INTERNATIONAL STANDARD

ISO 5841-2

Second edition
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Implants for surgery — Cardiac pacemakers —

Part 2: Reporting of clinical performance of populations of pulse generators or leads

Implants chirurgicaux — Stimulateurs cardiaques —

Partie 2: Établissement d'un rapport sur le fonctionnement clinique de populations de générateurs d'impulsions ou de fils-électrodes

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this part of ISO 5841 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 5841-2 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants*.

This second edition cancels and replaces the first edition (ISO 5841-2:1986), which has been technically revised.

ISO 5841 consists of the following parts, under the general title *Implants for surgery — Cardiac pacemakers*:

— *Part 1: Implantable pacemakers*

— *Part 2: Reporting of clinical performance of populations of pulse generators or leads*

— *Part 3: Low-profile connectors (IS-1) for implantable pacemakers*

Annex A forms a normative part of this part of ISO 5841. Annexes B and C are for information only.

Introduction

ISO 5841-1 requires the clinician's manual to contain a statement of nominal pulse-generator service life. Expectations of available power-source energy are not always fulfilled, and changes in pulse-generator components and assemblies have resulted in an actual service life which is different from the nominal service life. Defined production groups of pulse generators or leads have required closer follow-up or replacement due to changes in performance exhibited in clinical use.

This experience shows the value of maintaining an accurate and discriminating view of clinical performance of a population of pulse generators or leads, referred to in this document as devices, so as to aid patient management. In order to do this, it is necessary to collect implant and explant information. ISO 5841-1 specifies the content of forms to report implant and explant information for pulse generators.

The primary purpose of this part of ISO 5841 is to describe the reporting responsibilities in sharing clinical performance information for patient management. When clinical performance reports discriminate by production group and focus on recent experience, they are of value in patient management.

This part of ISO 5841 concerns the clinical performance of devices, not the clinical reasons for their use. It is realized that reasons for use can be a guide in the design of future products.

Reporting parties may give cumulative clinical-experience information based on a variety of assumptions and statistical techniques. This part of ISO 5841 gives, in annexes, a method for categorizing devices, guidelines to the statistical techniques that should be used to obtain the most benefit from the data and a statement of the rationale for this part of ISO 5841.

Clinicians have emphasized that a device whose performance has changed, either expectedly or unexpectedly, is sometimes left implanted due to other medical considerations. Instances exist where the performance of a device has changed to stable but out-of-specification performance that is considered safe and effective by the attending clinician. This is an important reason why the term "failure" is avoided throughout the classification.

"Failure" is not sufficiently specific to express the significance of a change in performance. In addition, "failure" implies a negative connotation for pulse generators that meet all longevity claims and cease functioning due to normal power-source depletion.

Implants for surgery — Cardiac pacemakers —

Part 2:
Reporting of clinical performance of populations of pulse generators or leads

1 Scope

This part of ISO 5841 specifies requirements for reports on the clinical performance in humans of population samples of pulse generators or leads, intended for long-term implantation as cardiac pacemakers, hereinafter referred to as devices. It includes general requirements for all reports and supplementary requirements for reports on cumulative experience with devices and estimates of future clinical performance for devices, when appropriate.

Annex A provides requirements for categorizing devices. Annex B provides guidelines for statistics, including a discussion of application of the results obtained. As with other statistical methods, the benefit of the analytical methods in this part of ISO 5841 is limited by the size of population under consideration. Annex C gives the rationale for this part of ISO 5841.

2 Normative reference

The following normative document contains provisions which, through reference in this text, constitute provisions of this part of ISO 5841. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 5841 are encouraged to investigate the possibility of applying the most recent edition of the normative document indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 5841-1, *Implants for surgery — Cardiac pacemakers — Part 1: Implantable pacemakers.*

3 Terms and definitions

For the purposes of this part of ISO 5841, the terms and definitions given in ISO 5841-1 and the following apply.

3.1
advisory notification
<of a device> any action taken to inform the clinicians concerned by a manufacturer who has become aware that a device may fail to conform to any claims made relating to effectiveness, benefits, performance characteristics or safety

3.2
clinical performance period
calendar period, defined by the reporting party, during which the clinical performance of a specific population sample of devices is assessed

3.3
damaged, adj
<of a device> having characteristics which have changed outside the limits stated by the manufacturer, due to some external agency

3.4
dysfunctional, adj
<of a device> having some characteristic outside the limits specified in the technical manual, except changes to the characteristics of a pulse generator due to expected battery depletion

3.5
follow-up centre
medical centre, hospital, clinic or individual responsible for the care of a patient after the implantation of a device

3.6
in service
<of a device> functioning in such a manner as to provide potential medical benefits to the patient

NOTE This term can apply to a device that may be out of specification (see 3.10).

