American National Standard

ANSI/AAMI/ISO 14155-2:2003

Clinical investigation of medical devices for human subjects—Part 2: Clinical investigation plans

AAMI Association for the Advancement of Medical Instrumentation

The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decisionmaking.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

INTERPRETATIONS OF AAMI STANDARDS AND RECOMMENDED PRACTICES

Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the Manager for Technical Development. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News.* The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News.*

American National Standard

ANSI/AAMI/ISO 14155-2:2003
(Partial revision of ANSI/AAMI/ISO 14155:1996)

Clinical investigation of medical devices for human subjects—Part 2: Clinical investigation plans

Approved 14 March 2003 by
Association for the Advancement of Medical Instrumentation

Approved 27 March 2003 by
American National Standards Institute

Abstract: Defines procedures for the conduct and performance of clinical investigations of medical devices.

Keywords: biological evaluation, medical devices, clinical investigation plans

AAMI Standard

This Association for the Advancement of Medical Instrumentation (AAMI) standard implies a consensus of those substantially concerned with its scope and provisions. The existence of an AAMI standard does not in any respect preclude anyone, whether they have approved the standard or not, from manufacturing, marketing, purchasing or using products, processes or procedures not conforming to the standard. AAMI standards are subject to periodic review, and users are cautioned to obtain the latest editions.

CAUTION NOTICE: This AAMI standard may be revised or withdrawn at any time. AAMI procedures require that action be taken to reaffirm, revise or withdraw this standard no later than 5 years from the date of publication. Interested parties may obtain current information on all AAMI standards by calling or writing AAMI.

All AAMI standards, recommended practices, technical information reports and other types of technical documents developed by AAMI are *voluntary*, and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary technical documents are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

Published by

Association for the Advancement of Medical Instrumentation
1110 N. Glebe Road, Suite 220
Arlington, VA 22201-4795

Printed in the United States of America

ISBN 1–57020–200–1

Contents

Glossary of equivalent standards

International standards adopted in the United States may include normative references to other international standards. For each international standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the international standard. (Note: Documents are sorted by international designation.)

Other normatively referenced international standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1-2:2001	ANSI/AAMI/IEC 60601-1-2:2001	Identical
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 & Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:1998	Major technical variations
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:2002	ANSI/AAMI/ISO 10993-4:2002	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:2002	ANSI/AAMI BE78:2002	Minor technical variations
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:2002	ANSI/AAMI/ISO 10993-12:2002	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2003	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002	Identical
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995 and Amdt 1:2001	ANSI/AAMI/ISO 11137:1994 and A1:2002	Identical
ISO 11138-1:1994	ANSI/AAMI ST59:1999	Major technical variations

International designation	U.S. designation	Equivalency
ISO 11138-2:1994	ANSI/AAMI ST21:1999	Major technical variations
ISO 11138-3:1995	ANSI/AAMI ST19:1999	Major technical variations
ISO TS 11139:2001	ANSI/AAMI/ISO 11139:2002	Identical
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:2003	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO TR 13409:1996	AAMI/ISO TIR13409:1996	Identical
ISO 13485:2003	ANSI/AAMI/ISO 13485:2003	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003	Identical
ISO 14155-2:2003	ANSI/AAMI/ISO 14155-2:2003	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:2000 and A1:2003	ANSI/AAMI/ISO 14971:2000 and A1:2003	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15223/A1:2002	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical
ISO 25539-1:2003	ANSI/AAMI/ISO 25539-1:2003	Identical

Committee representation

Association for the Advancement of Medical Instrumentation

Biological Evaluation Committee

The adoption of ISO 14155-2:2003 as an American National Standard was initiated by the AAMI Biological Evaluation Committee, which also functions as a U.S. Technical Advisory Group (TAG) to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Clinical Investigations Working Group (U.S. Sub-TAG for ISO/TC 194/WG 4), chaired by Kimber C. Richter, MD, of the U.S. Food and Drug Administration and Nancy J. Stark, PhD, of Clinical Device Group, Inc., played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Biological Evaluation Committee** had the following members:

Cochairs: Donald E. Marlowe
Peter W. Urbanski

Members: James M. Anderson, MD, PhD, Case Western Reserve University
Eric R. Claussen, PhD, Becton Dickinson & Company
Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc.
Lawrence H. Hecker, PhD, Abbott Laboratories
Edward Mueller, MS, Annapolis, MD
Barry F.J. Page, Garner, NC
Melvin E. Stratmeyer, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health/OST
Paul J. Upman, PhD, NAMSA
Peter W. Urbanski, Medtronic, Inc.

