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Medical electrical equipment —

Part 2-85: Particular requirements for the basic safety and essential performance of cerebral tissue oximeter equipment

Appareils électromédicaux —

Partie 2-85: Exigences particulières pour la sécurité de base et les performances essentielles des oxymètres pour tissu cérébral

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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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 of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared jointly by Technical Committee ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 3, *Respiratory devices and related equipment used for patient care,* and Technical Committee IEC/TC 62, *Electrical equipment in medical practice*, Subcommittee 62D, *Electromedical equipment*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 215, *Respiratory and anaesthetic equipment*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

A list of all parts in the ISO and IEC 80601 series can be found on the ISO and IEC websites.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The estimation of blood oxygen saturation in the brain tissue by *cerebral tissue oximetry equipment* is increasingly used in many areas of medicine. This document covers *basic safety* and *essential performance* requirements achievable within the limits of existing technology.

Annex AA contains a rationale for some of the requirements. It is included to provide additional insight into the reasoning of the committees that led to a requirement and into the *hazards* that the requirement addresses.

Annex BB is a literature review and provides recommendations relevant to determining the maximum safe temperature of the interface between a *cerebral tissue oximeter probe* and a *patient's* tissue.

Annex CC discusses both the formulae used to evaluate the *StO_2 accuracy* of *cerebral tissue oximeter equipment* measurements, and the names that are assigned to those formulae.

Annex DD presents guidance on using in-vitro methods (phantoms) for *verification* of *StO_2 accuracy* of *cerebral tissue oximeter equipment*.

Annex EE presents a guideline for an in-vivo (human subjects) *controlled desaturation study* for the *verification* of *StO_2 accuracy* of *cerebral tissue oximeter equipment*.

Annex FF is a description of *functional testers* for use with *cerebral tissue oximeter equipment*.

Annex GG describes concepts of *cerebral tissue oximeter equipment* response time.

Annex HH describes data interface requirements.

Annex II is a comparison between human desaturations (in-vivo) and *tissue haemoglobin phantom* desaturations (in-vitro) for assessing *StO_2 accuracy*.

In this document, the following print types are used:

— requirements and definitions: roman type;

— *Instructions, test specifications and terms defined in Clause 3 of the general standard, in this document or as noted: italic type*;

— informative material appearing outside of tables, such as notes, examples and references: in smaller type; normative text of tables is also in a smaller type.

In referring to the structure of this document, the term

— "clause" means one of the numbered divisions within the table of contents, inclusive of all subdivisions (e.g. Clause 201.7 includes subclauses 201.7.1, 201.7.2) and

— "subclause" means a numbered subdivision of a clause (e.g. 201.7.1, 7.2 and 201.7.2.1 are all subclauses of Clause 201.7).

References to clauses within this document are preceded by the term "Clause" followed by the clause number. References to subclauses within this document are by number only.

In this document, the conjunctive “or” is used as an “inclusive or” so a statement is true if any combination of the conditions is true.

For the purposes of this document, the auxiliary verb:

— “shall” means that conformance with a requirement or a test is mandatory for conformance with this document;

— “should” means that conformance with a requirement or a test is recommended but is not mandatory for conformance with this document; and

— “may” is used to describe permission (e.g. a permissible way to achieve conformance with a requirement or test);

— "can" is used to describe a possibility or capability; and

— "must" is used to express an external constraint.

Annex C contains a guide to the marking and labelling requirements in this document.

Annex D contains a summary of the symbols referenced in this document.

An asterisk (*) as the first character of a title or at the beginning of a paragraph or table title indicates that there is guidance or rationale related to that item in AA.

Medical electrical equipment —

Part 2-85:
Particular requirements for the basic safety and essential performance of cerebral tissue oximeter equipment

201.1 Scope, object and related standards

Clause 1 of the general standard applies, except as follows.

NOTE The general standard is IEC 60601-1:2005+AMD1:2012+AMD2:2020.

201.1.1 * Scope

Replacement:

This document applies to *basic safety* and *essential performance* of *cerebral tissue oximeter equipment*, that employs light at multiple wavelengths to derive a quantitative measure of oxygen saturation of haemoglobin within the volume of tissue sampled under the *probe* attached to the head. The *cerebral tissue oximeter equipment* can be based on continuous light, frequency domain or time domain technologies. This document applies to *ME equipment* used in a hospital environment as well as when used outside the hospital environment, such as in ambulances and air transport. Additional standards may apply to *ME equipment* for those environments of use.

NOTE 1 *Cerebral tissue oximeters* are sometimes referred to as near infrared spectroscopy equipment in medical literature.

Not included within the scope of this document are:

— invasive tissue or vascular oximeters;

— oximeters that require a blood sample from the *patient*;

— equipment measuring dissolved oxygen;

— *ME equipment*, or part thereof, that measures path-length-dependent haemoglobin change. The requirements for functional near-infrared spectroscopy equipment are found in ISO 80601-2-71[4];

— *ME equipment*, or part thereof, that measures arterial saturation based on pulsatile changes in tissue optical properties (SpO_2). The requirements for pulse oximeter equipment are found in ISO 80601-2-61[3];

— *ME equipment*, or any part thereof, that claims to monitor tissue in parts of the body other than the head.

