INTERNATIONAL STANDARD

ISO 5841-2

Third edition
2014-08-01

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 concernant le fonctionnement clinique de populations de générateurs d'impulsions ou de fils-électrodes

Reference number
ISO 5841-2:2014(E)

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Published in Switzerland

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 6, *Active implants*.

This third edition cancels and replaces the second edition (ISO 5841-2:2000), which has been technically revised.

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

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

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

Introduction

ISO 14708-2:2012, 28.19 requires the clinician's manual to document the projected service life using defined settings. 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 projected 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.

Programmed settings and differing or changing patient therapy needs might also result in a device having more or less than the projected service life as defined by ISO 14708-2. In addition, clinical management and implant technique can have a significant impact on long term performance of lead and pulse generators. These variables are reflected in the product performance report data.

These factors underscore the value of maintaining an accurate and discriminating view of clinical performance of a population of devices within the scope of this part of ISO 5841, so as to aid patient management. In order to do this, it is necessary to collect implant and explant information as allowed by local law. Physicians and clinicians are encouraged to report their complaints and return associated explanted devices to the device manufacturers to support the accuracy of product performance reports.

It is recognized that certain devices are marketed in geographies where device implant and explant data are not available due to patient privacy laws. This situation requires manufacturers to apply alternative methods to calculate survival probability.

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 can give cumulative clinical-experience information based on a variety of assumptions and statistical techniques. This part of ISO 5841 provides a method for categorizing devices, requirements for the statistical techniques (see Annex A) that shall be used to obtain the most benefit from the data and a statement of the rationale (see Annex B) 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 cardiac pulse generators or leads, intended for long-term implantation, hereinafter referred to as devices. Devices to be reported has to be market approved in one or more geographies. 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. It also provides normative requirements for statistical calculations, 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 B gives the rationale for this part of ISO 5841.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 14708-2:2012, *Implants for surgery — Active implantable medical devices — Part 2: Cardiac pacemakers*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 14708-2 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 might 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
complaint
any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution[15]

3.4
confirmed malfunction
malfunction of an implanted device, confirmed by returned product analysis, not including induced malfunctions

3.5
damaged
<of a device> having characteristics which have changed outside the limits stated by the manufacturer, due to some external agency

3.6
device
cardiac pulse generators or leads, intended for long-term implantation

3.7
device family
specified group of device model numbers with the same indications for use and designs that differ only with respect to parameters not reasonably expected to significantly affect malfunction incidence or longevity, such as pulse generator header differences or lead length

3.8
follow-up centre
medical centre, hospital, clinic, or individual responsible for the care of a patient after the implantation of a device

3.9
implanted
status of a device after the surgical incisions are closed (implant pocket closed); if relevant clinical details are not available to the manufacturer, at least one calendar day shall have passed after the implant date in order to classify the device as implanted

3.10
implant damage — leads
damage which occurred after opening the lead package and during an attempt to implant the lead, i.e. the implant was not completed using the lead in question

3.11
induced malfunction — pulse generators
device malfunction caused by external factors (e.g. therapeutic radiation, excessive physical damage, etc.) including but not limited to hazards addressed in product labeling

Note 1 to entry: Damage to a pulse generator caused by a lead malfunction will be reported as a lead malfunction.

3.12
induced malfunction — leads
lead malfunction caused by use error or other external factors (e.g. scalpel cuts, damage caused during implant, sutures applied directly to lead body, explant or after explant etc.) including applications outside of labeling recommendations or addressed in product labeling as cautions or hazards in product labeling

Note 1 to entry: Damage to a lead caused by a pulse generator malfunction will be reported as a pulse generator malfunction.

3.13
in service
<of a device> functioning in such a manner as to provide potential medical benefits to the patient

Note 1 to entry: This term can apply to a device that may be out of specification (see 3.23).

3.14
in specification
<of a device> having characteristics within the limits recommended by the manufacturer for clinical use

3.15
lead modified — electrically
lead that remains connected to a pulse generator whose function is automatically altered or manually reprogrammed (e.g. changing from bipolar to unipolar or DDD to VVI mode) in response to a problem with the mechanical or electrical integrity of the lead

3.16
lead modified — surgically
any mechanical alteration of the lead (e.g. replacing a connector or the rate sensing portion of an ICD lead) in response to a problem with the mechanical or electrical integrity of the lead

Note 1 to entry: Does not include leads that have been successfully repositioned.

3.17
malfunction
failure of a device to meet its performance specifications or otherwise perform as intended

Note 1 to entry: Performance specifications include all claims made in the labelling for the device. The intended performance of a device refers to the intended use for which the device is labelled or marketed.[14]

3.18
malfunction without compromised therapy — pulse generator
pulse generator malfunction that did not compromise pacing or defibrillation therapy while implanted and in service

Note 1 to entry: Therapy is not compromised as long as the critical patient-protective pacing and defibrillation therapies are available. This includes changes in device settings that occur as intended by the design and do not result in loss of critical patient protective therapies but are the reported reasons for explant. Examples include (but are not limited to): reversion to a designed "safe mode", "backup mode", "power-on reset" or other manufacturer-specific terminology, error-affecting diagnostic functions, telemetry function, data storage, malfunction of a component that causes battery to lose power quickly enough to cause premature battery depletion, but slowly enough that the condition is detected through normal follow-up before therapy is lost; mechanical problems with connector header that do not affect therapy.