Alternates: Raju G. Kammula, DVM, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health/ODE
Donald E. Marlowe, U.S. Food and Drug Administration/Center for Devices and Radiological Health
Sharon J. Northup, PhD, U.S. Pharmacopeial Convention, Inc.

At the time this document was published, the **AAMI Clinical Investigations Working Group** had the following members:

Cochairs: Kimber C. Richter, MD
Nancy J. Stark, PhD

Members: James M. Anderson, MD, PhD, Case Western Reserve University
Carolyn Braithwaite, Gambro BCT, Inc.
Ioana G. Carabin, MD, Burdock Group
Eric R. Claussen, PhD, Becton Dickinson & Company
Duane R. Dey, Bausch & Lomb, Inc.
Dean Elfath, MD, Baxter Healthcare Corporation
Roobert L. Fuson, MD, Zimmer, Inc.
Joel Gorski, PhD, NAMSA
Sarah E. Moeller, Medtronic, Inc.
Susan Moritz, Boston Scientific Corporation
Patrick J. Parks, MD, PhD, 3M Healthcare
Kimber C. Richter, MD, U.S. Food and Drug Administration/Center for Devices and Radiological Health/OC
Cheryl D. Spencer, Abbott Laboratories
Kenneth R. St. John, PhD, University of Mississippi Medical Center
Nancy J. Stark, PhD, Clinical Device Group, Inc.
Rodney A. White, MD, Harbor-UCLA Medical Center

Alternates: Carol Brozek, 3M Healthcare
Stephen P. Costanzo, Bausch & Lomb, Inc.
David W. Eaker, PhD, DABT, Becton Dickinson & Company
Daniel Hamilton, Ross Products (Abbott Laboratories)
Edward Reverdy, PhD, Boston Scientific Corporation
Harold E. Sargent, PhD, Baxter Healthcare Corporation
Russell A. Schenck, PhD, Zimmer, Inc.
Celia Witten, U.S. Food and Drug Administration/Center for Devices and Radiological Health

NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 14155-2:2003

As indicated in the foreword to the main body of this document (page viii), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard.

International standard ISO 14155-2 was developed by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, to provide requirements for the preparation of Clinical Investigation Plans (CIPs) for the clinical investigation of medical devices.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation (AAMI) on behalf of the American National Standards Institute (ANSI). The U.S. made a considerable contribution to this International Standard.

AAMI encourages its committees to harmonize their work with International Standards in the area of biological evaluation of medical devices as much as possible in order to help reduce unnecessary repetition of testing. Upon review of ISO 14155-2, the AAMI Biological Evaluation Committee and the AAMI Clinical Investigations Working Group proposed adoption of ISO 14155-2:2003 verbatim as a partial revision of ANSI/AAMI/ISO 14155:1996. ISO (and AAMI, through the adoption process) has also issued ISO 14155-1:2003, covering conduct and performance of clinical investigations, to complete the revision of 14155:1996.

AAMI and ANSI procedures require that American National Standards be reviewed and, if necessary, revised within five years to confirm currency or reflect technological advances that have occurred since publication, as appropriate.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI, which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the ISO foreword on page viii, this American National Standard is identical to ISO 14155-2:2003.

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 14155-2 was prepared by the European Committee for Standardization (CEN) in collaboration with Technical Committee ISO/TC 194, *Biological evaluation of medical device*s, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Throughout the text of this document, read "...this European Standard..." to mean "...this International Standard…."

