INTERNATIONAL STANDARD

ISO 11980

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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

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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*.

This second edition cancels and replaces the first edition (ISO 11980:1997), of which it constitutes a technical revision. It also incorporates the Technical Corrigendum ISO 11980:1997/Cor.1:1998.

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. Widespread adoption of this International Standard should represent yet another step toward mutual recognition. This International Standard can also be used as a basis to fulfil design elements of ISO 9001[1].

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

1 Scope

This International Standard gives guidelines for the clinical investigation (CI) 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 CI 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 14534 and ISO 18369-1 apply.

4 Clinical investigational requirements

4.1 General

The general requirements for a 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 should include:

   1) subjects with normal eyes who are not using any ocular medications, aged 18 years or over [except when contact lens investigations have a special indication for use in “children” (for the purposes of this International Standard, persons less than 18 years of age) such as orthokeratology and paediatric aphakic lenses];

   2) lens powers within the range available for the test lenses;

   3) the manifest cylinder less than or equal to 0,75 D (for a study with only spherical power correcting lenses);

   4) best spectacle corrected visual acuity greater than or equal to 20/25 (less than or equal to LogMAR 0,1).

b) The exclusion criteria for subject selection shall relate to the study objectives and should include, but not be limited to:

   1) anterior segment infection, inflammation or abnormality;

   2) any active anterior segment ocular disease that would contraindicate contact lens wear;

   3) the use of systemic or ocular medications that would contraindicate contact lens wear;

   4) history of herpetic keratitis;

   5) history of refractive surgery or irregular cornea (except when the contact lenses under investigation are indicated for irregular cornea, keratoconus or refractive surgery);

   6) slit lamp findings that are equal to or more serious than trace findings (greater than or equal to grade 1);

   7) corneal vascularization greater than 1 mm of penetration;

   8) a pathologically dry eye;

   9) participation of the subject 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 shall include a statistical analysis plan. Sample size shall be justified, calculated by a validated statistical software package.

4.2.1.2 Contact lenses

4.2.1.2.1 General. A CI of contact lenses, including daily wear and extended wear hydrogel, silicone hydrogel, and rigid gas-permeable contact lenses, shall be designed as one of 4.2.1.2.2 or 4.2.1.2.3.

For CIPs to demonstrate safety and performance, as well as special claims (e.g. comfort), labelling or additional indications, the following is required: a pre-determined statistical analysis plan (including sample

size calculations) shall be specified in the clinical protocol. 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 regarding subject compliance.

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

4.2.1.2.2 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 or a contra-lateral eye (i.e. intra-subject) design 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.

4.2.1.2.3 As an uncontrolled study. Here, 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.

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 between 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, the following is required for the care products: a pre-determined statistical analysis plan (including sample size calculations) shall be specified in the clinical protocol. Where feasible, the protocol should 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 regarding subject compliance.

In a contact lens care 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 at 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 and safety is a primary objective, one post-dispensing visit should be done 1 h to 2 h after lens insertion in order to permit observation of corneal and conjunctival staining caused by an immediate toxicity reaction.

A contact lens care 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 contact 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.

If the CI 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 CI.

4.2.2 Variables

4.2.2.1 Contact lenses

The following variables should be considered during the CI 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 CI 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 should be assessed during the CI 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 CI 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 shall be collected during monitoring.

Annex A
(informative)

Elements of a clinical investigation

A.1 General

The following are elements of a CIP 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 completed per group at end of trial	Duration	Material and design
Daily wear	50	3 months	Containing new or new ratio material components; significant design changes
	30	30 days	All materials and designs
Daily wear orthokeratology	50	3 months or longer if necessary to reach defined stability	All materials and designs
Extended wear, up to 7 days	160	12 months	All materials and designs
Extended wear, up to 30 days	570	12 months	All materials and designs
Overnight wear (may include orthokeratology)	300	12 months	All materials and designs

A.2.2 Contact lens care product investigations

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 using the test solution and 15 subjects using the control solution (a currently marketed solution for the same indication) for each appropriate material group.

A.2.2.4 For a contact lens solution that does not contain any new active ingredients (as described in A.2.2.1), 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 about half of that recommended in A.2.2.2 and A.2.2.3, 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.