3.19
malfunction with compromised therapy
device malfunction causing compromised pacing or defibrillation therapy (including complete loss or partial degradation) while implanted and in service

3.20
medical reasons
reasons unrelated to the device or its operation

Note 1 to entry: Examples include (but are not limited to): 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.

3.21
normal battery depletion
for pulse generators, the condition when (a) a device is returned with no associated complaint and the device has reached its elective replacement indicator(s) with implant time that meets or exceeds the nominal (50 percentile) predicted longevity at default (labeled) settings, or (b) a device is returned and the device has reached its elective replacement indicator(s) with implant time exceeding 75 % of the expected longevity using the longevity calculation tool available at time of product introduction, calculated using the device's actual use conditions and settings

3.22
other conditions affecting performance — leads
non-electrical findings which do not affect clinical usage or outcomes, but might, for example, influence the length of a procedure

Note 1 to entry: Anomalous findings are those occasions where lab analysis reveals a secondary finding on a returned lead. These findings are not associated with a complaint. Examples include evidence of partial insulation abrasion, no conductor exposed or other cosmetic issues. Lead may have been successfully implanted.

3.23
out of service
<of a device> not providing a medical benefit to the patient

Note 1 to entry: A device thus described is not necessarily out of specification (see 3.24) or explanted.

3.24
out of specification
<of a device> having one or more characteristics outside the limits established by the manufacturer for clinical use

3.25
population sample
group of devices that is assumed to be representative of the worldwide population of implanted devices

Note 1 to entry: Typically, devices registered as implanted in the United States can serve as the population sample, but other data sources can be utilized, including, but not limited to remote monitoring and clinical studies.

3.26
post-approval surveillance study
enrollment of a sample of patients in identified centers for the purpose of prospective, active, systematic, scientifically valid collection, analysis, and interpretation of data, or other information, collected to report on device performance

3.27
post-market surveillance
activity performed by a manufacturer to assess product performance using analysis of complaints and returned products

3.28
premature battery depletion
for pulse generators, the condition when a device is returned and confirmed to have depleted the battery in a time period less than normal battery depletion

3.29
product performance report
document published by a pulse generator or leads manufacturer intended to report long term clinical performance of individual products

3.30
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.

3.31
prophylactic explantation
explantation for reasons based on the anticipated performance of the device or other medical reasons

3.32
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.

3.33
registered explant
registered implant for which the date of explantation is known by the reporting party

3.34
registered implant
implanted device for which the date of implantation is known by the reporting party

3.35
registered implant month
one month of operation by a registered implant

3.36
reporting party
individual or organization publishing clinical pacemaker data or the analysis thereof

4 General requirements

4.1 Frequency of publication

Each manufacturer shall publish an updated performance report at least semi-annually. The report shall include data for the most recently completed clinical performance period.

4.2 Method of publication

Product performance reports shall be publicly available on the manufacturers' website.

4.3 Report organization

The product performance report shall be organized so that data are presented for each model or device family within the scope of this part of ISO 5841 that meet the inclusion criteria given in 4.4.

4.4 Criteria for inclusion and removal of reported models and device families

Models or device families shall be included in the product performance report at or before 500 worldwide sales.

Models or device families can be removed from the report when the earlier of the following occurs:

— fewer than 500 of the devices in the sample population are estimated (following corrections for under reporting) to remain in service;

— 20 years have elapsed since first market approval of the sample population.

4.5 Source of performance report data

Performance data can be obtained from various data sets, including, but not limited to post-market surveillance, registries, clinical studies, and remote monitoring. As a minimum, manufacturers shall utilize data obtained from post-market surveillance.

4.6 Product performance report — Required content

4.6.1 Textual and numeric data

For each model or device family being reported, the following data shall be provided in the product performance report:

a) model designation(s);

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

c) sample size and how the population and population sample are defined; if the manufacturer chooses to provide results segregated by sub-populations (e.g. production group, header differences, etc), the report shall explain the basis on which the sub-populations are established;

d) for the population described in item c), the number or percentage of devices that have been returned and analysed;

e) criteria for including and excluding data;

f) the clinical performance period;

g) units of time of the data;

h) category assigned to the device, in accordance with Annex A;

i) for devices subject to an advisory, the advisory description and associated recommendations shall be included if the number of devices susceptible to the anomaly described in the advisory is greater than 200. For these devices, the number of confirmed malfunctions for the affected sub-population shall be provided;

j) explanation of methods used to adjust for any sources of bias known to be present (see Annex A);

k) 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;

l) the manufacturer shall disclose their level of conformity with this part of ISO 5841. Any non-conformities shall also be disclosed.