3.7
in specification
<of a device> having characteristics within the limits recommended by the manufacturer for clinical use

3.8
medical reasons
reasons unrelated to the device or its operation

EXAMPLES Infection, extrusion, indication for an alternative medical device (e.g. the replacement of a single-chamber pacemaker in a patient with pacemaker syndrome with a dual-chamber pacemaker), etc.

3.9
out of service
<of a device> not providing a medical benefit to the patient

NOTE A device thus described is not necessarily out of specification (see 3.10) or explanted.

3.10
out of specification
<of a device> having one or more characteristics outside the limits established by the manufacturer for clinical use

3.11
population sample
group of devices designated for the purpose of reporting performance experience that is assumed to be representative of the population

3.12
production group
population sample of devices designated by the manufacturer on the basis of a particular parameter

EXAMPLE Such a parameter may be, for example, time or place of manufacture or a change in the manufacturing process or components.

3.13
prophylactic explantation
explantation for reasons based on the anticipated performance of the device or other medical reasons

3.14
recommended replacement condition
condition in which the device exhibits characteristic(s) identified by the manufacturer as signalling that the device should be taken out of service

EXAMPLE A pulse generator that exhibits the maximum allowable changes in the battery-condition indicators stated by the manufacturer is in a condition where replacement is recommended.

3.15
registered explant
registered implant for which the date of explantation is known by the reporting party

3.16
registered implant
implanted device for which the date of implantation is known by the reporting party

3.17
registered implant month
one month of operation by a registered implant

3.18
reporting party
individual or organization publishing clinical pacemaker data or the analysis thereof

4 General requirements

A report on the clinical performance that conforms to this part of ISO 5841 shall contain the following information:

a) model designation(s) of the devices covered by the report;

b) sources of the data and the methods used to collect them;

c) sample size and how the population and population sample are defined;

d) criteria for including and excluding data;

e) time period over which the data were acquired;

f) units of time of the data;

g) category assigned to the device, in accordance with annex A;

h) explanation of methods used to adjust for any sources of bias known to be present (see annex B);

i) statement of the basis for adjusting registered implant months to compensate for unreported mortality and unreported explants.

Each report shall explain the presentation of the information and any methods of analysis used to calculate numerical expressions of performance. Any generalizations or inferences from data shall be qualified as to assumptions, limitations and associated confidence levels.

Devices referred to in an advisory notification shall be identified by means of the serial numbers of the devices.

If the results are segregated by production group, the report shall explain the basis on which the production groups are established.

It shall be stated in the report that it has been prepared in accordance with this part of ISO 5841.

It is recommended that supplementary information be included in the report, for instance lower confidence limits (see annex B).

NOTE Reports applicable to any number of production groups or population samples may be included in one document. However, they should be arranged in an easily distinguishable manner.

5 Reporting cumulative experience with devices

In addition to the requirements in clause 4, a report of this type shall comply with the qualifications and limitations given in this clause. (See also annex C.)

For a given population sample, the report shall compare the total number of registered implant months with the total number of devices categorized, in accordance with annex A, as being out of specification (including subcategories). As a minimum, the cumulative survival probability for the population sample and population sample size shall be given.

NOTE Examples of data sets and analyses are given in annex B.

The manufacturer shall provide a report on each model at least once a year for as long as there are devices known to be in service or for a period equal to 1,25 times the manufacturer's predicted lifetime of the device, measured from the time of the last unit implanted, whichever is shorter. This report shall be made available to the implanting and follow-up centres and regulatory authorities at their request.

6 Reporting estimated future clinical performance for devices

In addition to the requirements in clause 4, reports of this type shall comply with the qualifications and limitations given in this clause.

From time to time, a manufacturer may wish to estimate the future clinical performance of a particular device. Such estimates of future clinical performance shall be developed by extrapolating the cumulative survival data (see B.2.3).

The report shall explain the method used to smooth and extrapolate the cumulative survival probability.

The report shall state that the analysis assumes that each patient will survive through the period covered by the report, and that the device will not be removed for any reason other than a device-related complication.

Annex A
(normative)

Categorization of devices

The device shall be assigned the appropriate category in accordance with the following criteria and according to the evidence available to the reporting party. Figure A.1 is intended to illustrate these criteria.

A device shall be classified in that category that best describes its status after implant, use being made of the best information available. The reporting party should detail the composition of the categories A, B, C, D and L, with special attention given to distinguishing units in categories C_1 and C_2.