This first edition, together with the first edition of ISO 14155-1, cancels and replaces ISO 14155:1996, which has been technically revised.

ISO 14155 consists of the following parts, under the general title *Clinical investigation of medical devices for human subjects:*

— *Part 1: General requirements*

— *Part 2: Clinical investigation plans*

For the purposes of this part of ISO 14155, the CEN annex regarding fulfilment of European Council Directives has been removed.

Introduction

This standard is the second part of EN ISO 14155 “Clinical investigation of medical devices for human subjects,” and should be read in conjunction with that standard.

The standard is intended to assist manufacturers, sponsors, monitors, and clinical investigators in the design and conduct of clinical investigations. It is also intended to assist regulatory bodies and ethics committees in their roles of reviewing Clinical Investigation Plans (CIP). The CIP is a framework within which appropriate experience, insight, judgment, qualification, and education need to be applied. The scientific rigor of a CIP can be verified and possibly improved by an independent review of the CIP.

Clinical investigation of medical devices for human subjects—Part 2: Clinical investigation plans

1 Scope

This part of EN ISO 14155 provides requirements for the preparation of a Clinical Investigation Plan (CIP) for the clinical investigation of medical devices. The compilation of a CIP in accordance with the requirements of this standard and adherence to it will help in optimizing the scientific validity and reproducibility of the results of a clinical investigation.

This Standard does not apply to *in vitro* diagnostic medical devices.

2 Normative references

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text, and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references, the latest edition of the publication referred to applies (including amendments).

EN ISO 14155-1:2003, *Clinical investigation of medical devices for human subjects—Part 1: General requirements. (ISO 14155-1:2003)*

3 Terms and definitions

For the purposes of this European Standard, the terms and definitions given in EN ISO 14155-1:2003 and the following apply.

3.1 end point—primary: principal indicator measured or determined to assess the primary objective of a clinical investigation.

3.2 end point—secondary: indicator measured or determined in addition to the primary end point to assess some other objective of a clinical investigation.

3.3 point of enrollment: time at which, following recruitment, a subject has signed the informed consent form and is regarded as part of the study population.

3.4 follow-up period: period of the clinical investigation after the application of the device under investigation in each subject during which the effects of the device are observed.

3.5 recruitment: process of identifying subjects who may be suitable for enrollment into the clinical investigation.

4 Requirements

4.1 General

All requirements of EN ISO 14155-1 apply.

4.2 Clinical Investigation Plan (CIP)

The CIP shall be a document developed by the sponsor and the clinical investigator(s). The CIP shall be designed in such a way as to optimize the scientific validity and reproducibility of the results of the study in accordance with current clinical knowledge and practice so as to fulfil the objectives of the investigation.

The CIP shall include the information specified in the subsequent clauses. Alternatively, if the required information is written in other documentation, (for example, the clinical investigator's brochure or the sponsor's standard operating procedures), such documentation shall be referenced in the CIP and shall be made available on request.

In the event of the sponsor deciding that any requirement given in 4.3 to 4.10 is not applicable, relevant, or appropriate, a clear statement justifying the omission of the information specified shall be provided on each occasion.

4.3 General information

4.3.1 Identification of the clinical investigation plan

The CIP and any amended version shall state the title of the clinical investigation and its reference number. The CIP shall also include a version/issue number and date to ensure that it may be traced to the signatories (see 4.3.7). Each page of the CIP shall be referenced with the version number.

4.3.2 Clinical investigators, principal clinical investigator, coordinating clinical investigator, investigation centers/site(s)

The CIP shall state or refer to a list of the name(s), address(es), and professional position(s) of the clinical investigator(s), of the principal clinical investigator(s), and of the coordinating clinical investigator, if appointed. The CIP shall document the name(s) and address(es) of the Institution(s) in which the clinical investigation will be conducted. Where it may affect the validity of the clinical investigation, the name(s) and address(es) of other establishments or persons involved in patient management and associated testing and analysis shall be given.

4.3.3 Sponsor

The CIP shall state the name and address of the sponsor of the clinical investigation.