4.6.2 Estimated device survival probability

For each model or device family being reported, an estimate of the cumulative device survival probability derived through actuarial analysis using the method described in Annex A shall be provided. The results shall be presented in both graphical and tabular form. Graphical results shall be presented using consistent scales and sizes.

The report shall include, in addition to survival statistics, either effective sample size data for each time interval, or confidence limits, or both.

When the survival performance of a sub-population of devices subject to an advisory diverges from the population sample, survival curves for the sub-population should be shown separately.

Data for survival estimates can be collected using a prospective clinical study, remote monitoring, post market surveillance, or a combination of these or other methods.

The population for which cumulative survival probability is estimated for any given lead model or device family can be chosen by the manufacturer.

Manufacturers shall select methods that properly categorize devices in order to avoid problems affecting accuracy described in A.3.2.

Two methods of estimating device survival probability are detailed in this part of ISO 5841, either of which can be utilized. A methodology using data obtained solely from remote monitoring, while feasible, is not described in this part of ISO 5841. However, manufacturers can use remote monitoring data to augment the results of the two methods described below. In this case, manufacturers shall provide a description of how such data has been used.

These methods should not be construed as equivalent alternatives, nor should these methods be construed as the only methods available to the reporting party.

Manufacturers shall indicate the data collection methods used in preparing its reports and, thus, the nature of any bias that might be present.

4.6.2.1 Survival probability using data from a post approval surveillance study

If a manufacturer chooses to estimate survival probability using data from a post approval surveillance study, study design should include provisions to ensure meaningful data are collected for survival reporting. These provisions include

— sufficient number of enrolled subjects to support survival probability calculation,

— sufficient diversity among participating centers to reduce bias due to centre or physician selection and to promote a sample representative of the total population,

— procedures to ensure all active devices are regularly followed by the study centre,

— evaluation of centre compliance with study protocol through regular clinical monitoring at each study site, and

— procedures designed to promote consistent adjudication of events over long periods of time (years).

The report shall include a description of the study approach taken. The following shall also be included with the survival probability data:

— number of devices enrolled in the study as of the date of the report;

— number of devices active in the study as of the data cutoff date of the report;

— cumulative months of follow-up accrued;

— qualifying complications observed and the number of each type of complication;

— effective sample size at the annual intervals.

A study-based reportable event or device complication is said to have occurred when

a) at least one of the clinical observations described in Table 2 has been reported (in accordance with the study protocol) or a returned device malfunction was confirmed, and

b) the device

   — was modified either electrically or surgically to remedy the situation, or

   — was left in use based on medical judgment despite a known clinical performance issue.

While post approval surveillance studies represent a well-controlled and prospective surveillance method, there are limitations related to measuring device performance. For example, such studies might not identify the mechanism or root cause of the complication reported. This can lead to over-reporting or misclassification of certain complications due to device malfunction as opposed to physiologic changes related or unrelated to the device condition. Enrollment rates at the study centres might not be commensurate with of the rate of implantation across the general population and might not fully represent the general population.

4.6.2.2 Survival probability using returned product analysis and complaint information

If a manufacturer chooses to estimate survival probability using returned product analysis and complaint information, the manufacturer shall include both device malfunctions identified by analysis and reported device complications.

Complications (as defined in Clause 5) should be used in conjunction with returned malfunction analysis as an adjustment to better represent survival probability in a broader population than either method would independently.

This methodology can be subject to under-reporting. Manufacturers should analyse sources of under-reporting and attempt to provide adjustments to correct for them. Remote monitoring is an example of a source of data used to make such adjustments.

4.7 Adjustment for underreported events

Manufacturers shall consider the need to adjust the calculated survival fraction at each interval to reduce bias due to underreporting. Manufacturers shall consider underreporting of

— pulse generators removed from service due to malfunction,

— leads removed from service due to malfunction or complication,

— pulse generators or leads removed from service due to patient death, where such deaths are not known to be associated with device performance,

— pulse generators or leads removed from service while in specification (such as devices lost to follow up or removed due to changes in patient condition), and

— pulse generators removed due to normal battery depletion.

Where survival fractions have been adjusted, manufacturers shall describe the techniques and rationale used to perform the adjustments. If the manufacturer chooses not to adjust survival fractions, a rationale for not doing so shall be provided.

5 Particular reporting requirements

5.1 Reporting pulse generator performance

This subclause elaborates on the reporting for pulse generators for category C devices as described in Annex A.

Reporting of survival probability of pulse generators (see 4.6.2) shall include

a) all-cause device survival curves (comprising devices exhibiting normal battery depletion, malfunction with compromised therapy, and malfunction without compromised therapy),

b) confirmed malfunction-free survival curves (comprising devices exhibiting malfunction with compromised therapy and malfunction without compromised therapy), and

c) the number (presented in tabular form) of devices classified as exhibiting

   — normal battery depletion,

   — confirmed malfunction with compromised therapy, or

   — confirmed malfunction without compromised therapy.