This document also applies to *cerebral tissue oximeter equipment*, including *cerebral tissue oximeter monitors*, *cerebral tissue oximeter probes* and *probe cable extenders*, that have been *remanufactured*.

If a clause or subclause is specifically intended to be applicable to *ME equipment* only, or to *ME systems* only, the title and content of that clause or subclause will say so. If that is not the case, the clause or subclause applies both to *ME equipment* and to *ME systems*, as relevant.

Hazards inherent in the intended physiological function of *ME equipment* or *ME systems* within the scope of this document are not covered by specific requirements in this document except in 201.11 and in 201.7.2.13 and 201.8.4.1 of the general standard.

NOTE 2 See also 4.2 of the general standard.

This document can also be applied to *ME equipment* and their *accessories* used for compensation or alleviation of disease, injury or disability.

This document is not applicable to remote or slave (secondary) equipment that displays StO_2 values that are located outside of the *patient environment*.

NOTE 3 *ME equipment* that provides selection between diagnostic and monitoring functions is expected to meet the requirements of the appropriate document when configured for that function.

201.1.2 Object

Replacement:

The object of this document is to establish particular *basic safety* and *essential performance* requirements for *cerebral tissue oximeter equipment* [as defined in 201.3.202] and its *accessories*.

NOTE 1 *Accessories* are included because the combination of the *cerebral tissue oximeter monitor* and the *accessories* needs to be adequately safe. *Accessories* can have a significant impact on the *basic safety* or *essential performance* of *cerebral tissue oximeter equipment.*

NOTE 2 This document has been prepared to address the relevant International Medical Device Regulators Forum (IMDRF) *essential principles* and labelling guidances as indicated in Annex JJ.

NOTE 3 This document has been prepared to address the relevant *essential principles of safety and performance* of ISO 16142-1:2016 as indicated in Annex KK.

NOTE 4 This document has been prepared to address the relevant general safety and performance requirements of European regulation (EU) 2017/745[20] as indicated in Annex LL.

201.1.3 Collateral standards

Addition:

This document refers to those applicable collateral standards that are listed in Clause 2 of the general standard and Clause 201.2 of this document.

IEC 60601-1-2:2014+AMD1:2020, IEC 60601-1-6:2010+AMD1:2013+AMD2:2020, IEC 60601-1-8:2006+AMD1:2012+AMD2:2020, IEC 60601-1-11:2015+AMD1:2020 and IEC 60601-1-12:2014+AMD1:2020 apply as modified in Clauses 202, 206, 208, 211 and 212 respectively. IEC 60601-1-3 does not apply. All other published collateral standards in the IEC 60601-1 series apply as published.

201.1.4 Particular standards

Replacement:

In the IEC 60601 series, particular standards define *basic safety* and *essential performance* requirements, and may modify, replace or delete requirements contained in the general standard, including the collateral standards, as appropriate for the particular *ME equipment* under consideration.

A requirement of a particular standard takes priority over the general standard or the collateral standards.

For brevity, IEC 60601-1:2005+AMD1:2012+AMD2:2020 is referred to in this document as the general standard. Collateral standards are referred to by their document number.

The numbering of clauses and subclauses of this document corresponds to those of the general standard with the prefix "201" (e.g. 201.1 in this document addresses the content of Clause 1 of the general standard) or applicable collateral standard with the prefix "2xx" where xx is the final digits of the collateral standard document number (e.g. 202.4 in this document addresses the content of Clause 4 of the IEC 60601-1-2 collateral standard, 208.4 in this document addresses the content of Clause 4 of the IEC 60601-1-8 collateral standard, etc.). The changes to the text of the general standard are specified by the use of the following words:

"Replacement" means that the clause or subclause of the general standard or applicable collateral standard is replaced completely by the text of this document.

"Addition" means that the text of this document is additional to the requirements of the general standard or applicable collateral standard.

"Amendment" means that the clause or subclause of the general standard or applicable collateral standard is amended as indicated by the text of this document.

Clauses, subclauses or figures that are additional to those of the general standard are numbered starting from 201.101. However, due to the fact that definitions in the general standard are numbered 3.1 through 3.147, additional definitions in this document are numbered beginning from 201.3.201. Additional annexes are lettered AA, BB, etc., and additional items aa), bb), etc.

Subclauses or figures that are additional to those of a collateral standard are numbered starting from 2xx, where "x" is the number of the collateral standard, e.g. 202 for IEC 60601-1-2, 203 for IEC 60601-1-3, etc.

The term "this document" is used to make reference to the general standard, any applicable collateral standards and this particular document taken together.

Where there is no corresponding clause or subclause in this particular document, the section, clause or subclause of the general standard or applicable collateral standard, although possibly not relevant, applies without modification; where it is intended that any part of the general standard or applicable collateral standard, although possibly relevant, is not to be applied, a statement to that effect is given in this particular document.

