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Ophthalmic optics — Contact lenses and contact lens care products — Guidance for clinical investigations

Optique ophtalmique — Lentilles de contact et produits d'entretien pour lentilles de contact — Directives pour les investigations cliniques

(Revision of first edition ISO 11980:1997 and ISO 11980:1997/Cor.1:1998)

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Pour accélérer la distribution, le présent document est distribué tel qu'il est parvenu du secrétariat du comité. Le travail de rédaction et de composition de texte sera effectué au Secrétariat central de l'ISO au stade de publication.

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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 11980 was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*, and by Technical Committee CEN/TC 170, *Ophthalmic optics* in collaboration.

This second edition cancels and replaces the first edition (ISO 11980:1997/COR1:1998) which has been technically revised.

Introduction

Currently contact lenses and contact lens care products are regulated in different ways in different countries. This International Standard has been developed to encourage global harmonization. It is hoped that the adoption of this International Standard will be yet another step toward Mutual Recognition. This International Standard could also be used as a basis to fulfil design elements of ISO 9001.

Ophthalmic optics — Contact lenses and contact lens care products — Guidance for clinical investigations

1 Scope

This International Standard provides guidance for the clinical investigation of the safety and performance of contact lenses and contact lens care products.

NOTE This International Standard attempts to harmonize the recognized regulatory requirements for the conduct of a clinical investigation to meet the marketing and labelling requirements for contact lenses and contact lens care products around the world. However, national requirements vary greatly. Wherever national practice or regulations dictate some legal requirement, this requirement takes precedence over this International Standard.

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 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 14534, *Ophthalmic optics — Contact lenses and contact lens care products — Fundamental requirements*

ISO 18369-1, *Ophthalmic optics — Contact lenses — Part 1: Vocabulary, classification system and recommendations for labelling specifications*

3 Terms and definitions

For the purposes of this document the terms and definitions given in ISO 14155-1, ISO 14155-2, ISO 18369-1 and ISO 14534 apply.

4 Clinical investigational requirements

4.1 General

The general requirements for a clinical investigation (CI) and for a clinical investigation plan (CIP) given in ISO 14155-2 shall apply, with additional requirements given below.

4.2 Additional requirements

4.2.1 Study design

4.2.1.1 General

a) The inclusion criteria for subject selection shall relate to the study objectives and shall include:
Subjects with normal eyes and be using no ocular medications, age equal to or greater than 18 years of age (except when contact lens investigations have a special indication for use in children (for the purpose of this discussion less than 18 years of age) such as orthokeratology, pediatric aphakic lenses, etc) ; lens powers within the range available for the test lenses; the manifest cylinder should be equal to or less than 0,75 D (for a study with only spherical power correcting lenses); best spectacle corrected visual acuity equal to or greater than 20/25 (equal to or less than LogMAR 0,1).

b) The exclusion criteria for subject selection shall relate to the study objectives and shall include but not be limited to:
Anterior segment infection, inflammation or abnormality; any active anterior segment ocular disease that would contraindicate contact lens wear; the use of systemic or ocular medications that would contraindicate contact lens wear; history of herpetic keratitis; history of refractive surgery or irregular cornea (except when the contact lenses under investigation are indicated for irregular cornea, keratoconus or refractive surgery; slit lamp findings that are equal to or more serious than trace findings (equal to or greater than grade 1); corneal vascularization greater than 1 mm of penetration; a pathologically dry eye; subject has participated in a contact lens or contact lens care product clinical trial within the previous 30 days.

c) The CIP shall provide a description of the monitoring procedure to ensure consistent quality of data collection and recording.

d) The CIP should include a validated statistical analysis plan. Sample size shall be justified. If multiple endpoints are used, then the statistical analysis plan shall specify the appropriate method that will be used to control the overall study Type I error (e.g., Bonferroni Correction, Hommel's Correction).

4.2.1.2 Contact lenses

A clinical investigation of contact lenses, including daily wear and extended wear hydrogel, silicone hydrogel and rigid gas permeable contact lenses, shall be designed as one of the following:

a) As a prospective, concurrently controlled study:
For investigations evaluating hydrogel, silicone hydrogel or rigid gas permeable contact lenses, a prospective, concurrent control study design shall be followed. Either a bilateral crossover design may also be a considered option or a contra-lateral eye (i.e., intra-subject) or inter-subject controls shall be utilized. If inter-subject controls are utilized, the ratio of test subjects to control subjects may be either 2:1 or 1:1. The control lens shall be a currently marketed contact lens in use for the same modality. Randomization and masking (subject, investigator and evaluator) shall be employed where possible to minimize the potential for bias. Subjects shall be divided evenly between study investigators.