This methodology can be subject to under-reporting. Manufacturers should analyse sources of under-reporting and attempt to provide adjustments to correct for them. Remote monitoring is an example of a source of data used to make such adjustments.

5.2 Reporting lead performance

This subclause provides additional requirements when applying Annex A in regard to calculating cumulative survival probability for implanted leads.

Performance reporting of cardiac leads shall include the results of returned product analysis for lead malfunctions (described in 5.2.1), lead complications based on complaint information for chronic lead complications (described in 5.2.2), acute lead complications (described in 5.2.3), and cumulative survival probability calculation (described in 5.2.4).

5.2.1 Reporting malfunctions — Leads

Returned product analysis data in product performance reports shall include, in addition to those items required in 4.6, the following for each product family:

a) the number of leads reported in 4.6 shall include full and partial leads returned;

b) number of confirmed malfunctions, post-implant.

Leads which are classified as having a confirmed malfunction are included in all-cause survival probability and shall be reported within one of the categories listed in Table 1. Only one primary lead malfunction shall be reported per lead. In those cases where more than one lead malfunction is identified, the malfunction most closely related to the clinical complaint shall be reported

Table 1 — Categories of confirmed malfunctions for leads

Category	Description of malfunction
Conductor fracture	Conductor break with complete or intermittent loss of continuity that could interrupt current flow (e.g. fractured conductors). This type of malfunction includes any conductor fracture such as those associated with clavicle flex-fatigue or crush damage.
Insulation breach	Any breach of inner or outer lead insulation. Examples include: proximal abrasions associated with lead-on-lead or lead-on-PG contact in the pocket; mid-lead insulation damage caused by clavicle flex-fatigue or crush, suture or suture sleeve, insulation wear in the region of vein insertion; and distal region wear due to lead-on-lead (intracardiac), lead-on-heart valve, or lead-on-other anatomy contact.
Crimps, welds, and bonds	Any interruption in the conductor or lead body associated with a point of connection.
Other	Includes lead malfunctions related to specific proprietary mechanical attributes or connectors. Examples of this category include, but are not limited to lead sensors, connectors (such as IS-1, DF-1, IS-4, DF-4), and seal rings.

5.2.2 Reporting chronic lead complications based on complaint information

Chronic lead complications shall be included in the calculation of survival probability when survival probability is based on return product analysis and complaints data.

A chronic lead complication (occurring more than 30 d after implant) is said to have occurred when

a) at least one of the lead observations in Table 2 has been reported, and

b) the lead was

- modified either electrically or surgically to remedy the situation, or
- left in use based on medical judgment despite a known clinical performance issue, or
- removed from service and returned for analysis, where analysis was inconclusive because only portions of the lead were available, or the returned lead was damaged by the explantation

process, or where returned product analysis could not determine an out of specification condition.

NOTE An example of a lead left in use based on medical judgment is (at a pulse generator replacement) an atrial lead that has low impedance and only a marginal safety margin for capture at an output level not causing pocket stimulation. Such a lead might be left in place in a dual chamber pacing mode if the patient's condition precludes safe replacement of the atrial lead.

Manufacturers shall include the number and category of chronic lead complications. Where more than one lead complication is identified, only one complication using the observation with the highest placement in the hierarchy shown in Table 2 shall be reported per lead in those cases.

The methods for identifying lead complications shall be described in the product performance report.

Table 2 — Categories of lead observations (in descending hierarchical order)

Lead observation	Description
Cardiac perforation	Penetration of the lead tip through the myocardium, clinically suspected and confirmed by chest X-ray, fluoroscopy, echocardiogram, or visual observation, which results in clinical symptoms, typically degradation of pacing/ICD lead electrical performance (high thresholds), chest pain, or tamponade.
Conductor fracture	A mechanical break within the lead conductor (includes connectors, coils and/or electrodes) observed visually, electrically, or radiographically.
Lead dislodgement	Radiographic, electrical, or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing and/or lead performance.
Failure to capture	Intermittent or complete failure to achieve cardiac stimulation (atrial or ventricular) at programmed output delivered outside of the cardiac refractory period. Sudden and significant increase in the pacing threshold value (elevated thresholds compared to previous measured value) at which 2:1 safety margin can no longer be achieved.
Oversensing	Misinterpretation of cardiac or non-cardiac events as cardiac depolarization, [e.g. T-waves, skeletal muscle potentials, and extra cardiac electromagnetic interference (EMI)].
Failure to sense (undersensing)	Intermittent or complete loss of sensing or failure to detect intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings.
Insulation breach	A disruption or break in lead insulation observed visually, electrically, or radiographically.
Abnormal pacing impedance	Pacing impedance is typically considered abnormal if a measurement is <200 Ω or >3000 Ω. (based on lead model and measurement range of the device).
Abnormal defibrillation impedance	Defibrillation impedance is typically considered abnormal if a measurement is < 20 Ω or > 200 Ω. (based on lead model and measurement range of the device). Including high or low shock impedance when attempting to deliver a shock.
Extracardiac stimulation	Clinical observation of inadvertent nerve/muscle stimulation other than cardiac muscle.
Other	Specific proprietary attributes of a lead such as sensors which affect a lead's ability to perform as designed or remain in service.