201.2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

Clause 2 of the general standard applies, except as follows:

Replacement:

ISO 15223-1:—[1], *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

Addition:

ISO 14155:2020, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 16142-1:2016, *Medical devices — Recognized essential principles of safety and performance of medical devices — Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards*

ISO 17664:2017, *Processing of health care products — Information to be provided by the medical device manufacturer for the processing of medical devices*

ISO 20417:2020, *Medical devices — Information to be supplied by the manufacturer*

IEC 60068-2-31:2008, *Environmental testing — Part 2-31: Tests — Test Ec: Rough handling shocks, primarily for equipment-type specimens*

IEC 60068-2-64:2008+AMD1:2019, *Environmental testing — Part 2-64: Tests — Test Fh: Vibration, broadband random and guidance*

IEC 60601-1:2005+AMD1:2012+AMD2:2020, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

IEC 60601-1-11:2015+AMD1:2020, *Medical electrical equipment — Part 1-11: General requirements for basic safety and essential performance — Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment*

IEC 60601-1-12:2014+AMD1:2020, *Medical electrical equipment — Part 1-12: General requirements for basic safety and essential performance — Collateral Standard: Requirements for medical electrical equipment and medical electrical systems intended for use in the emergency medical services environment*

ISO 80601-2-61:2017, *Medical electrical equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment*

IEC 62471:2006, *Photobiological safety of lamps and lamp systems*

[1] Under preparation. Stage at the time of publication: ISO/DIS 15223-1:2020.

AAMI 2700-1:2019[2], *Medical devices and medical systems — Essential safety requirements for equipment comprising the patient-centric integrated clinical environment (ICE) — Part 1: General requirements and conceptual model*

201.3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 16142-1:2016, ISO 17664:2017, ISO 20417:2020, IEC 60601-1:2005+AMD1:2012+AMD2:2020, IEC 60601-1-2:2014+AMD1:2020, IEC 60601-1-6:2010+AMD1:2013+AMD2:2020, IEC 60601-1-8:2006+AMD1:2012+AMD2:2020, IEC 60601-1-11:2015+AMD1:2020, IEC 60601-1-12:2014+AMD2:2020, ISO 80601-2-61:2017, AAMI 2700-1:2019 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

NOTE An alphabetized index of defined terms is found in Annex MM.

201.3.201
accuracy
A_{rms}
closeness of agreement between a test result and the true value

Note 1 to entry: 201.12.1.101.2 contains methods for estimating the *StO_2 accuracy* of *cerebral tissue oximeter equipment*.

Note 2 to entry: Additional information is found in Annexes CC, DD, EE and II.

Note 3 to entry: In this document, *accuracy* (A_{rms}) is stated in terms of the root mean square difference. See 201.12.1.101.3.

[SOURCE: ISO 3534-2:2006[6] 3.3.1, modified — Notes to entry replaced.]

201.3.202
cerebral tissue oximeter
cerebral tissue oximeter equipment
ME equipment for the non-invasive estimation of *functional oxygen saturation* of haemoglobin in cerebral tissue below the *probe* (*StO_2* or *rSO_2*), based on light interacting with tissue

Note 1 to entry: *Cerebral tissue oximeter equipment* comprises a *cerebral tissue oximeter monitor*, a *probe cable extender*, if provided, and a *cerebral tissue oximeter probe*, which can be combined in a single assembly.

Note 2 to entry: Light is more technically referred to as electromagnetic radiation (optical radiation). This document uses the common term.

Note 3 to entry: Measurements are based upon light interacting with all tissue under the *probe* to determine *StO_2*.

201.3.203
cerebral tissue oximeter monitor
monitor
part of the *cerebral tissue oximeter equipment* that encompasses the measurement electronics, display and *operator interface*, excluding the *cerebral tissue oximeter probe* and *probe cable extender*

[2] Formerly ASTM F2761-09.

Note 1 to entry: A *cerebral tissue oximeter monitor* can consist of multiple pieces of hardware in separate locations, e.g. a telemetry system in which the *applied part* and primary display are physically separated.

201.3.204
cerebral tissue oximeter probe
probe
part of the *cerebral tissue oximeter equipment* that includes the *applied part*

Note 1 to entry: The terms sensor and transducer have also been used for *cerebral tissue oximeter probe*.

Note 2 to entry: A reflectance *probe* design is the typical configuration.

201.3.205
controlled desaturation study
hypoxaemia induced in a group of human subjects performed under laboratory conditions

Note 1 to entry: This can also be referred to as a controlled hypoxaemia study. Additional information is found in Annex EE.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.202]

201.3.206
CO-oximeter
multiwavelength, optical analyser that measures *total haemoglobin concentration* and the concentrations of various haemoglobin derivatives via direct measurement of a blood specimen

Note 1 to entry: The relevant CO-oximetry values for this document are *functional oxygen saturation* of arterial and jugular venous blood, SaO_2 and $SjvO_2$.

Note 2 to entry: This excludes indirect measurements that are performed by pulse oximetry and other optical measurements methods on human tissue.

[SOURCE: CLSI C46-A2: 2009, 4.1.9[7]]

201.3.207
data update period
interval in which the *cerebral tissue oximeter equipment* algorithm provides new valid data to the display or the *functional connection*

Note 1 to entry: This definition does not refer to the regular refresh period of the display, which is typically on the order of 1 s, but rather to the (typically longer) interval defined above.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.204, modified.]