NOTE A device that is not implanted because it is damaged is not included in this categorization.

A general category shall be assigned to the device, in accordance with the following criteria:

— Category A: Device that is in service and, as far as can be verified, in specification.

— Category B: Device removed from service for reasons not related to the functioning of the device.

— Category C: Device that is out of specification.

  — Subcategory C_1: Device is out of specification because it has become dysfunctional.

  — Subcategory C_2: Device is out of specification because it has reached the point in its service life at which the manufacturer recommends its replacement.

— Category D: Patient has died. However, the death, as far as can be verified, is unrelated to the functioning of the device.

— Category L: Device is lost to follow-up.

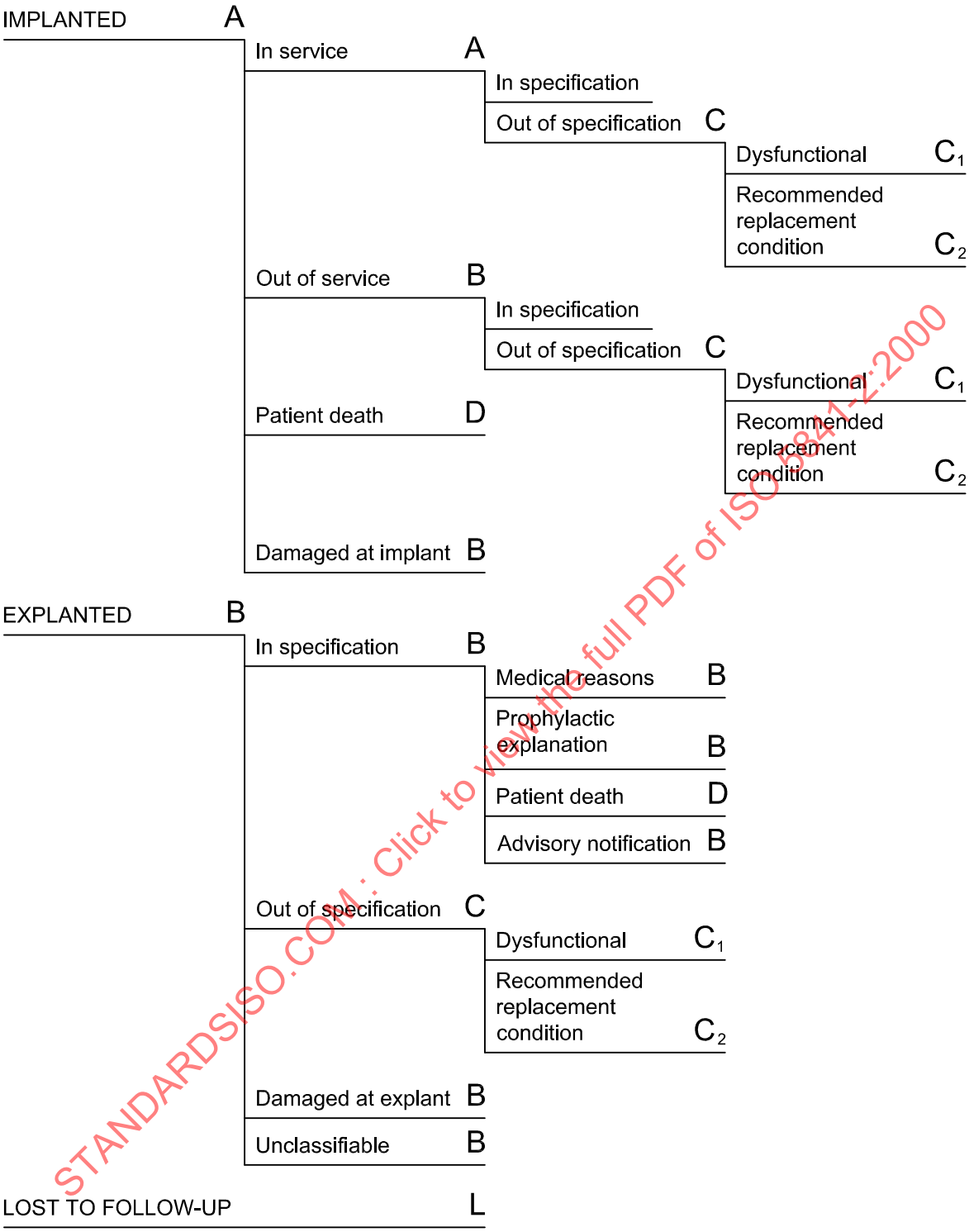


Figure A.1 —Assignment of category to devices

Annex B
(informative)

Statistical guidelines and discussion of application of results obtained

B.1 Introduction

This annex illustrates the application of actuarial analysis to obtaining the expressions of clinical performance for population samples of devices. It is intended only as an introduction to this type of analysis for users of this part of ISO 5841 unfamiliar with such statistical tools and their application to clinical experience with devices. For a further understanding of the assumptions, methods and use of actuarial techniques, the reader is encouraged to refer to the more comprehensive discussions contained in the Bibliography.