5.2.3 Reporting acute lead complications based on complaint information

Lead performance in the first 30-days post-implant (acute) can be subject to a number of factors, including patient-specific anatomy, clinical conditions, and/or varying implant conditions/techniques. Therefore,

acute lead observations (those occurring within the first 30-days post implant) shall be reported separately in performance reports as acute lead complications. Those complications might or might not be attributable directly to lead design and therefore are not included in lead survival probability.

An acute complication (occurring within the first 30 d after implant) is said to have occurred when

a) at least one of the lead observations in Table 2 has been reported, and

b) the lead

— was modified either electrically (see 3.15) or surgically to remedy the situation, or

— was left in use based on medical judgment despite a known clinical performance issue, or

— was removed from service and returned for analysis, where analysis was inconclusive because only portions of the lead were available, or the returned lead was damaged by the explantation process, or where returned product analysis could not determine an out of specification condition.

Manufacturers shall include the number and category of acute lead complications. Where more than one lead complication is identified, only the complication highest in the hierarchy shown in Table 2 shall be reported per lead in those cases.

5.2.4 Reporting leads cumulative survival probability

This subclause provides additional requirements for reporting cumulative survival probability of leads in relationship to 4.6.2.

Leads shall not be considered for inclusion in lead survival probability calculations in those cases where the lead implant was attempted but failed, lead damage was induced, or there were findings that did not affect the electrical function of the lead (e.g. discoloration, cosmetic).

5.2.4.1 Lead survival probability using data from post market surveillance

When manufacturers choose to estimate lead survival probability using post market surveillance, they shall include complication categories and return product analysis malfunction categorization as shown in Table 3.

Table 3 also describes which events shall be included in survival probability estimations.

Table 3 — Summary of leads performance reporting criteria

<table>
<tr><th colspan="2">Lead complications</th><th>Lead return product analysis (RPA)</th><th>Leads events not included in survival probability</th></tr>
<tr><td>Acute
Implanted ≤30 d
at time of observation</td><td>Chronic
Implanted >30 d
at time of observation</td><td colspan="2">While implanted</td></tr>
<tr><td colspan="2">and</td><td colspan="2">and</td></tr>
<tr><td colspan="2">Reported observation and lead was removed from service (surgically or electronically), but not returned</td><td>Returned with a complaint</td><td>Returned or not returned</td></tr>
<tr><td colspan="2">or</td><td>and</td><td>or</td></tr>
<tr><td colspan="2">Reported observation and lead returned where malfunction analysis is inconclusive or unconfirmed</td><td>Regardless of implant time</td><td>Induced damage or not lead related</td></tr>
<tr><td>Do not include in lead survival probability</td><td>Include in lead survival probability</td><td>Include in lead survival probability</td><td>Do not include in lead survival probability</td></tr>
<tr><td colspan="2">and</td><td>and</td><td>Induced damage examples
— scalpel cuts;
— no suture sleeve (use error);
— twiddler syndrome;
— infection;
— pt. outgrows lead.</td></tr>
<tr><td colspan="2">Complications shall be reported as one of the following observation categories:
— cardiac perforation;
— conductor fracture;
— lead dislodgement;
— failure to capture;
— oversensing;
— failure to sense;
— insulation breach;
— abnormal pacing impedance;
— abnormal defibrillation impedance;
— extracardiac stimulation.</td><td>Malfunctions confirmed through RPA shall be reported as one of the following categories:
— conductor fracture;
— insulation breach;
— crimps, welds, and bonds;
— other.</td><td>Not lead related examples
— implant damage;
— non-electrical;
— secondary findings.</td></tr>
</table>

Annex A
(normative)

Statistical method for survival analysis and discussion of application of results obtained

A.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, who might be 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. This annex demonstrates the use of actuarial methods on a hypothetical set of data on implanted devices. It is assumed that complete information is available on the classification status and on the important dates associated with each unit.

A.2 Statistical method for device performance reporting

A.2.1 Categorization of devices

Each implanted and explanted device shall be assigned the appropriate category in accordance with the following criteria and according to the best evidence available.

— Category A: Device that is in service. No complication recorded or malfunction confirmed by returns analysis.

— Category B: Device removed from service for reasons not related to the functioning of the device. No complication recorded or malfunction confirmed by returns analysis.

— Category C1: Devices with a malfunction confirmed by returned product analysis or leads with a reported complication.

— Category C2: Pulse generator battery depleted. No malfunction confirmed by returns analysis.

— Category D: Patient has died. However, the death, as far as can be verified, is unrelated to the functioning of the device. No complication recorded or malfunction confirmed by returns analysis.

— Category L: Device is lost to follow-up. No complication recorded or malfunction confirmed by returns analysis.

NOTE Devices subject to an advisory are subject to the same criteria as non-advisory devices.