201.3.208
declared range
range of the *reference haemoglobin oxygen saturation* (S_R) over which there is specified *accuracy* performance

[SOURCE: ISO 80601-2-61:2017[3], 201.3.202]

201.3.209
displayed range
range of StO_2 values that can be displayed by the *cerebral tissue oximeter equipment*

Note 1 to entry: The *displayed range* can extend beyond the *declared range*.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.206, modified.]

201.3.210
functional oxygen saturation
saturation given by the oxyhaemoglobin concentration (cO_2Hb) divided by the sum of the oxyhaemoglobin concentration and the deoxyhaemoglobin concentration (cHHb)

$$\frac{cO_2Hb}{cO_2Hb + cHHb}$$

Note 1 to entry: The CLSI[7] term for this ratio is haemoglobin oxygen saturation, and its notation is SO_2.

[SOURCE: CLSI C46-A2: 2009, 4.1.10.2[7]]

201.3.211
functional tester
test equipment that presents the *cerebral tissue oximeter equipment* with a tissue analogue representing a predictable value of tissue haemoglobin saturation so that the *operator* can observe the resulting displayed value of StO_2 and compare it to the expected value.

Note 1 to entry: Additional information is found in Annex FF.

Note 2 to entry: Not all *functional testers* and *cerebral tissue oximeter equipment* are compatible.

201.3.212
local bias
b
difference between the expectation of the results (StO_2) and a reference value

Note 1 to entry: For human desaturation studies, the reference is $SavO_2$.

Note 2 to entry: For phantom desaturation studies, the reference values are obtained from a reference measurement.

Note 3 to entry: For *cerebral tissue oximeter equipment*, this is, at a given value of the reference oxygen saturation, the difference between the y-value of the regression line at that coordinate and the y-value of the line of identity, in a plot of StO_2 versus S_R, or given by:

$$b_i = StO_{2\,fit,i} - S_{R,i}$$

where $StO_{2fit,i}$ is the value of the curve fitted to the test data at the i^{th} reference oxygen saturation value, $S_{R,i}$.

Note 4 to entry: Additional information is found with the term *mean bias* and in the discussion in Annex CC.

[SOURCE: ISO 80601-2-61: 2017[3], 201.3.211, modified.]

201.3.213
mean bias
B
mean difference between the test and reference values, preserving sign

$$B = \frac{\sum_{i=1}^{n} (StO_{2i} - S_{Ri})}{n}$$

where

n is the number of data pairs in the sample;

StO_{2i} is the i^{th} StO_2 datum; and

S_{Ri} is the i^{th} reference oxygen saturation value.

Note 1 to entry: Additional information also is found with the term *local bias* and in the discussion in Annex CC.

Note 2 to entry: When defined in this way, *mean bias* is the average of all *local bias* values, b_i.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.211]

201.3.214
operator settings
current state of any *cerebral tissue oximeter monitor* controls, including *alarm settings*

[SOURCE: ISO 80601-2-61:2017[3], 201.3.213, modified.]

201.3.215
precision
closeness of agreement between independent test results obtained under stipulated conditions

$$s_{res} = \sqrt{\frac{\sum_{i=1}^{n}(StO_{2i} - StO_{2\,fit,\,i})^2}{n-2}}$$

where

n is the number of data pairs in the sample within the range of interest;

$(StO_{2i} - StO_{2\text{fit},\,i})$ is the difference between the i^{th} StO_2 datum and the value of the fitted curve corresponding to the i^{th} reference oxygen saturation value, S_{Ri}.

Note 1 to entry: Additional information is found in Annex CC.

Note 2 to entry: s_{res} is the sample standard deviation of the residuals.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.214, modified.]

201.3.216
probe cable extender
cable that connects a *cerebral tissue oximeter monitor* to a *cerebral tissue oximeter probe*

Note 1 to entry: Not every *cerebral tissue oximeter equipment* utilizes a *probe cable extender*.

Note 2 to entry: A *probe cable extender* can be an *applied part*.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.215, modified.]

201.3.217
probe fault
abnormal condition of the *cerebral tissue oximeter probe* or *probe cable extender* which, if not detected, could cause *patient harm*

Note 1 to entry: *Patient harm* can be caused by providing incorrect values, by exposing the *patient* to high *cerebral tissue oximeter probe* temperatures or by introducing a *risk* of electric shock.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.216, modified.]

201.3.218
*** remanufacturing**
DEPRECATED: reprocessing
any activity, which is not specified in the *accompanying document*, that renders a product suitable for use or reuse

Note 1 to entry: Such activities are often referred to as refinishing, restoring, recycling, refurbishing or repairing.

Note 2 to entry: Such activities can occur in healthcare facilities.

Note 3 to entry: The term "*remanufactured*" is used to designate the corresponding status.

[SOURCE: ISO 80601-2-61:2017[3], 201.3.221, modified — Replaced 'reprocessed' with '*remanufactured*'.]