NOTE—If the sponsor is not resident in the country (countries) in which the clinical investigation is to be carried out, the name and address of a representative in that country (those countries) may be required according to national or regional regulations.

4.3.4 Monitoring arrangements

The CIP shall state the monitoring arrangements to be followed during the investigation and the planned extent of source data verification.

4.3.5 Data and quality management

The CIP shall describe or refer to the procedures for database management, treatment of data, source data verification, data archiving, retention period, and other aspects of quality assurance as appropriate.

4.3.6 An overall synopsis of the clinical investigation

The CIP shall provide a summary or overview of the clinical investigation.

NOTE—It may be useful to include a flow chart showing the key stages of the clinical investigation or any other information that may be of value for the conduct of the investigation.

4.3.7 Approval and agreement to the clinical investigation plan

The sponsor, the coordinating investigator (if appointed), and the principal clinical investigator(s) in each center shall agree to the CIP and any amendments and indicate their approval and agreement by signing and dating an appropriate document.

4.4 Identification and description of the medical device to be investigated

The CIP shall include or refer to a summary description of the device to be investigated and its intended purpose. The following information shall be given:

a) the manufacturer of the device, its model or type number including software version and accessories, if any, to permit full identification and traceability. If this information is not known at the time the CIP is written, a description shall be given as to how traceability shall be achieved during and after the study;

b) the intended purpose of the device as stated by the manufacturer including the clinical indications and contra-indications for use in the proposed study and the populations for which it is intended;

c) a description of the device including any materials that will be in contact with tissues or body fluids. This shall include details of any medicinal products, human and/or animal tissues or their derivatives, or other biologically active substances;

d) instructions for installation and use of the device including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g., sterilization), any pre-use checks of safety and performance, and any precautions to be taken after use (e.g., disposal);

e) a summary of necessary training and experience needed for the use of the device under investigation;

f) a description of the necessary medical or surgical procedures involved in the use of the device.

4.5 Preliminary investigations and justification of the study

4.5.1 Literature review

The CIP shall contain a critical review of the relevant scientific literature and/or unpublished data and reports together with a list of the literature reviewed. The conclusions from this review shall justify the design of the proposed investigation. The review shall be relevant to the intended purpose of the device to be investigated and the proposed method of use. It should also help in the identification of relevant end points and confounding factors that should be considered, and the choice and justification of control methods.

NOTE—Guidance on literature review and appraisal is provided in EN ISO 14155–1:2003, Annex A.

4.5.2 Preclinical testing

The CIP shall summarize the preclinical testing that has been performed on the device to be investigated to justify its use in human subjects, together with an evaluation of the results of such testing. The summary shall include or refer to preclinical experimental data including, where applicable, the results of design calculations, *in vitro* tests, mechanical and electrical tests, reliability checks, and the validation of software relating to the function of the device. Also to be included are the results of any performance tests, *ex vivo* testing, biological testing, and/or safety tests in animals, including the relevance of tests and the timescale of such tests.

NOTE—Guidance on the biological evaluation of medical devices is given in EN ISO 10993 [6].

4.5.3 Previous clinical experience

The CIP shall summarize the results from previous clinical investigations and clinical usage that are relevant to the proposed investigation and/or relevant experience with the device, or devices with similar features, including that relating to other indications for use of the device to be investigated. This shall include an analysis of adverse device effects and any history of modification or recall.

4.5.4 Device risk analysis and risk assessment

The CIP shall include the results of a risk analysis and assessment. This shall describe the balance of anticipated clinical benefit against the risks associated with the device itself and the procedures involved in its use, as identified by the risk assessment. Possible interactions with concurrent medical interventions shall be listed, together with a statement of the anticipated clinical benefit.

This shall include an analysis of adverse device effects and any history of modification or recall in relation to safety and clinical performance in relation to both the device under investigation and the devices described in 4.5.3.

NOTE—The process of risk analysis and risk assessment is described in EN ISO 14971 [1].