A.2.2 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 assigned category;

c) the earlier of the following dates:

— the date that a confirmed device malfunction or a lead complication was reported to have occurred (category C1);

— the reported date of battery depletion (category C2);

— the date of explant;

— the date of patient's death;

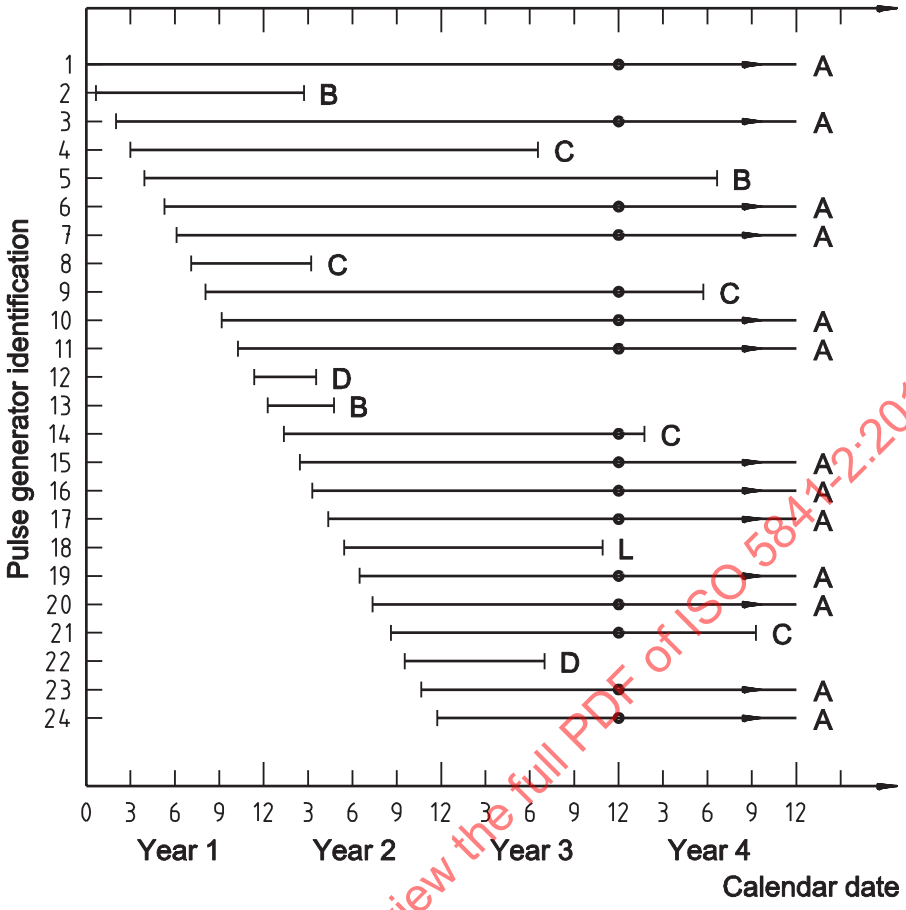
— the date of return;

— the date a device was deemed to have been lost to follow-up (category L).

For units still in service (category A), the dates above will not apply, in which case, the end date of the clinical performance period described by a particular report shall be used.

The associated time to categorization is calculated as the difference between the date associated with categorization and the implant date.

Figure A.1 shows the implant lifetime, according to calendar time, of a hypothetical group of 24 devices. 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 A.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 can 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. A.3 describes how the bias that arises from this assumption can be compensated for in part.

A.2.3 Cumulative experience reports

A.2.3.1 Actuarial analysis

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

Figure A.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 A.1.

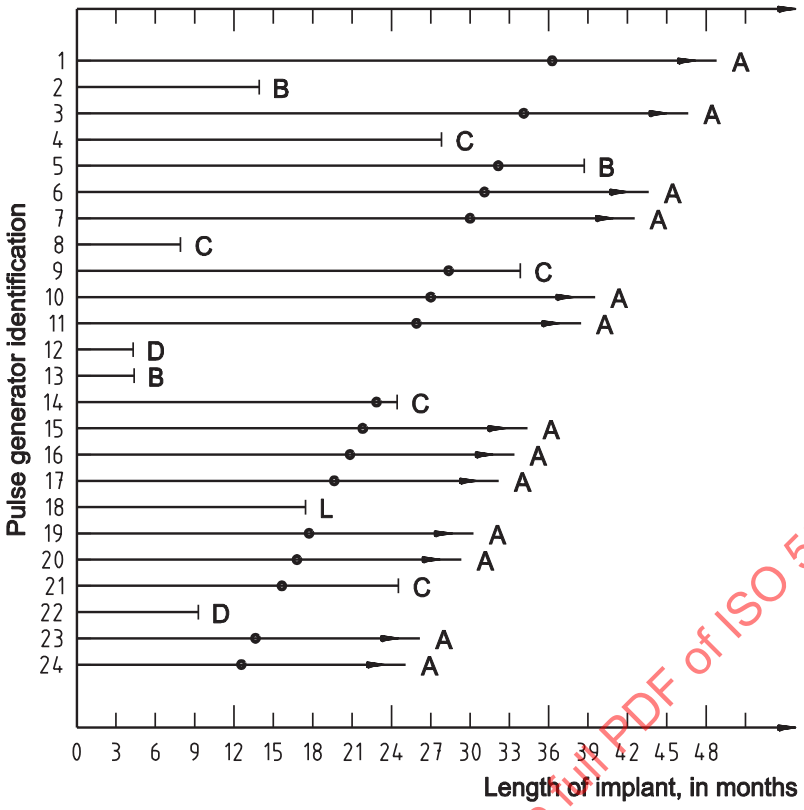


Figure A.2 — Length of implant, in months, for the devices in the sample data set as in Figure A.1