The main advantage of actuarial methods is that no underlying statistical distribution of the data needs to be assumed. As such, actuarial techniques are suitable for use with a wide variety of the kinds of data arising from clinical experience with devices. It is because of this wide applicability in the analysis of device data that this annex presents an outline of these methods. Nothing in this annex is intended to preclude the use of additional analytical techniques, which may be appropriate for specific data sets and other reporting objectives.

This part of ISO 5841 is aimed at all individuals or organizations who publish reports of clinical experience with devices. For a manufacturer to be in compliance with this part of ISO 5841, there are additional requirements for reporting (as discussed in clauses 5 and 6). Analysis techniques and actuarial displays are illustrated in this annex. Additional or more detailed analyses of such clinical data are, of course, not precluded.

This annex demonstrates the use of actuarial methods on a hypothetical set of data on implanted pulse generators. It is assumed that complete information is available on the classification status and on the important dates associated with each unit.

B.2 Statistical guidelines

B.2.1 Organizing the data

There are three pieces of data about a device that are needed to proceed with an actuarial analysis:

a) the date of implantation;

b) the assignment of the category (see annex A);

c) the date associated with the assignment of the category.

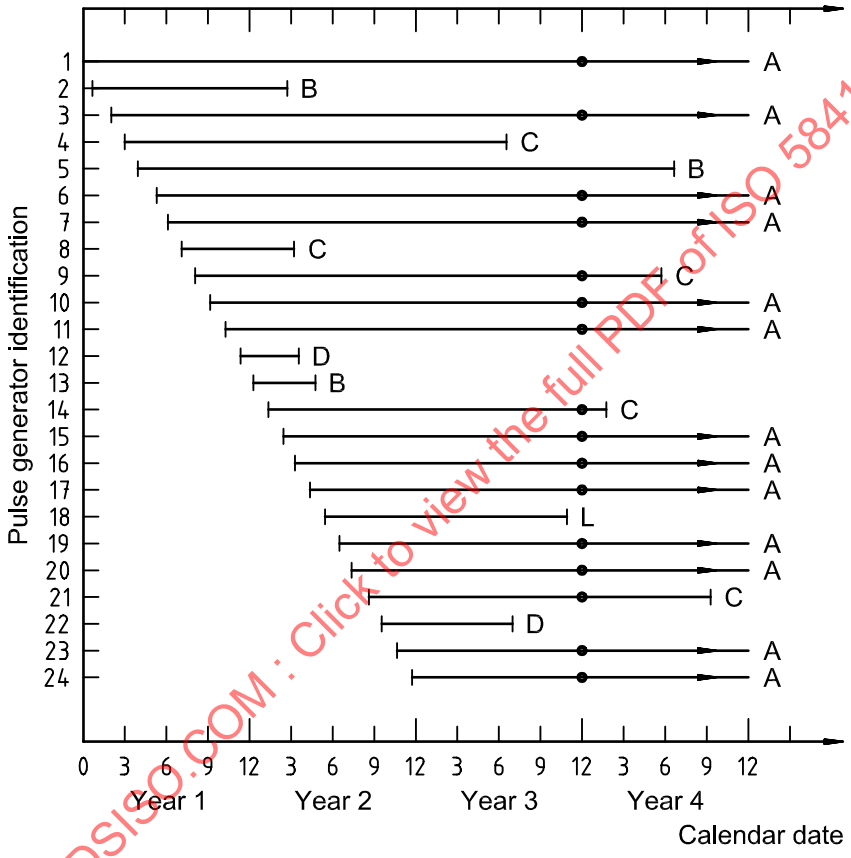
The date associated with the assignment is the date on which a category is assigned to a device. This would be, for example, the date on which a unit was explanted for reasons not related to its function (category B), the date an implanted unit went out of specification (category C), or the date the patient died but the death, as far as can be verified, is unrelated to the functioning of the device (category D). For units still in service and in specification (category A), it is the date on which the clinical performance period described by a particular report ends.