Or:

b) As an uncontrolled study, in which case the results are compared to a historical control:
Alternative investigational study designs, such as historical controls, shall be utilized when a sponsor has a clinical database on a marketed contact lens to use as a comparator. If any historical control is used, the control group shall be defined and adequately characterized for comparison to the test group. Compatibility of test and control groups shall be demonstrated by comparison of the selection criteria, demographics, refractive characteristics, contact lens wearing history and CIPs used.

For CIP's to demonstrate safety and performance as well as special claims (e.g. comfort), labelling or additional indications are proposed, a pre-determined statistical analysis plan (including sample size calculations) shall be described in the CIP. Where feasible, the CIP shall define objective endpoints to help support such claims.

NOTE 1 Inter-subject controls are preferred to intra-subject controls due to the potential dependence between the two eyes and concerns over subject compliance.

NOTE 2 Annex A provides guidance for the design of a clinical investigation.

4.2.1.3 Contact lens care products

For investigations evaluating contact lens care products, a prospective concurrent control study design shall be followed. It is recommended that the ratio of test to control subjects be either 2:1 or 1:1. The control care product shall be a currently marketed contact lens care product. Randomization and masking (subject, investigator and evaluator) shall be employed where possible to minimize the potential for bias. Subjects shall be divided evenly among study investigators. Alternative investigational study designs, such as use of historical controls, may be utilized when a manufacturer has a clinical database on a marketed care product to use for comparison. If any historical control is used, the control group should be defined and adequately characterized for comparison to the test group. Compatibility of test and control groups should be demonstrated by comparison of the selection criteria and CIPs used.

For CIPs to demonstrate safety and performance, as well as special claims (e.g. comfort), labelling or additional indications are proposed for the care products, a pre-determined statistical analysis plan (including sample size calculations) shall be described in the clinical protocol. Where feasible, the protocol should define objective endpoints to help support such claims.

Inter-subject controls are preferred to intra-subject controls due to the potential dependence between the 2 eyes and concerns regarding subject compliance.

In a product investigation, a daily wear schedule shall be followed for most products in order to maximize the subject's exposure to those products. However, a study of a lens or a periodic cleaner, used on weekly intervals, may provide more valuable clinical data concerning efficacy when extended wear subjects are enrolled, than a similar investigation with daily wear subjects.

When a daily wear schedule is used, clinical study follow-up visits shall generally be done at least four hours after lens insertion; however, one post-dispensing visit should be done at between one to two hours after lens insertion, in order to permit observation of corneal and conjunctival staining due to an immediate toxicity reaction.

A product with a cleaning indication shall have an objective measure of lens cleanliness on at least one lens collected from each subject at the end of the clinical study.

If the manufacturer of a lens care product wishes to recommend its use with a specific type of lens in the labelling, the compatibility with the lens type should be confirmed pre-clinically and during the clinical trial.

NOTE 1 If the clinical investigation has not collected any data on use with a particular type of lens material (such as silicone-hydrogel lenses), the product label should clearly state this fact.

NOTE 2 Annex A provides guidance for the design of a clinical investigation.

4.2.2 Variables

4.2.2.1 Contact lenses

The following variables shall be assessed during the clinical investigation for contact lenses, in addition to the variables listed in 4.2.2.2:

a) visual performance;

b) refractive performance;

c) keratometric measurements;

d) lens centration;

e) lens movement;

f) lens surface wettability;

g) lens surface deposits;

h) subject acceptance of comfort;

i) subject acceptance of vision;

j) subject acceptance of handling.

Additional variables can be studied in the clinical investigation to support specific claims.

NOTE Annex C provides guidance on classifications for each of these variables.

4.2.2.2 Contact lens care products

The following variables shall be assessed during the clinical investigation for contact lens care products:

a) corneal oedema;

b) corneal infiltrates;

c) endothelial irregularity;

d) corneal vascularization;

e) corneal staining;

f) conjunctival observations;

g) palpebral conjunctival observations;

h) corneal ulcers;

i) corneal opacification;

j) hyphema;

k) hypopyon;

l) iritis;

m) corneal scarring.