The focus of this discussion is the actuarial data presented in Table A.1. The sample data set shown in Figures A.2 and A.3 is given numerically in Table A.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 $N(t)$. In the example above, the selection of a time interval of three months was arbitrary. Manufacturers shall calculate survival probability estimates using one-month intervals.

— Number entering $N(t)$: The number of category A devices entering the given time interval (t).

— Survivors $A(t)$: The number of category A devices whose implant duration, calculated at the end of the clinical reporting period, falls within the given time interval (t).

— Withdrawn for non-product related reasons $E(t)$: Number of category D, L, and B devices with an associated time to categorization within the given time interval (t), such that:

If the survival calculations are being performed for leads or pulse generators where non-survival includes normal battery depletion

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

If the survival calculations are being performed for pulse generators where non-survival excludes normal battery depletion

$$E(t) = D(t) + B(t) + L(t) + C2(t) \tag{A.2}$$

— Non-survivors $C(t)$: Number of category C1 or C2 devices with an associated time to categorization within the given time interval (t).

If the survival calculations are being performed for pulse generators where non-survival includes normal battery depletion

$$C(t) = C1(t) + C2(t) \tag{A.3}$$

If the survival calculations are being performed for leads or pulse generators where non-survival excludes normal battery depletion

$$C(t) = C1(t) \tag{A.4}$$

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

$$U(t) = N(t) - \frac{A(t) + E(t)}{2} \tag{A.5}$$

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

$$P(t) = 1 - \frac{C(t)}{U(t)} \tag{A.6}$$

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

$$S(t) = P(t) \times P(t-1) \times \ldots P(1) \tag{A.7}$$

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

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

Implant interval	(t) Length of time months	(N) Number entering	(A) Incomplete lifetimes	(D) Patient 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	$0 < t \leq 3$	24	0	0	0	0	24,0	1,000 0	1, 0
2	$3 < t \leq 6$	24	0	1	1	0	23,0	1,000 0	1,000 0
3	$6 < t \leq 9$	22	0	0	0	1	22,0	0,954 5	0,954 5
4	$9 < t \leq 12$	21	0	1	1	0	20,5	1,000 0	0,954 5
5	$12 < t \leq 15$	20	0	0	1	0	19,5	1,000 0	0,954 5
6	$15 < t \leq 18$	19	0	0	1	0	18,5	1,000 0	0,954 5
7	$18 < t \leq 21$	18	0	0	0	0	18,0	1,000 0	0,954 5
8	$21 < t \leq 24$	18	0	0	0	0	18,0	1,000 0	0,954 5
9	$24 < t \leq 27$	18	2	0	0	2	17,0	0,882 4	0,842 3
10	$27 < t \leq 30$	14	2	0	0	1	13,0	0,923 1	0,777 5
11	$30 < t \leq 33$	11	2	0	0	0	10,0	1,000 0	0,777 5
12	$33 < t \leq 36$	9	1	0	0	1	8,5	0,882 4	0,686 1

Table A.1 *(continued)*

Implant interval	(*t*) Length of time months	(*N*) Number entering	(*A*) Incomplete lifetimes	(*D*) Patient death	(*E*) Withdrawn or lost to follow-up	(*C*) Withdrawn out of specification	(*U*) Units at risk	(*P*) Survival fraction	(*S*) Cumulative survival probability
13	$36 < t \leq 39$	7	2	0	1	0	5,5	1,000 0	0,686 1
14	$39 < t \leq 42$	4	1	0	0	0	3,5	1,000 0	0,686 1
15	$42 < t \leq 45$	3	1	0	0	0	2,5	1,000 0	0,686 1
16	$45 < t \leq 48$	2	2	0	0	0	1,0	1,000 0	0,686 1
		Total	13	2	4	5	224,5		

NOTE In this example, category C includes both subcategories C_1 and C_2, and category E includes categories B, D, and L.

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

A.2.3.2 Confidence limit

Those parties reporting cumulative survival statistics shall provide for each monthly interval the cumulative survival probability (*S*), the effective sample size data for each interval (*U*), and 95 % standard error (as calculated by Greenwood's method). 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.