201.3.219
SaO_2
fraction of functional haemoglobin in arterial blood that is saturated with oxygen

Note 1 to entry: *SaO_2* is *functional oxygen saturation* in arterial blood. Additional information is found in 201.3.211.

Note 2 to entry: *SaO_2* is normally expressed as a percentage (by multiplying the fraction by 100 %).

[SOURCE: CLSI C46-A2: 2009, 4.1.10.2[7]]

201.3.220
$SavO_2$
composite of the oxygenation state of the arterial and jugular venous blood to derive a reference for *StO_2*, as described by

$$SavO_2 = R \times SaO_2 + (1 - R) \times SjvO_2$$

where *R* is the fraction of arterial blood and (1-*R*) is the fraction of jugular venous blood

Note 1 to entry: 201.12.1.101.2 contains requirements for collection of data from *controlled desaturation studies*.

Note 2 to entry: *Sav*O_2 is normally reported as a percentage (multiplying the fraction by 100 %). *R* is the relative weighting of the sampled arterial blood and jugular venous blood oxygenation, and is based on the assumed arterial:venous blood volumes in the cerebral tissue beneath the *probe*.

201.3.221
$SjvO_2$
fraction of functional haemoglobin in jugular venous blood that is saturated with oxygen

Note 1 to entry: 201.12.1.101.2 contains requirements for collection of data from *controlled desaturation studies*.

Note 2 to entry: *$SjvO_2$* is normally expressed as a percentage (multiplying the fraction by 100 %).

201.3.222
SpO_2
estimate of *SaO_2* made by *pulse oximeter equipment*

Note 1 to entry: Two-wavelength *pulse oximeter equipment* cannot compensate for the interference caused by the presence of dyshaemoglobins in their estimation of *Sa*O_2.

Note 2 to entry: *SpO_2* is normally reported as a percentage (multiplying the fraction by 100 %).

[SOURCE: ISO 80601-2-61:2017[3], 201.3.223]

201.3.223
$SphanO_2$
functional haemoglobin oxygen saturation in the *tissue haemoglobin phantom* liquid

Note 1 to entry: Additional information is found in Annex DD.

Note 2 to entry: *Sphan*O_2 is normally expressed as a percentage (by multiplying the fraction by 100 %).

201.3.224
S_R
reference haemoglobin oxygen saturation

Note 1 to entry: For *verification* based on a *controlled desaturation study*, S_R is replaced with $SavO_2$; for *verification* based on phantoms, with $SphanO_2$.

Note 2 to entry: S_R is normally expressed as a percentage (by multiplying the fraction by 100 %).

201.3.225
StO_2
rSO_2
cerebral tissue oxygenation
estimate of *functional oxygen saturation* of haemoglobin in cerebral tissue below the *probe* made by *cerebral tissue oximeter equipment*

Note 1 to entry: StO_2 is often expressed in the medical literature as rSO_2 (regional oxygen saturation) and both notations are considered interchangeable in this document.

Note 2 to entry: StO_2 is normally expressed as a percentage (multiplying the fraction by 100 %).

201.3.226
tissue haemoglobin phantom
artificial physical model that exhibits optical properties approximating in-vivo biological conditions which includes turbid media and haemoglobin, blood or other haemoglobin-simulating material

Note 1 to entry: Additional information is found in Annex DD.

201.3.227
total haemoglobin concentration
ctHb
sum of concentrations of all haemoglobin species in a medium including, but not limited to, oxyhaemoglobin (cO_2Hb), methaemoglobin (cMetHb), deoxyhaemoglobin (cHHb), sulfhaemoglobin (cSHb) and carboxyhaemoglobin (cCOHb)[7]

Note 1 to entry: CLSI denotes "concentration" by a prefixed letter c, while in the past the convention of square brackets, e.g. [O_2Hb], was used.

Note 2 to entry: CLSI (Clinical and Laboratory Standards Institute)[7] uses the following notations:
- oxyhaemoglobin (O_2Hb);
- deoxyhaemoglobin (HHb);
- carboxyhaemoglobin (COHb);
- methaemoglobin (MetHb);
- sulfhaemoglobin (SuHb); and
- total haemoglobin (tHb).

Note 3 to entry: When total haemoglobin concentration is used in the context of tissue or a tissue haemoglobin phantom, it refers to the concentration per tissue volume (spatial average) or per volume of turbid liquid, respectively, usually given in micromoles per litre (µM/l). In the context of CO-oximetry of whole blood, it refers to the concentration per volume of blood, usually given in g/dl.

[SOURCE: CLSI C46-A2: 2009, 4.1.9[7]]

201.4 General requirements

Clause 4 of the general standard applies, except as follows:

Addition:

201.4.3.101 * Additional requirements for *essential performance*

Additional *essential performance* requirements are found in the subclauses listed in Table 201.101.