Additional variables can be studied in the clinical investigation to support specific claims.

NOTE Annex B provides guidance on classifications for some of these variables.

4.3 Other considerations

Serious ophthalmic adverse events and all adverse device effects shall be reported using a special case report form and forwarded to the sponsor as required. All other ophthalmic adverse events shall be reported using the standard visit case report forms and are collected during monitoring.

Annex A
(informative)

Elements of a clinical investigation

A.1 General

The following are elements of a clinical investigation plan which can assist in collecting data for the purpose of determining the safety and performance of contact lenses and contact lens care products.

A.2 Study size and duration

A.2.1 Contact lens investigations

Table A.1 —Guide to the subject numbers (completed subjects) suggested for contact lens clinical investigations (informative)

Wearing modality	Subject number evaluable per group at end of study	Duration	Material
Daily wear	50 subjects	3 months	Containing new or new ratio material components; or significant design changes
	30 subjects	30 days	Existing materials
Daily wear orthokeratology	50 subjects	3 months or longer, if necessary to reach defined stability	Existing materials
Extended wear, up to 7 days	160 subjects	12 months	Existing materials
Extended wear, up to 30 days	570 subjects	12 months	Existing materials
Overnight wear (may include orthokeratology)	300 subjects	12 months	Existing materials

A.2.2 Contact lens care products

A.2.2.1 Contact lens care products, including saline solutions, daily cleaners, periodic cleaners, disinfecting solutions, neutralizers, “in-eye” solutions, conditioning solutions, and multipurpose solutions that have any new active ingredient, or any active ingredient outside the concentration range used in a comparable marketed product, should undergo a 3 month clinical study.

A.2.2.2 Products for use with soft (hydrophilic) lenses: Sample size (completed) should be 30 subjects in the test solution and 15 subjects in the control solution (a currently marketed solution for the same indication) for each appropriate representative category such as:

— Group I,

— Group IV,

— A separate group for each silicone-hydrogel lens. If more than one lens is made by a given manufacturer, and they all have the same general chemistry, it is sufficient to use only the lens of highest water content.

A.2.2.3 Products for use with rigid lenses: Sample size (completed) should be 15 or 30 subjects in the test solution and 15 subjects in the control solution (a currently marketed solution for the same indication) for each appropriate material category.

A.2.2.4 For a contact lens solution that does not contain any new active ingredients (as described above), but contains any active ingredient lower than the concentration range used in a comparable marketed product, a 1 month clinical study should be conducted. In this case, the sample size should be half of that recommended above, using the same general distribution of subjects.

A.2.3 Statistical considerations for extended wear evaluations

A.2.3.1 General

Primary safety analysis: The key safety endpoint should be the frequency of serious and significant adverse events.

The null hypothesis (H_0) is that the test rate of endpoint adverse events (p_t) minus the control rate of endpoint adverse events (p_c) is greater than or equal to the clinically insignificant difference (δ) between the two rates.

The alternative hypothesis (H_a) is that the test rate of endpoint adverse events (p_t) minus the control rate of endpoint adverse events (p_c) is less than a clinically insignificant difference (δ) between the two rates.

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

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

where
p_t is the proportion in the test population, and
p_c is the proportion in the control population.

When using a 1:1 ratio of patient allocation between treatment and control, the minimum number n of completed patients necessary for each treatment group is determined by the equation below:

$$n = \frac{(Z_{1-\beta} + Z_{1-\alpha})^2 \times [p_t(1-p_t) + p_c(1-p_c)]}{\delta^2}$$

where
α is the significance level (also known as the type 1 error rate);
1 - β is the power of the test; and
Z is the standard normal quantile.

The following is an example of the calculation that makes assumptions found to be reasonable for clinical studies of 7-day extended wear hydrogel or silicone hydrogel contact lenses. With a control rate (p_c) and a test rate of 0;033 (under H_a), a clinically insignificant difference (δ) of 0,05, a power (1 - β) of 0,80, and a significance level (α) of 0,05, the minimum number of completed patients per treatment group is:

$$n = \frac{(0{,}84 + 1{,}64)^2 \times [0{,}033(1-0{,}033) + 0{,}033(1-0{,}033)]}{0{,}05^2} \cong 158$$