Special consideration is required for handling those patients with devices who lose contact with the follow-up centre (category L). In an “active” data system, the units are effectively withdrawn from the population at the moment continuing contact with the patient is broken. If the device was performing in specification up until the time contact was lost, it is reasonable to treat the device as if it were withdrawn in specification (category B). Combining categories B and L makes the assumption that the reason contact was lost was unrelated to the functioning of the device. This would be the case, for example, if a patient changes address without notification. If the follow-up

centre re-establishes contact with a lost patient, information about the device's condition can once again be determined. That unit could resume its place with other units in the population sample being monitored.

One method for reducing the number of unreported explants is to cross-reference new implant patient names with records of existing patients. Thus, if a new pulse-generator implant is recorded for a patient who already has a pacemaker, it can be inferred that the previous pulse generator has been explanted.

Figure B.1 shows the implant lifetime, according to calendar time, of a hypothetical group of 24 pulse generators. A group of units would, in practice, be selected on the basis of some common characteristic, making it suitable to report on their collective performance. The conclusion of the clinical reporting period in this example is taken to be at the end of year 4. In accordance with annex A, the letters A, B, C, D or L are assigned to general categories to facilitate analysis of the population sample.



NOTE The letters A, B, C, D and L represent status category for a performance report on clinical experience gathered up to the end of year 4. The dot (•) denotes the beginning of year 4.

Figure B.1 — Implant lifetimes, according to calendar time, for a sample data set of 24 pulse generators

It is important to note that categories are assigned on the basis of the best information available to the reporting party. For some devices, the reporting party may have information that they are functioning in specification (or out of specification). If all that is known is that a device has been implanted, then the general category A is assigned. Clause B.3 describes how the bias that arises from this assumption can be compensated for in part.

B.2.2 Cumulative experience reports

B.2.2.1 Actuarial analysis

This subclause presents the steps involved in performing an actuarial analysis for the purpose of preparing a report on cumulative experience.

Figure B.2 shows the implant lifetime of the sample data set on a scale measuring the length of implant time for each pulse generator. The notation remains the same as that defined for Figure B.1.

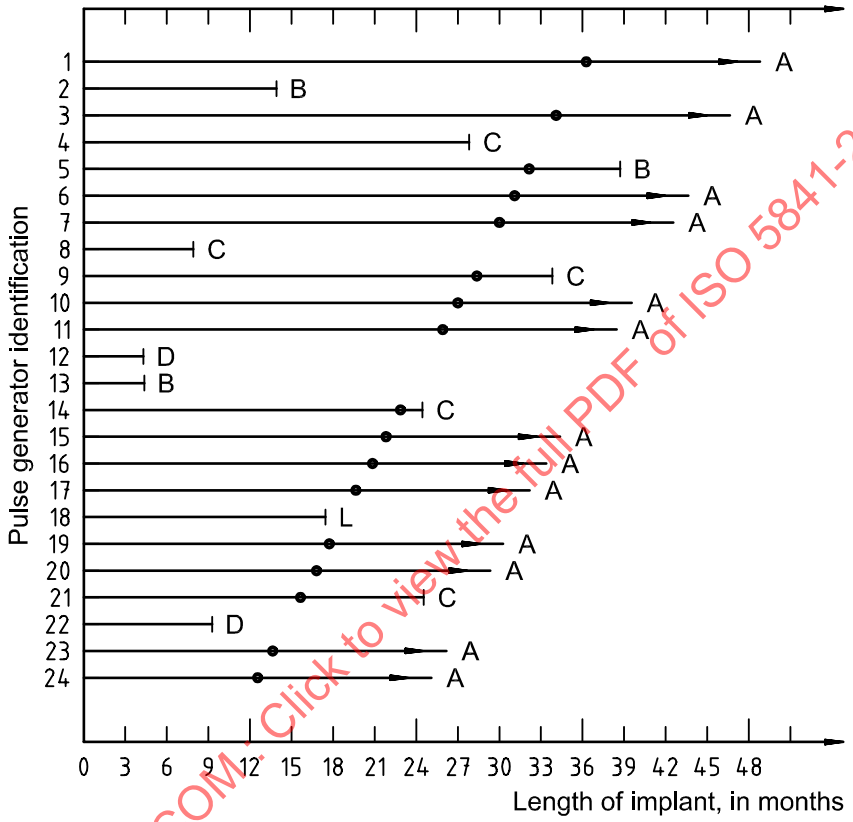


Figure B.2 — Length of implant, in months, for the pulse generators in the sample data set as in Figure B.1

The focus of this discussion is the actuarial data presented in Table B.1. The sample data set shown in Figures B.2 and B.3 is given numerically in Table B.1 in columns N, A, D, E and C. These variables and the other calculated quantities shown are described below. Each of the variables is actually a function of time. Thus, for example, the quantity N can be represented as $N(t)$. The selection of a time interval of three months was arbitrary.