Table 201.101 — Distributed *essential performance* requirements

Requirement	Subclause
For *cerebral tissue oximeter equipment* provided with an *alarm system* that includes the capability to detect a *physiological alarm condition*:	
[StO_2 *accuracy* and limit *alarm conditions*][a]	201.12.1.101 208.6.1.2.101
or generation of a *technical alarm condition*[a]	201.11.8.101.1 201.12.4 201.13.101
For *cerebral tissue oximeter equipment* not provided with an *alarm system* that includes the capability to detect a *physiological alarm condition*:	
StO_2 *accuracy*[a]	201.12.1.101
or indication of abnormal operation[a]	201.12.4 201.13.101
[a] Subclause 202.8.2 indicates methods of evaluating the performance of *cerebral tissue oximeters* as acceptance criteria following specific tests required by this document.	

201.4.102 Additional requirements for acceptance criteria

Many of the clauses and subclauses within this document establish acceptance criteria for performance aspects. These acceptance criteria shall always be met.

When the *manufacturer* specifies in the *accompanying document* performance levels better than those specified within this document, these *manufacturer*-specified levels become the acceptance levels.

For a *manufacturer*-specified (declared) level of StO_2 *accuracy* of 10 %, the *cerebral tissue oximeter equipment* is still required to exhibit less than 4 % StO_2 deviation during *immunity* tests (see 202.8.1.101 d)). If the *cerebral tissue oximeter equipment* has a *manufacturer*-specified (declared) *accuracy* of 3 % then it shall have less than ±3 % StO_2 deviation for all requirements (e.g. during *immunity* tests).

201.4.103 Additional requirements for *cerebral tissue oximeter equipment*, parts and *accessories*

a) The *cerebral tissue oximeter equipment*, as well as all individual parts and *accessories* specified for use with a *cerebral tissue oximeter monitor*, shall conform with all requirements specified in this document. This includes all combinations of parts or *accessories* that are specified by a *manufacturer* for use in *cerebral tissue oximeter equipment.*

NOTE 1 This requirement ensures *basic safety* and *essential performance* of parts and *accessories* of the *cerebral tissue oximeter equipment*, in combination with their intended *cerebral tissue oximeter monitors*.

NOTE 2 *Cerebral tissue oximeter monitors* are sometimes used with *cerebral tissue oximeter probes* and cables from different *manufacturers*. This requirement ensures the compatibility of such combinations.

b) All specified combinations of *cerebral tissue oximeter equipment*, as well as all individual parts and *accessories* specified for use with a *cerebral tissue oximeter monitor*, shall be disclosed in the instructions for use.

NOTE 3 Additional information is found in 201.7.9.2.1.101 g) and 201.7.9.2.14.101 a) and b).

201.5 General requirements for testing of *ME equipment*

Clause 5 of the general standard applies.

201.6 Classification of *ME equipment* and *ME systems*

Clause 6 of the general standard applies.

201.7 *ME equipment* identification, marking and documents

201.7.1.101 *Information to be supplied by the manufacturer*

The *information supplied by the manufacturer* of *cerebral tissue oximeter equipment* and its accessories shall conform with ISO 20417:2020.

In applying ISO 20417:2020, the terms in this document and those in IEC 60601-1:2005+AMD1:2012+A2:2020 shall be used as follows.

a) The term "*accompanying information*" shall assume the same meaning as *accompanying documents*.

b) The term "*medical device*" shall assume the same meaning as *ME equipment*.

c) The term "*user*" shall assume the same meaning as *operator*.

d) The term "*patient*" shall include animals.

Check conformance by application of ISO 20417:2020.

Clause 7 of the general standard applies, except as follows:

201.7.2.3 Consult *accompanying documents*

Replacement:

The *cerebral tissue oximeter equipment* shall be *marked* with the *safety sign* for the mandatory action: 'follow instructions for use', ISO 7010-M002 (see IEC 60601-1:2005 and IEC 60601-1:2005/AMD1:2012/COR1:2014, Table D.2, Number 10).

Addition:

201.7.2.9.101 IP classification

a) Notwithstanding the requirements of IEC 60601-1:2005+AMD1:2012+AMD 2:2020, 7.2.9, the *enclosure* of *ME equipment* shall be marked with the IP classification required by 201.11.6.5.101.

b) If some or all of the protection against the ingress of water or particulate matter is provided by a carrying case, then

1) the degree of protection provided by the *enclosure* shall be marked on the *enclosure*; and

2) the degree of protection provided by the carrying case shall be marked on the carrying case.

EXAMPLE If for *portable ME equipment*, the *enclosure* provides the protection against the ingress of particulate matter and the carrying case provides the protection against the ingress of water, the *enclosure* of the *ME equipment* would be marked IP2X and the carrying case would be marked IPX2.

c) An *enclosure* or a carrying case that is classified IPX0 need not be marked as such.

d) If an *enclosure* does not provide the minimum required degree of protection against the ingress of water, it shall be marked 'keep dry' or with Symbol ISO 7000-0626 (see Table 201.D.1.101, Symbol 2).

Check conformance by inspection and by application of the tests and criteria of IEC 60601-1:2005+AMD1:2012, 7.1.2 and 7.1.3.

201.7.2.101 Additional requirements for marking on the outside of *ME equipment* parts

a) If a *cerebral tissue oximeter monitor* is not provided with a low *StO_2 alarm condition*, a statement to the effect "No StO_2 Alarms" or Symbol IEC 60417-5319 (DB-2002-10) (see Table 201.D.1.101, Symbol 3).

b) For a *remanufactured cerebral tissue oximeter probe*, *marked* as such.