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

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

where

p_t is the proportion in the test population;

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:

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

where

α is the significance level (also known as the type 1 error rate);

$1 - \beta$ is the power of the test;

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, p_t, of 0,033 (under H_a), a clinically insignificant difference, δ, of 0,05, a power, $1 - \beta$, of 0,80, and a significance level, α, of 0,05, the minimum number of completed patients per treatment group is:

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

This equation is only valid when it is assumed for the alternative hypothesis, H_a, that the test rate of adverse events is equal to the control rate, $p_t = p_c$. When this is not a valid assumption, the following equation can be used to provide an approximate calculation for the sample size:

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

For clinical studies of 30 day extended wear hydrogel contact lenses, it is recommended that a 7 day extended wear lens (worn for up to 6 nights/7 days) be used as the control. The following is an example of the calculation that makes assumptions found to be reasonable for many clinical studies of 30 day extended wear hydrogel contact lenses. With a control rate, p_c, of 0,033 and a test rate, p_t, of 0,053 (under H_a), a clinically insignificant difference, δ, of 0,05, a power, $1 - \beta$, of 0,80, and a significance level, α, of 0,05, the minimum number of completed subjects per treatment group is:

$$n = \frac{(0,84 + 1,64)^2 \times [0,053 \times (1-0,053) + 0,033 \times (1-0,033)]}{(0,053 - 0,033 - 0,05)^2} \approx 562$$

Enrolment should be adjusted to compensate for drop-out which is typically 20 % to 25 % in 1 year contact lens studies. Therefore, for the above example of a clinical study of a 7 day extended wear contact lens, the recommended sample size would be adjusted to approximately 215 per subject group. For the above example of a study of a 30 day extended wear lens, the recommended sample size would be approximately 760 per subject group.

At the conclusion of the study, sensitivity analyses (e.g. multiple imputation analyses) should be conducted to evaluate the robustness of the study result accounting for missing observations, if there is more than minimal subject drop-out.

A.2.3.2 Daily wear hydrogel, silicone hydrogel or rigid gas-permeable contact lens evaluations

Sample sizes are designed to give reasonable assurance of obtaining at least one complication, as a function of the expected complication rate (i.e. 5 % for a 60 subject test group, 10 % with a 30 subject test group), with a probability of greater than 95 %. Therefore, in a subject group of 30 (completed) subjects exposed to a short-term duration (90 days) of a test product, an adverse event occurrence in two to three subjects may cause concern as to the biocompatibility and fundamental safety of the device being tested. Any investigation resulting in more than one adverse reaction should include adequate justification in order to establish safety and efficacy.

A.2.3.3 Contact lens care product evaluations

Clinical sample sizes are designed so that there is 95 % confidence that a study has at least one complication in a material category, if the true complication rate is $\geqslant$ 10 %. This implies that a study should have at least 30 (completed) subjects exposed to a short-term duration (90 days) of a test care product, for each material grouping. Studies should include all material groupings of interest for the product.

Any investigation resulting in more than one adverse reaction should include adequate justification in order to establish safety and efficacy.

A.2.4 Adverse events and adverse device effects

A.2.4.1 General

Adverse events should be differentiated into device related and non-device related. Any corneal infiltrate, ulcer, neovascularization, etc. shall be presumed to be device related unless the case history clearly indicates some other origin. All corneal ulcers shall be recorded in the study report.

A.2.4.2 Serious adverse events

Serious adverse events are those events that result in, or have potential to cause, either permanent impairment of an ocular function or damage to an ocular structure, and may necessitate medical or surgical intervention.

Serious adverse events may include any hazardous, sight-threatening conditions occurring after exposure to test article, including but not limited to the following.

a) A presumed infectious ulcer (defined as a progressive erosion of the corneal tissue). Signs may include irregular focal infiltrates (> 1 mm); active lesions with raised edges; significant diffuse infiltration; anterior corneal to mid-stromal involvement; erosion with overlying staining; conjunctival and lid oedema; anterior chamber reaction (iritis); severe bulbar and limbal redness. Symptoms associated with a presumed infectious ulcer (microbial keratitis) may include pain of rapid onset; severe redness; purulent or muco-purulent discharge; tearing; photophobia. For the purposes of reporting, a corneal ulcer which has *any* of the following characteristics should be considered in this category:

   1) central or paracentral location;

   2) penetration of Bowman's membrane;

   3) infiltrate > 2 mm diameter;

   4) associated with iritis ⩾ grade 2;

   5) associated with any increase in intraocular pressure;

   6) culture positive for microorganisms;

   7) increasing size or severity at subsequent visits.

b) Any central or paracentral corneal event (such as vascularization) that results in permanent opacification.

c) Any serious adverse ophthalmic events including hypopyon and hyphema.

d) Any neovascularization within the central 6 mm of the cornea.

e) The loss of two or more lines of visual acuity that fail to resolve.

f) All cases of iritis.

Significant but non-serious adverse events should include, but not be limited to:

g) peripheral non-progressive non-infectious ulcers;

h) all symptomatic corneal infiltrative events;

i) all cases of corneal staining greater than or equal to grade 3;

j) a temporary loss of two or more lines of best corrected visual acuity (for greater than or equal to 2 weeks);

k) cases greater than or equal to grade 2 neovascularization;

l) any ocular event that necessitates temporary lens discontinuation of greater than or equal to 2 weeks.

A.3 Reporting of results

Tables A.2 to A.12 give guidance for sample tables of results. Separate tables may be used for test and control groups. Not all tables apply to studies for all product categories.

Table A.2 — Accountability by eyes enrolled in the study and distribution status

Status	Number of eyes	
	Control eyes N_C	Trial eyes N_T
Enrolled dispensed		
Completed	N_C	N_T
Active lens wearers (visit completed)		
dispensed	N_C	N_T
1st follow-up	N_C	N_T
2nd follow-up	N_C	N_T
(list through nth follow-up)		
Discontinued	N_C	N_T
Lost to follow-up (no-show)	N_C	N_T
Enrolled not dispensed	N_C	N_T
Total enrolled	N_C	N_T

Table A.3 — Tabulation of eyes by most recent lens-wearing experience and demographics

Total	Eyes				
	Rigid lens	Hydrogel lens	Silicone hydrogel lens	Other	Subtotal
Previous experience unreported					
No prior lens experience					
New wearers (less than 2 months' wear)					
Previous wearers: most recent experience					
Successful:					
daily wear					
extended wear					
Unsuccessful:					
daily wear					
extended wear					
Total lens wearers					
Total enrolled					

Demographics			
Age of patients:	From	to	Average:
Sex:	Female:	Male:	Ratio:
Lens power range: (maxima)	+	D	
	–	D	
	Cylinder	D	

Table A.4 — Adverse events

Non-device related							
Adverse event	**Time in investigation** (from dispensing)	**Date first seen by investigator**	**Date of resolution**	**Intervention**	**Subject discontinued?**	**Severity**	**Outcome**
1 2 3 4 etc.							
Total number of non-device-related adverse events:							
Device related							
Adverse device event (ADE)	**Time in investigation** (from dispensing)	**Date first seen by investigator**	**Date of resolution**	**Intervention**	**Subject discontinued?**	**Severity**	**Outcome**
1 2 3 4 etc.							
Total eyes with adverse device events requiring treatment:							

Table A.5 — Slit lamp findings (example: epithelial oedema) by visit, tabulated by eyes and incidence rate

Epithelial oedema	**Initial dispensing visit**		**Intermediate visits**								**Un-scheduled visits**		**Final visit**	
			1		**2**		**3**		**4**					
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0 = none 1 = trace 2 = mild 3 = moderate 4 = severe														
Total eyes														

Table A.6 — Symptoms, problems, and complaints (example: comfort) by visit, tabulated by eyes and incidence rate

Total eyes at visit	Initial dispensing visit	Intermediate visits				Un-scheduled visits	Final visit	Overall total
		1	2	3	4			
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Comfort 0 = excellent, cannot be felt 1 = very comfortable, just felt occasionally 2 = comfortable, noticeable but not irritating 3 = slightly uncomfortable, just irritating or annoying 4 = very uncomfortable, very irritating or annoying 5 = causes pain, lens cannot be tolerated								
Total number positive reports:								

Table A.7 — Keratometry change (absolute value) from baseline to final visit by meridian