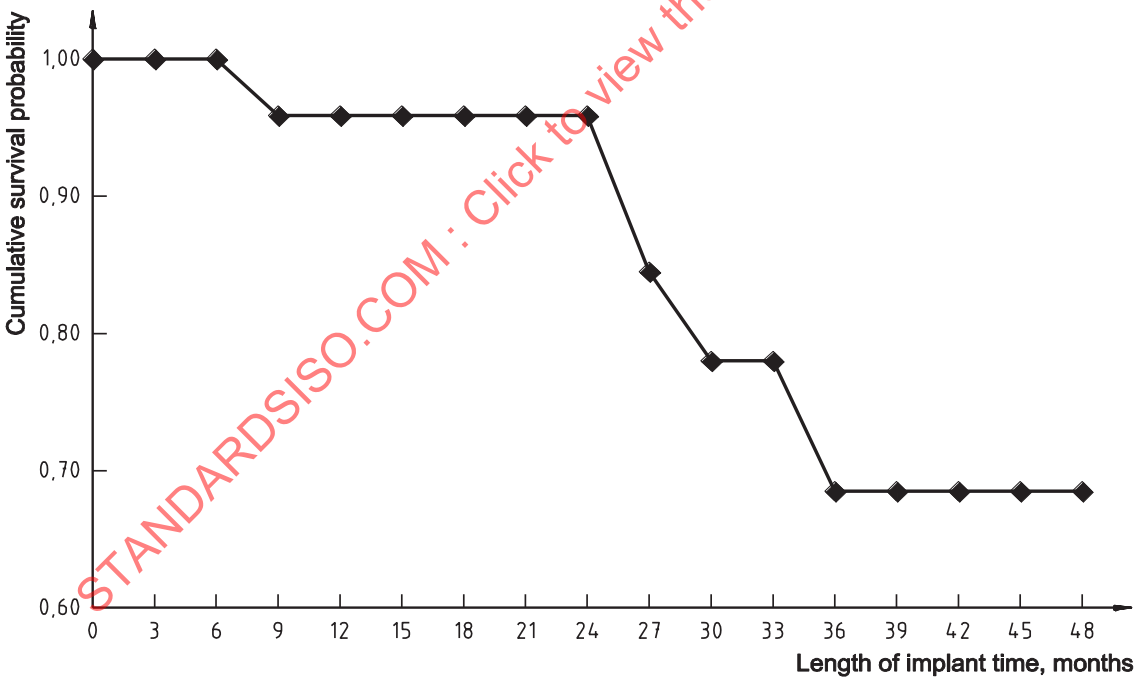


Figure A.3 — Plot of cumulative survival probability against length of implant time, in months
[Values taken from column (*S*) in Table A.1]

A.3 Discussion of application of results obtained

A.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.

A.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 can return to follow-up after an extended absence. The population sample can 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 can 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 can 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.

A.3.3 Adjustment for under-reported events

Under-reporting of events is a persistent problem, particularly when clinical performance data are 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 Formula (A.6) should be considered. Assume that through some method, such as a random audit, the following reporting rates, bounded between 0 and 1 (i.e. $0 < \Pi \leq 1$), 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;

— Π_E is the fraction of devices withdrawn in specification or lost to follow-up that are reported.

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

$$\hat{C}(t) = \frac{C(t)}{\Pi_C} \tag{A.8}$$

$$\hat{D}(t) = \frac{D(t)}{\Pi_D} \tag{A.9}$$

$$\hat{E}(t) = \frac{E(t)}{\Pi_E} \tag{A.10}$$

The above formulae 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 Formulae (A.8), (A.9), and (A.10) 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:

$$\Delta(t) = \left[\hat{C}(t) + \hat{E}(t)\right] - \left[C(t) + E(t)\right] \tag{A.11}$$

Corrections are also required for $A(t)$ and $N(t)$ to reflect the corrections made in Formulae (A.8), (A.9), and (A.10).

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

— $n(t)$ is the number of devices implanted during the tth 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 exist:

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

$$N'(t) = N'(1) - \sum_{i=1}^{t-1} n(i) \tag{A.13}$$

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:

$$\hat{A}(t) = A(t) - \Delta A(t) \tag{A.14}$$

where

$$\Delta A(t) = \left[\left(\sum_{i=1}^{t-1} \frac{\Delta(i)}{N'(i) - \frac{n(i)}{2}} \right) + \frac{\Delta(t)}{2N'(t) - n(t)} \right] \tag{A.15}$$

$\Delta A(t)$ accounts for the correction needed for the cohort group $n(t)$ and the above derivation ensures that:

$$\sum_{i=1}^{T} \Delta(i) = \sum_{i=1}^{T} \Delta A(t) \tag{A.16}$$

where T represents the maximum time interval in the life table.

Formula (A.14) allows $N(t-1)$ to be correctly adjusted as:

$$N'(t+1) = N'(t) - \left[C'(t) + E'(t) + A'(t) \right] \tag{A.17}$$

Also, the units at risk $U(t)$ from Formula (A.5) can be correctly adjusted as:

$$U'(t) = N'(t) - \frac{A'(t) + E'(t)}{2} \tag{A.18}$$

The survival fraction (P) and the cumulative survival (S) can be calculated using Formulae (A.6) and (A.7).