Check conformance by inspection.

201.7.4.3 Units of measurement

IEC 60601-1:2005+AMD1:2012, 7.4.3 applies, except as follows:

Amendment (add to the bottom as a new row in Table 1):

Cerebral tissue oxygenation shall be expressed in percent and shall be marked as %.

201.7.9.2 Instructions for use

IEC 60601-1:2005+AMD1:2012+AMD2:2020, 7.9.2 applies, except as follows:

Addition:

201.7.9.2.1.101 Additional general requirements

The instructions for use shall indicate the following:

a) for each *cerebral tissue oximeter equipment* and *cerebral tissue oximeter probe*, the specified use of the *cerebral tissue oximeter equipment* and *cerebral tissue oximeter probe* regarding:

1) whether *cerebral tissue oximeter probe* replacement or repositioning requires re-establishment of baseline;

b) that the *cerebral tissue oximeter equipment* displays StO_2 or rSO_2;

c) the range of the peak wavelengths of the light emitted by the *cerebral tissue oximeter probe*;

d) the maximum optical output power of the light emitted by the *cerebral tissue oximeter probe*;

e) description of the effect on displayed and transmitted StO_2 data values by:

1) the data averaging and other signal processing,

2) the *data update period,*

3) the *alarm condition delay,*

4) the *alarm signal generation delay*, and

5) the effects of any selectable operating mode on the previous 4 list items;

NOTE 1 Annex GG provides an example of how to assess and describe response time graphically.

f) the *displayed ranges* of StO_2;

g) if no *alarm system* that includes the capability to detect an *StO_2 physiological alarm condition* is provided, a statement to that effect and Symbol IEC 60417-5319 (DB-2002-10) (see Table 201.D.1.101, Symbol 3) may be used for this indication;

h) for *cerebral tissue oximeter monitors,* the list of *cerebral tissue oximeter probe(s)* and *probe cable extenders* with which the *cerebral tissue oximeter monitor* has been *verified* and tested for conformance with this document. This may be made available by electronic means;

NOTE 2 Additional information is found in 201.4.103.

i) the *verification* method used to assess the *accuracy*;

j) a statement to the effect that performance assessment based on in-vivo and in-vitro methods are not equivalent;

NOTE 3 In-vivo *verification* involves testing on a variety of human subjects in a clinical setting and captures inter-subject variability. In-vitro *verification* involves testing with reproducible tissue phantom(s) in a controlled, non-clinical laboratory setting. Both methods can differ in the level of uncertainty and its sources.

k) information to indicate that StO_2 values from different *cerebral tissue oximeters* might not be directly comparable;

l) *accuracy*, A_{rms};

m) *mean bias, B*;

n) ± standard deviation of the bias; and

NOTE 4 Standard deviation refers to the differences between the test and reference values, StO_2 and S_R. Refer to Annex CC.

o) if trend accuracy is provided, the method used to determine trend accuracy.

Check conformance by inspection of the instructions for use.

201.7.9.2.2.101 Additional requirements for warnings and safety notices

For each *cerebral tissue oximeter probe* and *probe cable extender,* the instructions for use shall include:

a) a warning to the effect that *probes* and cables are designed for use with specific monitors;

b) a warning statement to the effect that the *responsible organization* or *operator* needs to confirm the compatibility of the monitor, probe and cable before use, or patient injury can result; and

c) a warning statement to the effect that misapplication of a *probe* with excessive pressure for prolonged periods can induce pressure injury.

Check conformance by inspection of the instructions for use.

201.7.9.2.9.101 Additional requirements for operating instructions

The instructions for use shall indicate the following:

a) a description of the signal inadequacy indicator and its function, if applicable;

b) the recommended maximum application time for each type of *cerebral tissue oximeter probe* at a single site;

c) the IP classification of the *cerebral tissue oximeter equipment enclosure*;

   1) If applicable, the IP classification on any carrying case provided with the *cerebral tissue oximeter equipment.*

   2) A brief description of the meaning of any IP classification.

      EXAMPLE IPX2 means this *cerebral tissue oximeter* is protected against harmful effects of dripping water when tilted at 15° according to IEC 60529.

d) if the *cerebral tissue oximeter equipment* is provided with a capability such that the *cerebral tissue oximeter probe* can operate at a temperature greater than 41 °C, specific instructions emphasizing the importance of proper *cerebral tissue oximeter probe* application, without excessive pressure; and

   1) In addition, specific instructions for any changes in recommended maximum application time when using temperatures greater than 41 °C.

e) The *declared range* of *alarm limit* adjustment.

201.7.9.2.14.101 Additional requirements for *accessories*, supplementary equipment, used material

The instructions for use shall include the following:

a) for *cerebral tissue oximeter probes,* the *cerebral tissue oximeter monitor(s)* and *probe cable extenders* with which the *cerebral tissue oximeter probes* have been *verified* and tested for conformance with this document;

   NOTE 1 Additional information is found in 201.4.103.