Dioptres	Flattest		Steepest		Total eyes	
	No.	%	No.	%	No.	%
0,00 D to 1,00 D [a] 1,12 D to 1,50 D [a] 1,62 D to 2,00 D [a] (continue as needed)						
Mean keratometry change:		D				
Minimum keratometry change:		D				
Maximum keratometry change:		D				

Listing of vertical and horizontal keratometry readings and changes (absolute value) from baseline to final visit for eyes that changed by more than 1 D

Investigator	Patient	Eye	H/V	Baseline	Final [b] visit	Absolute change	Reason
1 2 3							

[a] Keratometric measurements can be reported in millimetres, where 1,00 D difference is equivalent to 0,20 mm difference.

[b] Final study visit for completed subjects or exit visit for discontinued subjects.

Table A.8 — Spherical refractive changes (absolute value) from baseline to final visit

Dioptres	Total eyes No. %
0,00 D to 1,00 D 1,12 D to 1,50 D 1,62 D to 2,00 D (continue as needed)	
Mean refractive change: D	
Minimum refractive change: D	
Maximum refractive change: D	

Listing of refractive changes (absolute value) from baseline to final visit for eyes that changed by more than 1 D

Investigator	Patient	Eye	Baseline	Final visit	Absolute change	Reason
1 2 3 etc.						

Table A.9 — Visual acuity (VA) results [1)]

With contact lens (no over-refraction) at final visit								
Initial best corrected contact lens visual acuity with spherical over-refraction	**Number of eyes**	**20/15 LogMAR –0,1** No. %	**20/20 LogMAR 0,0** No. %	**20/25 LogMAR 0,1** No. %	**20/30 LogMAR 0,2** No. %	**20/40 LogMAR 0,3** No. %	**Not reported** No. %	**Total** No. %
20/15 LogMAR –0,1								
20/20 LogMAR 0,0								
20/25 LogMAR 0,1								
20/30 LogMAR 0,2								
20/40 LogMAR 0,3								
(continue as needed)								
Total								

The percentage at each VA (or total), $p_{\mathrm{VA},i}$, is given by

$$p_{\mathrm{VA},i} = \frac{\sum_{i=1}^{n} N_{\mathrm{e},i}}{N_{\mathrm{e},1}} \times 100$$

where

$\sum_{i=1}^{n} N_{\mathrm{e},i}$ is the number of eyes at each VA (or total);

$N_{\mathrm{e},1}$ is the number of eyes at initial visit corrected of corresponding row.

Visual acuity summary:

Number of eyes with initial best corrected VA of 20/30 or better:

Number of eyes with final VA with lens of 20/30 or better:

Number of eyes with final VA with lens within 1 LogMAR VA line (or Snellen equivalent) of best corrected:

Number of eyes with final VA with lens of worse than 1 LogMAR VA line (or Snellen equivalent) of best corrected:

Listing of eyes that changed by two or more LogMAR VA lines (or Snellen equivalent)

Investigator	Patient	Eye	Initial VA	VA at visit	Reason
1					
2					
3					
etc.					

1) Table A.9 should be replicated for every scheduled study visit with contact lenses.

Table A.9 (*continued*)

Best corrected visual acuity at subject's final visit with contact lenses or over-refraction					
Initial best corrected	**20/15 LogMAR –0,1** No. %	**20/20 LogMAR 0,0** No. %	**20/25 LogMAR 0,1** No. %	**20/30 LogMAR 0,2** No. %	**20/40 LogMAR 0,3** No. %
20/15 LogMAR –0,1					
20/20 LogMAR 0,0					
20/25 LogMAR 0,1					
20/30 LogMAR 0,2					
20/40 LogMAR 0,3					
Best corrected visual acuity at subject's final visit with other means of correction					
Initial best corrected	**20/15 LogMAR –0,1** No. %	**20/20 LogMAR 0,0** No. %	**20/25 LogMAR 0,1** No. %	**20/30 LogMAR 0,2** No. %	**20/40 LogMAR 0,3** No. %
20/15 LogMAR –0,1					
20/20 LogMAR 0,0					
20/25 LogMAR 0,1					
20/30 LogMAR 0,2					
20/40 LogMAR 0,3					