— **Number entering** (N): The number of units entering any given time interval within the category A.

— **Incomplete lifetime** (A)**:** The number of units in a general category A whose implant time, at the end of the clinical reporting period, falls within the given time interval.

— **Withdrawn patient death** (D)**:** Number of units categorized as D within the given time interval.

— **Withdrawn in specification or lost to follow-up** (E)**:** Number of units within the given time interval that are categorized as B plus the number of units categorized as L, such that:

$$E(t) = B(t) + L(t). \tag{B.1}$$

— **Withdrawn out of specification** (C)**:** Number of units categorized as C within the given time interval. This includes units categorized as C_1 and C_2.

— **Units at risk** (U)**:** The effective number of units in service that are subject to a change in category during the given time interval:

$$U(t) = N(t) - \frac{A(t) + D(t) + E(t)}{2} \tag{B.2}$$

— **Survival fraction** (P): The estimated probability that a unit entering the interval will operate normally to the end of the given interval:

$$P(t) = 1 - \frac{C(t)}{U(t)} \tag{B.3}$$

— **Cumulative survival** (S)**:** The estimated probability of a unit surviving from the time of implant to the end of the given interval:

$$S(t) = P(t) \cdot P(t-1) \cdot \ldots P(1) \tag{B.4}$$

That is, the product of the survival fractions $P(1)$ . . . to $P(t)$.

Table B.1 — Actuarial analysis of sample data set for use in preparing a cumulative experience report

(In this example, category C includes both subcategories C_1 and C_2 and category E includes categories B and L)

Implant interval	(t) Length of time months	(N) Number entering	(A) Incomplete lifetimes	(D) Patent death	(E) Withdrawn or lost to follow-up	(C) Withdrawn out of specification	(U) Units at risk	(P) Survival fraction	(S) Cumulative survival probability
1	$0 < t \leqslant 3$	24	0	0	0	0	24,0	1,000 0	1,000 0
2	$3 < t \leqslant 6$	24	0	1	1	0	23,0	1,000 0	1,000 0
3	$6 < t \leqslant 9$	22	0	0	0	1	22,0	0,954 5	0,954 5
4	$9 < t \leqslant 12$	21	0	1	0	0	20,5	1,000 0	0,954 5
5	$12 < t \leqslant 15$	20	0	0	1	0	19,5	1,000 0	0,954 5
6	$15 < t \leqslant 18$	19	0	0	1	0	18,5	1,000 0	0,954 5
7	$18 < t \leqslant 21$	18	0	0	0	0	18,0	1,000 0	0,954 5
8	$21 < t \leqslant 24$	18	0	0	0	0	18,0	1,000 0	0,954 5
9	$24 < t \leqslant 27$	18	2	0	0	2	17,0	0,882 4	0,842 3
10	$27 < t \leqslant 30$	14	2	0	0	1	13,0	0,923 1	0,777 5
11	$30 < t \leqslant 33$	11	2	0	0	0	10,0	1,000 0	0,777 5
12	$33 < t \leqslant 36$	9	1	0	0	1	8,5	0,882 4	0,686 1
13	$36 < t \leqslant 39$	7	2	0	1	0	5,5	1,000 0	0,686 1
14	$39 < t \leqslant 42$	4	1	0	0	0	3,5	1,000 0	0,686 1
15	$42 < t \leqslant 45$	3	1	0	0	0	2,5	1,000 0	0,686 1
16	$45 < t \leqslant 48$	2	2	0	0	0	1,0	1,000 0	0,686 1
		Total	13	2	4	5	224,5		

The information in column (S) of Table B.1 is presented in graphical form in Figure B.3.

B.2.2.2 Confidence limit

Those parties reporting cumulative survival statistics are encouraged to present additional information to that in column (S). The effective sample size data for each interval, column (U), or confidence limits (for example, 90 %, 95 %) would aid greatly in interpreting the data. For the statistical techniques involved in preparing such confidence limits, the reader is referred to the Bibliography.

