
Hyphema	☐	☐

Cont.: Other pathology and complications

	present	absent
Vitreous in anterior chamber	☐	☐
Vitreous to wound	☐	☐
Raised IOP requiring treatment	☐	☐
Pupillary block	☐	☐
Anterior Synechiae	☐	☐
Posterior Synechiae	☐	☐
Inflammatory deposits on IOL	☐	☐
Fibrin in pupil	☐	☐
Cortical remnants	☐	☐
Nuclear remnants	☐	☐
IOL optic decentration	☐	☐
If present; _____ mm		
IOL dislocation out of the posterior chamber	☐	☐
Retinal detachment	☐	☐
Diabetic retinopathy	☐	☐
Cystoid macular oedema	☐	☐
If present, how diagnosed?		
Clinical ☐		
Fluorescein angiography ☐		
Macular degeneration	☐	☐
Optic atrophy	☐	☐
Other (specify) _____	☐	☐

	yes	no
Is the anterior capsule intact?	☐	☐
If intact:		
Posterior capsule fibrosis	☐	☐
Elschnig's Pearls	☐	☐
If not intact: Has the capsule been opened since the last reported visit?	☐	☐

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

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

	yes	no
Has the patient experienced any adverse event?	☐	☐

If yes, fill in the adverse event report form

If serious, fill in the adverse event report form and contact the sponsor within one working day

Table C.3 — Pre-operative case report form for anterior chamber lens study

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

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

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

Pre-operative report

_ _ _ _ _ _ (DD MM YY)

Operative eye right ☐ left ☐

Best corrected visual acuity or check one:	Operative eye	Fellow eye
finger count	☐	☐
hand movement	☐	☐
light perception	☐	☐
no light perception	☐	☐

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

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

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

Pachymetry (if done): _____ mm

Cataract

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

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

Biometry K1_____D Axial length

K2_____D _____mm

Target postoperative refraction _____

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

Operative report

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

Viscoelastic used yes ☐ no ☐

If yes, specify _____

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

Irrigating solution used yes ☐ no ☐

If yes, specify _____

Periocular medication (check yes or no for each)	yes (specify)	no
Antibiotic	☐ _____	☐
Corticosteroid	☐ _____	☐
Other (specify)	☐ _____	☐

Incision

Incision size _____

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

Type of lens extraction (check one)

Planned ECCE ☐

Phacoemulsification ☐

Other (specify) _____ ☐

Type of capsulotomy (check one)

CCCR (continuous curvilinear capsulorhexis) ☐

Can Opener ☐

Other (specify) _____ ☐

Position of the loops (check one)

in the bag ☐

partly in the bag ☐

in the sulcus ☐

uncertain ☐

Other surgical procedures (check yes or no for each)	yes	no
Peripheral iridotomy/iridectomy	☐	☐
Sphincterotomy	☐	☐
Other (specify) _____	☐	☐

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

If study lens not implanted indicate reason:

Lens implanted. Place label here:

Time incision to closure ____ _____ min

Signature of investigator

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

Table C.4 — Post-operative case report form for anterior chamber lens study

Investigator name: _____ Clinical trial no: _ _ _ _

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

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

Eye right ☐ left ☐

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

Refraction
Sphere _____
Cylinder _____
Axis _____

Keratometry
K1_____D
K2_____D

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

IOP (Applanation) _____mmHg

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

Other (specify) _____

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

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

Other pathology and complications (check present or absent for each)	present	absent
Wound leak	☐	☐
Flat anterior chamber	☐	☐
Hyphema	☐	☐
Vitreous in anterior chamber	☐	☐
Vitreous to wound	☐	☐
Hypopyon	☐	☐
Endophthalmitis	☐	☐

If present infectious ☐
sterile ☐

Cont.: Other pathology and complications

	present	absent
Raised IOP requiring treatment	☐	☐
Pupillary block	☐	☐
Anterior synechiae	☐	☐
Posterior synechiae	☐	☐
Short lens	☐	☐
Iris tuck	☐	☐
Inflammatory deposits on IOL	☐	☐
Fibrin in pupil	☐	☐
Cortical remnants	☐	☐
Nuclear remnants	☐	☐
IOL optic decentration	☐	☐
If present, _____mm		
IOL dislocation out of the anterior chamber	☐	☐
If present, specify _____		
Retinal detachment	☐	☐
Diabetic retinopathy	☐	☐
Cystoid macular oedema	☐	☐
If present, how diagnosed?		
clinical ☐		
fluorescein angiography ☐		
Macular degeneration	☐	☐
Optic atrophy	☐	☐

Other (specify) _____

Lens axis _____°

	yes	no
Is the posterior capsule intact?	☐	☐
If intact: Posterior capsule fibrosis	☐	☐
Elschnig's pearls	☐	☐
If not intact: Has the capsule been opened since last reported visit?	☐	☐

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

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

If yes, specify:

Has the patient experienced any adverse event?	yes	no
	☐	☐

If yes, fill in the Adverse Event Report Form.
If serious, fill in the Adverse Event Report Form and contact the sponsor within one working day.

Signature of investigator

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

Table C.5 — Adverse event report form

Investigator name: _____ Clinical trial no: _ _ _ _

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

Investigators must report all adverse events, whether or not considered related to the test product. Serious and/or unexpected reactions should immediately, within one working day, be reported to the sponsor by phone and/or telefax. In case of a serious adverse event, the Adverse Event Report Form must also be completed, signed and sent to the sponsor within 5 working days. Please use registered mail when sending an Adverse Event Report Form and/or relevant documents to:

1. Operative eye right (OD) ☐
left (OS) ☐

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

3. Lens model no. _ _ _ _

4. Lens serial no. _ _ _ _ _ _ _

5. Power of IOL _ _ _

ADVERSE EVENT

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

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

8. Severity of adverse event (check one)
Mild ☐
Moderate ☐
Severe ☐

9. Describe course of adverse event (please print)

10. Diagnosis of adverse event (please print)

11. Treatment of adverse event (please print)

12. Outcome (check one)
Complete recovery ☐
Recovered with sequelae ☐
Not recovered on day of report ☐
Died ☐
Prognosis, if not recovered:
_____
_____

Comments (please print)

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

Comments (please print)

14. Was adverse event serious/sight-threatening? yes ☐ no ☐
If yes, fill in the adverse event report form and contact the sponsor within one working day.

_____
Signature of investigator
Date: _ _ _ _ _ _
DD MM YY

Telephone _ _ _ - _ _ _ _ _ _ _ - _ _ _
Area Code Number Ext.