4.6 Objectives of the clinical investigation

The CIP shall identify clearly the hypothesis and objectives, primary and secondary, of the clinical investigation and the populations for which the device is to be used in the investigation. These shall include as appropriate the particular

a) claims and intended performance of the devices that are to be verified;

NOTE 1—These may include claims implicit in the intended purpose of the device as well as those made explicit in labelling, instructions for use, or promotional material.

NOTE 2—It should be clearly stated whether or not the determinations of the long-term effects are part of the objectives of the current clinical investigation (see also 4.7 p).

b) risks and foreseeable adverse device effects that are to be assessed;

c) specific hypotheses to be accepted or rejected by statistical data from the clinical investigation.

4.7 Design of the clinical investigation

NOTE—The scientific integrity of the clinical investigation and the credibility of the data from the investigation depend substantially on its design.

The CIP shall provide the following information:

a) a description of the type of investigation to be performed (e.g., comparative double-blind, parallel design, with or without a control group) with rationale for the choice;

b) a discussion of the controls;

c) a description of the measures to be taken to minimize or avoid bias;

d) the primary and secondary end points, with rationale for their selection;

e) the variables to be measured with rationale for selecting these to demonstrate the achievement of the end points;

f) the methods and timing for assessing, recording, and analyzing variables;

g) the test equipment to be used for the assessment of study variables and the arrangements for monitoring the maintenance and calibration;

h) the inclusion criteria for subject selection;

i) the exclusion criteria for subject selection;

j) the point of enrollment (see 3.3);

k) a detailed description of the procedure(s) that the subjects undergo during the investigation, as well as a list of any other device or medication to be used either during the application of the device or during the follow-up period;

l) the criteria and procedures for withdrawal and discontinuation of subjects from the investigation and how they are accounted for, together with procedures for the follow-up of these subjects, if possible (see also clauses 4.8 f and 4.9).

m) the number of subjects required to be included in the clinical investigation together with the estimated time needed to include this number and the number of devices to be used and a justification for these figures, (see also 4.8 a). In multicenter investigations, the minimum number of subjects to be included for each center shall be specified and justified. Where it may affect the validity of the study results, considerations shall be made on the minimum and maximum number of subjects to be included in each center;

NOTE—The period for enrollment should not be so great as to confound comparison of data relating to subjects enrolled at different times.

n) the procedures for recording and investigating adverse events, adverse device effects and/or outcomes;

o) the period of use of the device or its control and its follow-up period in a particular subject within the clinical investigation and the justification for this;

NOTE—The follow-up period of the clinical investigation should permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the device and allow identification and risk assessment of any associated adverse device effects over that period.

p) any known or foreseeable factors that may compromise outcomes or the interpretation of results. These may include, for example, subject baseline characteristics, concomitant medication, the use of other devices, or subject-related factors such as age, gender, or lifestyle. The methods for addressing these factors in the investigation—for example, by subject selection, study design (such as stratified randomization) or by statistical analysis—shall be described.

4.8 Statistical considerations

The CIP shall include a description and justification of hypothesis and statistical design, method, and the analytical procedures to be used. This shall include

a) the reasons for the choice of sample size, including the level of significance to be used, the power of the trial, and expected drop-out rates, together with the justification for these aspects;

NOTE—Special reasoning and sample sizes may apply for the early phases of clinical experience (e.g., feasibility studies).

b) pass/fail criteria to be applied to the results of the investigation;

c) provision for an interim analysis, where applicable, and the criteria for the termination of the investigation on statistical grounds;

d) procedures for reporting any deviation(s) from the original statistical plan; (Any deviation(s) from the original statistical plan shall be described and justified in the CIP or final report, as appropriate);

e) the criteria for the selection of subjects to be included in the analyses with justification;

f) the procedures for accounting for all data, together with treatment of missing, unused, or spurious data, including drop-outs and withdrawals, together with a justification for excluding particular information from the testing of the hypothesis, if relevant.

4.9 Deviations from the clinical investigation plan

Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance.

The reasons for withdrawal and discontinuation of any subject from the investigation shall be recorded. If such discontinuation is because of problems of safety or lack of effectiveness, that subject shall still be followed up in the investigation, if possible;

NOTE—When relevant, ethics committees, competent authorities, or the appropriate regulatory bodies should be informed.

