

BS EN ISO 11980:2012

Incorporating corrigendum December 2012



BSI Standards Publication

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

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The UK participation in its preparation was entrusted by Technical Committee CH/172, Ophthalmic optics, to Subcommittee CH/172/9, Contact lenses and contact lens care products.

A list of organizations represented on this subcommittee can be obtained on request to its secretary.

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Published by BSI Standards Limited 2013

ISBN 978 0 580 81665 9

ICS 11.040.70

Compliance with a British Standard cannot confer immunity from legal obligations.

This British Standard was published under the authority of the Standards Policy and Strategy Committee on 31 December 2012.

Amendments/corrigenda issued since publication

Date	Text affected
31 October 2013	Implementation of ISO corrigendum December 2012: Standard replaced with ISO corrected version

EUROPEAN STANDARD
NORME EUROPÉENNE
EUROPÄISCHE NORM

EN ISO 11980

November 2012

ICS 11.040.70

Supersedes EN ISO 11980:2009

English Version

Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations (ISO 11980:2012)

Optique ophtalmique - Lentilles de contact et produits d'entretien pour lentilles de contact - Directives pour les investigations cliniques (ISO 11980:2012)

Augenoptik - Kontaktlinsen und Kontaktlinsenpflegemittel - Leitfaden für die klinische Prüfung (ISO 11980:2012)

This European Standard was approved by CEN on 14 November 2012.

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Ref. No. EN ISO 11980:2012: E

Foreword

This document (EN ISO 11980:2012) has been prepared by Technical Committee ISO/TC 172 "Optics and photonics" in collaboration with Technical Committee CEN/TC 170 "Ophthalmic optics" the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by May 2013, and conflicting national standards shall be withdrawn at the latest by May 2013.

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Endorsement notice

The text of ISO 11980:2012 has been approved by CEN as a EN ISO 11980:2012 without any modification.

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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, *Clinical investigation of medical devices for human subjects — Good clinical practice*

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, 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 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 more serious than 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)	100 pre-market/ 200 post-market	6 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.