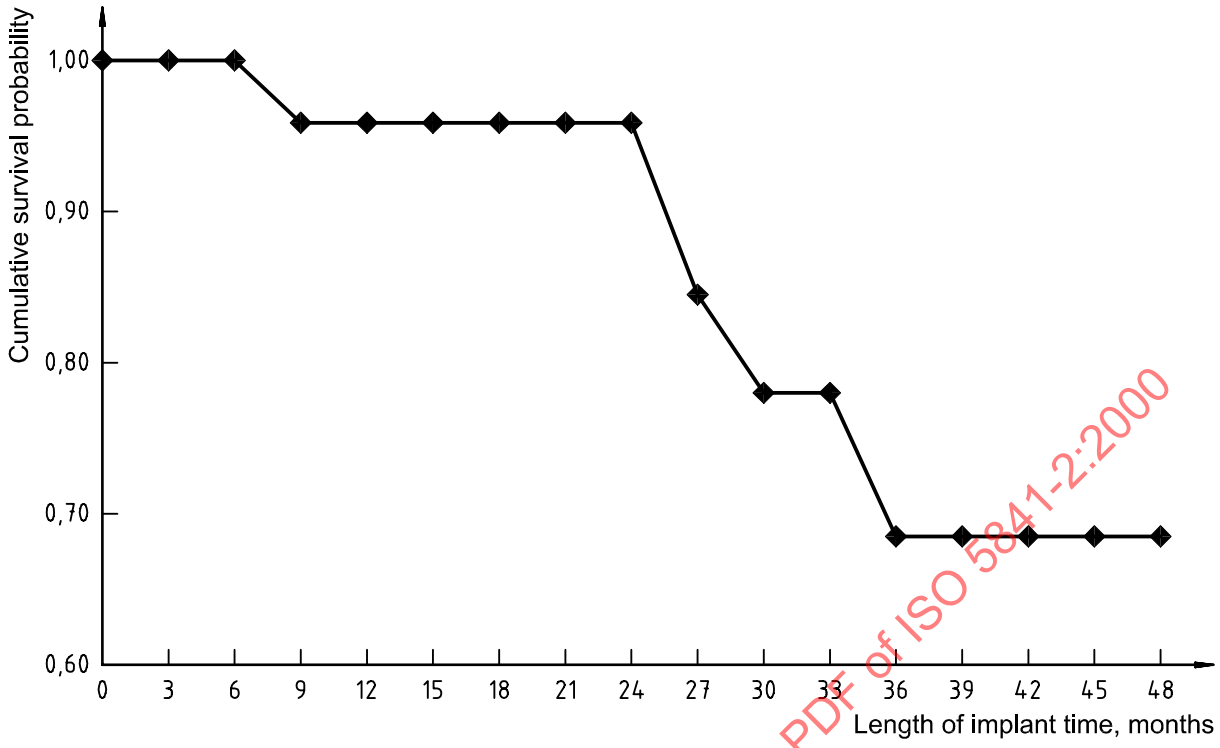


Figure B.3 — Plot of cumulative survival probability against length of implant time, in months
[Values taken from column (S) in Table B.1]

B.2.3 Estimating future survival probability

Once the cumulative survival probability is established (see Figure B.3), the future clinical performance can be estimated using the following technique.

A reliability distribution, such as Weibull or log-normal, is used to smooth and extrapolate the cumulative survival probability where no implant information exists. From the extrapolated curve, the survival probability (S) at any time since implant (t) can be estimated. The probability that the device will survive the next ith interval given that it survived time t, $S(i;t)$, is calculated as:

$$S(i;t) = \frac{S(t+i)}{S(t)} \tag{B.5}$$

The probability that a device will be out of specification in the next ith interval, $O(i;t)$, is calculated as:

$$O(i;t) = 1 - S(i;t) \tag{B.6}$$

B.3 Discussion of application of results obtained

B.3.1 Limitation of the example

It should be noted that the proportion of devices assigned to general category C is highly exaggerated to illustrate the method. Such a rate of performance change should not be expected in actual data unless a pulse generator is having serious problems or it has passed the recommended replacement condition.

B.3.2 Problems affecting accuracy

There are a number of practical problems that limit the ability of any population sample to characterize accurately a population of implanted devices. A fundamental statistical issue is the degree to which a population sample reflects the population as a whole. More specific to implanted device population samples is the fact that some patients are lost to follow-up. Some of these may return to follow-up after an extended absence. The population sample may reflect only those devices which function long enough to enter a follow-up programme, thus causing earlier events to be under-represented,

Product performance reports may be based on data collected actively, passively, or both. Active collection requires the existence of procedures to verify all data relating to the clinical performance period being reported. Such procedures may include determination of the status of all devices during the relevant period, or assurances that all changes in device status are reported as they occur.

Passive data collection, in the absence of such verification procedures, leads to the need to make assumptions about the status of devices for which no data have been received during the clinical performance period being reported. Typically, the assumption is that the devices retained their last known status.