Table A.10 — Average hours worn

Wearing time h	**Intermediate visits** **1** No. %	**2** No. %	**3** No. %	**4** No. %	**Unscheduled** No. %	**Final visit** No. %
0 to 4,0						
> 4,0 to 6,0						
> 6,0 to 8,0						
> 8,0 to 10,0						
> 10,0 to 12,0						
> 12,0 to 14,0						
> 14,0 to 16,0						
> 16,0 to 18,0						
> 18,0						
Wearing time average/visit (hours)						

Table A.11 — Reasons for not completing the investigation

Reasons	Eye at (or after) visit completed						Aggregate eyes discontinued %
	Initial	Intermediate visits				Un-scheduled visit	
		1	2	3	4		
Visual acuity	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	(N_C/N_T)
Vision							
Adverse device event							
Adverse reaction							
Lens position							
Discomfort							
Handling							
Disinterest							
Other (specify)							
Subtotal	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	(N_C/N_T)
Lost to follow-up							
Total	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	(N_C/N_T)

N_C is the number of control eyes

N_T is the number of trial eyes

The percentage incidence, p_I, is given by

$$p_I = \frac{\sum N_{e,disc/reason}}{\sum N_{e,comp} + \sum N_{e,disc}} \times 100$$

where

$\sum N_{e,disc/reason}$ represents the aggregate eyes discontinued per reason;

$\sum N_{e,comp}$ represents the total eyes completed;

$\sum N_{e,disc}$ represents the total eyes discontinued.

NOTE Visual acuity is an objective assessment of the subject's vision (perception of how they see).

Table A.12 — Lens replacement by visit

For completed subjects							
Reason for replacement	**Initial**	**Intermediate visits**				**Un-scheduled visits**	**Total**
		1	**2**	**3**	**4**		
	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Visual acuity	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T
Comfort							
Pathology							
Base curve							
Diameter							
Lost							
Torn							
Lens deposits							
Bad edge							
Bad surface							
Discoloration							
Other (specify)							
Total	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T

N_C is the number of control eyes

N_T is the number of trial eyes

Purpose: to provide a tabulation of all lenses replaced during the study by reason for replacement

Lenses replaced for visual acuity, pathological or other physiological reasons should be listed individually, with the specific reason for replacement and the visual acuity with the replacement lens.

Number and percentage refer to the number of eyes for each reason for replacement for the corresponding row. Percentage, $p_{e,\,repl}$ should be calculated in accordance with

$$p_{e,repl} = \frac{N_{e,i}}{\sum_{i=1}^{n} N_{e,i}} \times 100$$

where

$N_{e,i}$ is the number of eyes at each visit;

$\sum_{i=1}^{n} N_{e,i}$ is the total number of eyes.

Table A.12 (*continued*)

For discontinued subjects							
Reason for replacement	**Initial**	**Intermediate visits**				**Un-scheduled visits**	**Total**
		1	**2**	**3**	**4**		
	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Visual acuity	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T
Comfort							
Pathology							
Base curve							
Diameter							
Lost							
Torn							
Lens deposits							
Bad edge							
Bad surface							
Discoloration							
Other (specify)							
Total	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T	N_C/N_T

N_C is the number of control eyes

N_T is the number of trial eyes

Purpose: to provide a tabulation of all lenses replaced during the study by reason for replacement

Lenses replaced for visual acuity, pathological or other physiological reasons should be listed individually, with the specific reason for replacement and the visual acuity with the replacement lens.

Number and percentage refer to the number of eyes for each reason for replacement for the corresponding row. Percentage, $p_{e,repl}$ should be calculated in accordance with

$$p_{e,repl} = \frac{N_{e,i}}{\sum_{i=1}^{n} N_{e,i}} \times 100$$

where

$N_{e,i}$ is the number of eyes at each visit;

$\sum_{i=1}^{n} N_{e,i}$ is the total number of eyes.

NOTE Bad surface (note specific reasons in report form).

Annex B
(informative)

Procedures for the evaluation of safety, physiological performance and effect on ocular tissues

B.1 General

The following classifications should be considered whenever the procedure is included in the CIP.

B.2 Corneal oedema

B.2.1 General

Corneal oedema should be classified separately for the epithelium and the stroma.