4.10 Amendments to the clinical investigation plan

All amendments to the CIP shall be agreed upon between the sponsor and the clinical investigator(s) and be recorded with a justification for the amendments. Deviations should be reviewed to determine the need to amend the CIP or to terminate the investigation.

However, when there are changes to the initial list of clinical investigators and centers (4.3.2) this list will not be formally updated by amendments at each change; the sponsor will maintain an updated list that will be available on request. The definitive list of all centers and investigators shall be provided with the final report.

NOTE—When relevant, ethics committees, competent authorities, or the appropriate regulatory bodies should be informed.

4.11 Adverse events and adverse device effects

The CIP shall include

a) emergency contact details for reporting serious adverse events and serious adverse device effects;

b) details of foreseeable adverse events and adverse device effects (e.g. serious/non-serious, device-related/non-device-related, their likely incidence, and the methods to be used for their management);

c) details of the procedures for reporting all adverse events and adverse device effects to the sponsor, ethics committee, and regulatory authority, in accordance with applicable regulations, including a specification of those types of events, device-related and non-device-related, that shall be reported and the timing for such reporting.

4.12 Early termination or suspension of the investigation

The CIP shall specify the criteria and arrangements for early termination or suspension of the investigation. This may apply to the whole clinical investigation or simply to one or more sites.

If the clinical investigation involves blinding techniques, the criteria for access to and breaking the code shall be stated.

Where appropriate, the CIP shall specify the subject follow-up required following an early termination or suspension.

4.13 Publication policy

The CIP shall specify whether the results of the investigation will be submitted for publication or the extent to which and conditions under which the results of the clinical investigation will be offered for publication.

NOTE—It is highly desirable that all results should be offered for publication in scientific journals.

4.14 Case Report Forms

The Case Report Form (CRF) provides the practical means to implement the CIP by way of a list of all the information to be recorded. The CRF shall reflect the contents of the CIP and make clear the version number of the CIP to which it relates. The CRF and any amendment to it shall bear a version number and each page shall be identifiable by the study number and identification of the subject whose data the CRF records. When it is necessary to amend the CRF, the sponsor shall review the CIP to determine whether or not an amendment to the CIP is necessary.

NOTE—Guidance on the content of a CRF is given in Annex A.

Annex A
(informative)

Case Report Forms

Case Report Forms (CRF) are established to implement the CIP and to facilitate subject observation and to record subject and device data during the clinical investigation according to the CIP. They can exist as printed, optical, or electronic documents. The CRF shall reflect the CIP and take into account of the nature of the device under investigation. In establishing a CRF, the following items should be considered:

a) the date, place, and identification of the investigation, including the version number of the CIP;

b) identification of the subject, date of enrollment, and demographic data;

c) identification of the medical device by lot number and/or serial number;

d) medical diagnosis for which the subject is to be treated with the device to be investigated together with any concomitant illness;

e) subject compliance information for concurrent procedures measures and for any emergency;

f) relevant previous medication and/or procedures;

g) subject baseline characteristics;

h) concomitant medication and/or procedures;

i) compliance with the inclusion/exclusion criteria;

j) dated clinical and non-clinical findings according to the CIP;

k) procedural data;

l) subject assessment during the use of the device and follow-up with dates;

m) reported adverse events and adverse device effects with dates;

n) date of the end of follow-up;

o) signature(s) of the clinical investigator(s) at the completion of follow-up.

Bibliography

[1] EN ISO 14971, *Medical devices—Application of risk management to medical devices. (ISO 14971:2000).*

[2] Essential Principles—Global Harmonization Task Force, 1999.

[3] EU Medical Devices Directive 90/385/EEC—Active implantable medical devices.

[4] EU Medical Devices Directive 93/42/EEC—Medical devices.

[5] Guideline for Good Clinical Practice. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1996.

[6] EN ISO 10993 (all parts), *Biological evaluation of medical devices.*