Such assumptions are not always correct. With passive data collection, failure to report the explantation of an out-of-warranty pulse generator, for example, will lead to a biased conclusion that the pulse generator is still implanted.

Active data collection is preferred for clinical performance reporting. However, economic and administrative constraints dictate that while it is likely that a clinical group will collect data actively, manufacturers usually have to rely on passive collection.

Any reporting party has a responsibility to indicate the data collection methods used in preparing its reports and, thus, the nature of any biases that might be present.

As with other statistical methods, the benefit of the analytical methods in this part of ISO 5841 is limited by the size of population under consideration.

B.3.3 Adjustment for under-reported events

Under-reporting of events is a persistent problem, particularly when clinical performance data is developed from a passive data-collection system. One methodology for correcting the survival estimates in the life table procedure was developed by the Health Industry Manufacturers' Association (HIMA) Pacemaker Task Force Statistical Working Group. This methodology adjusts the survival estimates by deriving a correction factor from a yearly random sample of patients. Data from the "active" component is used to adjust the survival estimates when significant under-reporting of follow-up events, such as patient deaths, devices withdrawn in specification, and devices withdrawn out of specification, are suspected.

If bias due to under-reporting exists, some adjustment to both numerator and denominator of equation (B.3) is necessary. Assume that through some method, such as a random audit, the following reporting rates are found:

Π_C is the fraction of devices withdrawn out of specification that are reported;
Π_D is the fraction of deaths actually reported, and
Π_E is the fraction of devices withdrawn in specification or lost to follow-up that are reported,

where these reporting rates are bounded between 0 and 1 (i.e. $0 < \Pi \leqslant 1$).

The corrected estimates for C, D and E can be obtained from the following relationships:

$$\hat{C}(t) = \frac{C(t)}{\Pi_C} \tag{B.7}$$

$$\hat{D}(t) = \frac{D(t)}{\Pi_D} \tag{B.8}$$

$$\hat{E}(t) = \frac{E(t)}{\Pi_E} \tag{B.9}$$

The above equations assume that Π_C, Π_D and Π_E are independent of implant time t. This assumption is a practical one if these parameters are estimated from a small audit samples. The number of devices withdrawn out of specification, patient deaths, and devices withdrawn in specification in a small sample are quite small. Thus, the probability of detecting the time dependency of Π_C, Π_D, and Π_E is very low.

On the other hand, if reporting rates are to be estimated from a larger audit sample, then the time dependency of the reporting rates can be estimated with relatively high precision. Assuming that $\Pi_{C(t)}$, $\Pi_{D(t)}$, and $\Pi_{E(t)}$ represent time-dependent reporting rates for devices withdrawn out of specification, deaths, and devices withdrawn in specification that can be estimated from a large sample, then equations (B.7) through equation (B.9) can be rewritten by substituting $\Pi_{C(t)}$, $\Pi_{E(t)}$ and $\Pi_{D(t)}$ in place of Π_C, Π_D, and Π_E.

The total number under-reported in time interval t can be expressed as:

$$\Delta(t) = \left[\hat{C}(t) + \hat{D}(t) + \hat{E}(t)\right] - \left[C(t) + D(t) + E(t)\right] \tag{B.10}$$

Corrections are also required for $A(t)$ and $N(t)$ to reflect the corrections made in equations (B.7), (B.8) and (B.9).

Correction of $A(t)$ and $N(t)$ requires the following additional definitions:

$n(t)$ is the number of devices implanted during the t th time interval prior to the closing date of the study

$N'(t)$ is the number of devices implanted by time t prior to the closing date (see annex C for a graphical description of $n(t)$ and $N'(t)$.)

Then the following relationships exists:

$$N(1) = \sum_{i=1}^{\max\ t} n(i) \tag{B.11}$$

$$N'(t) = N(1) - \sum_{i=1}^{t-1} n(i) \tag{B.12}$$

Also note that $A(t)$ comes from the cohort group $n(t)$. $A(t)$ are those patients remaining from the cohort $n(t)$ that have not experienced a device withdrawn out of specification, death, or loss to follow-up.

The corrected estimate $\hat{A}(t)$ shall account for the under-reported events from $n(t)$. $\hat{A}(t)$ can be estimated from the following relationship:

$$\hat{A}(t) = A(t) - \Delta A(t) \tag{B.13}$$

where

$$\Delta A(t) = n(t) \cdot \left[\left(\sum_{i=1}^{t-1} \frac{\Delta(i)}{N'(i) - \frac{n(i)}{2}}\right) + \frac{\Delta(t)}{2N'(t) - n(t)}\right] \tag{B.14}$$