B.2.2 Epithelial oedema

Epithelial oedema should be classified according to the number of microcysts observed.

0 = none	no microcysts; normal transparency
1 = trace	1 to 20 microcysts; barely discernable local epithelial haziness
2 = mild	21 to 50 microcysts; faint but definite localized or generalized haziness
3 = moderate	51 to 100 microcysts; significant localized or generalized haziness
4 = severe	> 100 microcysts; definite widespread epithelial cloudiness giving a dull glass appearance to the cornea or numerous coalescing bullae.

The presence/absence of fluid-filled or debris-filled cysts should be documented, along with their numbers.

B.2.3 Stromal oedema

Stromal oedema should be classified according to the following scale:

0 = none	no oedema
1 = trace	just detectable clouding
2 = mild	faint corneal striae (2 or fewer)
3 = moderate	pronounced corneal striae (3)
4 = severe	folds in Descemet's membrane and ⩾ 4 pronounced striae.

B.3 Corneal infiltrates

The severity of corneal infiltrates should be classified according to the following scale:

0 = none no infiltrates

1 = trace single or multiple epithelial infiltrates < 1 mm in diameter

2 = mild single or multiple epithelial infiltrates ⩾ 1 mm and < 2 mm in diameter

3 = moderate multiple infiltrates ⩾ 2 mm and < 3 mm in diameter

4 = severe multiple dense infiltrates ⩾ 3 mm in diameter

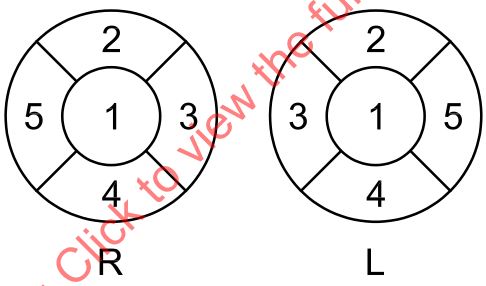
Location of corneal infiltrates in the cornea should be noted as indicated in Figure B.1.

Depth of corneal infiltrates should be abbreviated as follows:

E = epithelial

AS = anterior stromal

P = mid/posterior stromal



Key

R right eye
L left eye

1 C = central
2 S = superior
3 N = nasal
4 I = inferior
5 T = temporal

Figure B.1 — Method for recording location in/on the cornea

B.4 Endothelial regularity

Endothelial regularity should be classified according to the following scale:

0 = regular endothelial mosaic

1 = isolated difference in cell size

2 = just noticeable variation in cell size or bumpiness of cell layer

3 = easily detected difference in cell size or bumpiness of cell layer

4 = noticeable cell layer bumpiness and loss of definition of cell borders.

B.5 Corneal vascularization

Maximal corneal vascularization should be reported according to the following scale:

0 = none	no vessel penetration
1 = trace	< 1,00 mm vessel penetration
2 = mild	⩾ 1,00 mm to ⩽ 1,5 mm vessel penetration
3 = moderate	> 1,5 mm to ⩽ 2,00 mm vessel penetration
4 = severe	vessel penetration > 2,0 mm

The depth and location of vessel penetration should be reported as follows:

Depth:	a) superficial
	b) stromal
Location:	N = nasal
	T = temporal
	I = inferior
	S = superior
	CL = circumlimbal
	X = other (describe)

B.6 Corneal staining with fluoroscein

Corneal staining should be recorded according to the following scale (see Notes 1 and 2 below):

0 = none	no staining
1 = trace	minimal superficial staining or punctate staining
	a) dimpling, discrete dot staining, or
	b) trace superficial lens insertion marks or foreign body tracks
2 = mild	regional or diffuse punctate staining
	a) central or generalized, or
	b) peripheral including 3 to 9 o'clock staining, or
	c) foreign body tracks
3 = moderate	dense coalescent staining up to 2 mm in diameter
	a) corneal abrasion
	b) foreign body track
4 = severe	dense coalescent staining greater than 2 mm in diameter
☐	check box if staining is associated with an underlying infiltrate
☐	check box if staining is NOT associated with an underlying infiltrate

The location of the staining observed should be recorded as indicated in Figure B.1. The preferred method for recording the location is by numbers (see Figure B.1).

NOTE 1 All corneal staining observations should be carried out using a blue excitation light in conjunction with a yellow barrier filter in the observation system.

NOTE 2 Recurrent erosion and corneal ulceration should be recorded under a section “Other complications”.

B.7 Conjunctival observations

Limbal hyperaemia should be recorded on a five-point scale as follows:

0 = none	no hyperaemia
1 = trace	slight limbal hyperaemia (mild segmented)
2 = mild	mild limbal hyperaemia (mild circumcorneal)
3 = moderate	significant limbal hyperaemia (marked segmented)
4 = severe	severe limbal hyperaemia (marked circumcorneal)

Bulbar conjunctival hyperaemia should be recorded on a five-point scale as follows:

0 = none	no hyperaemia
1 = trace	slight regional hyperaemia
2 = mild	diffuse hyperaemia
3 = moderate	marked regional or diffuse hyperaemia
4 = severe	diffuse episcleral or scleral hyperaemia

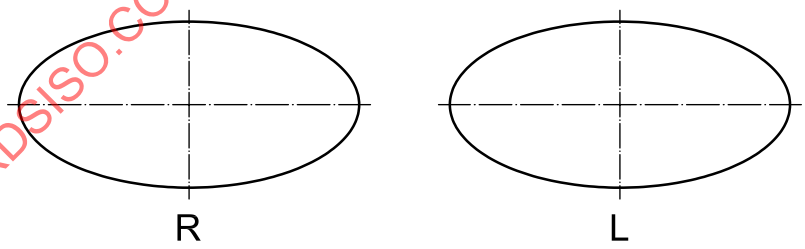
Bulbar conjunctival compression/indentation (0 = absence; 1 = presence): right eye _____

left eye _____

Presence or absence of chemosis (0 = absence; 1 = presence): right eye _____

left eye _____

See Figure B.2.



Key

R right eye

L left eye

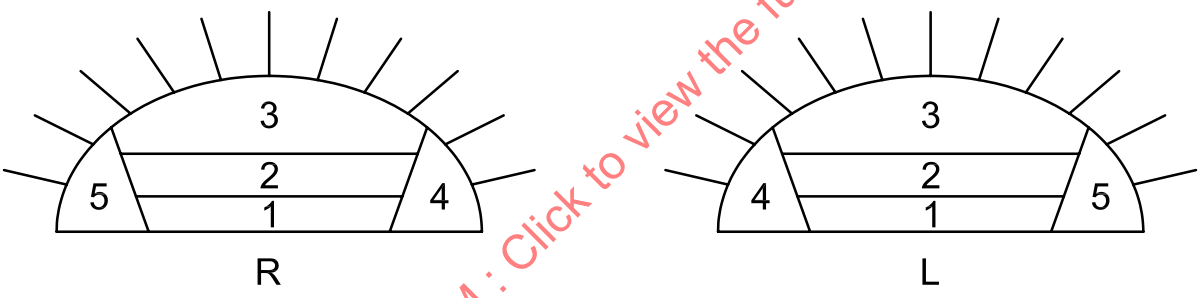
Figure B.2 — Method for recording (conjunctival areas) quadrants affected by conjunctival redness (0 = absence; 1 = presence)

B.8 Palpebral conjunctival observations

The severity of the maximal palpebral conjunctival response should be documented according to the following scale:

0 = none	uniform satin appearance of the conjunctiva	
1 = trace	slight conjunctival injection without texture	
2 = mild	mild or scattered papillae/follicles less than 1 mm in diameter	
3 = moderate	a)	significant papillae/follicles less than 1 mm in diameter, and/or marked conjunctival injection
	b)	staining of the top of one papilla
4 = severe	a)	localized or generalized papillae/follicles 1 mm or more in diameter
	b)	staining of the top of more than one papilla

The location of the maximal palpebral conjunctival response should be recorded for each of the six lid areas (see Figure B.3).



Key

R right eye lid

L left eye lid

Upper lid

1 S = superior tarsal conjunctiva

2 C = middle tarsal conjunctiva

3 I = inferior tarsal conjunctiva

4 N = nasal tarsal conjunctiva

5 T = temporal tarsal conjunctiva

Lower lid (not shown)

6 L = lower lid conjunctiva

Figure B.3 — Upper lid areas