   1) The list may be made available by electronic means.

b) for *probe cable extenders,* the *cerebral tissue oximeter monitor(s)* and *cerebral tissue oximeter probes* with which the *probe cable extenders* have been *verified* and tested for conformance with this document.

NOTE 2 Additional information is found in 201.4.103.

1) The list may be made available by electronic means.

Check conformance by inspection of the instructions for use and inspection of the risk management file for the identification of any residual risks and any adverse effect of any recommended accessory.

201.7.9.3.1.101 * Additional general requirements

The technical description shall include a statement to the effect that a *functional tester* cannot be used to assess the *accuracy* of a *cerebral tissue oximeter probe* or a *cerebral tissue oximeter monitor.*

NOTE Additional information is found in Annex FF.

Check conformance by inspection.

201.8 Protection against electrical *hazards* from *ME equipment*

Clause 8 of the general standard applies, except as follows:

Addition:

201.8.3.101 Additional requirements for classification of *applied parts*

Applied parts of *cerebral tissue oximeter equipment* shall be *type BF* or *type CF applied parts*.

Check conformance by inspection.

201.8.5.5.1.101 Defibrillation protection

Applied parts of *cerebral tissue oximeter equipment* expected to be used in an environment where defibrillators are common, shall be classified as *defibrillation-proof applied parts*.

Check conformance by inspection and inspection of the risk management file for assessment of a need for the applied part to be classified as defibrillation-proof applied part.

NOTE Some examples of environments where defibrillators are common include the operating room, emergency department, cardiac catheterization laboratory, and intensive care units.

201.8.7.4.7.101 Additional requirements for measurement of the *patient leakage current*

Cerebral tissue oximeter probes marked for temporary immersion shall:

a) conform to IPX7 of IEC 60529:1989+AMD1:1999+AMD2:2013;

b) be tested for *patient leakage current* according to 8.7.4.7 f) of the general standard.

Check conformance by the relevant tests of the general standard.

201.9 Protection against mechanical *hazards* of *ME equipment* and *ME systems*

Clause 9 of the general standard applies.

201.10 Protection against unwanted and excessive radiation *hazards*

Clause 10 of the general standard applies, except as follows:

201.10.4 Lasers

Replacement:

aa) Depending on the light source used in a *cerebral tissue oximeter probe*, the relevant requirements of IEC 60825-1:2014 or IEC 62471:2006 shall apply to a *cerebral tissue oximeter probe*.

bb) In the case of laser fibre optics, the requirements of IEC 60825-2:2004+AMD1:2006+AMD2:2010 shall apply.

NOTE IEC 60601-2-57[2] does not apply because there are no intended photobiological effects.

Check conformance by application of the requirements of IEC 60825-1:2014, IEC 60825-2:2004+AMD1:2006+AMD2:2010, and IEC 62471:2006 as applicable.

201.11 Protection against excessive temperatures and other *hazards*

Clause 11 of the general standard applies, except as follows:

201.11.1.2.2 *Applied parts* not intended to supply heat to a *patient*

Amendment (add at the end of 11.1.2.2):

aa) The *cerebral tissue oximeter probe*-tissue interface shall be evaluated when the skin temperature is initially at 35 °C for each *cerebral tissue oximeter monitor* and *cerebral tissue oximeter probe* indicated in the instructions for use.

NOTE Additional information is found in Annex BB.

If the surface temperature of the *cerebral tissue oximeter probe* at the tissue interface is capable of exceeding 41 °C, then

bb) the *cerebral tissue oximeter equipment* shall have an *operator*-adjustable control for activating any elevated temperature mode that exceeds 41 °C;

1) A deliberate sequence of *operator* actions shall be required to activate this mode.

2) The instructions for use shall describe this sequence of *operator* actions.

cc) the *cerebral tissue oximeter equipment* shall provide a means to limit the duration of an elevated temperature mode in excess of 41 °C;

1) The duration of the elevated temperature mode shall not exceed 4 h at 43 °C or 8 h at 42 °C.

dd) the instructions for use shall include a statement to the effect that the use of temperature settings greater than 41 °C requires special attention in *patients* with susceptible skin, such as neonates, geriatric *patients* or burn victims;

ee) the *cerebral tissue oximeter equipment* shall indicate when it is in the elevated temperature mode; and

ff) the technical description shall describe the test method used to measure the maximum temperature at the *cerebral tissue oximeter probe*-tissue interface.

1) When performing the temperature measurements for the *cerebral tissue oximeter probe*-tissue interface, as specified in IEC 60601-1:2005+AMD1:2012+AMD2:2020, 11.1.3, the test method disclosed in the technical description may be utilized.

NOTE Additional information is found in BB.3.

Addition:

201.11.6.5.101 * Additional requirements for ingress of water or particulate matter into the *ME equipment* or *ME system*

a) The *enclosure* of a *cerebral tissue oximeter equipment* shall provide a degree of protection to the harmful ingress of water of at least an IPX1 for *cerebral tissue oximeter equipment*.

b) The *enclosure* of *transportable cerebral tissue oximeter equipment* shall provide a degree of protection to the harmful ingress of water of at least an IPX2 for *cerebral tissue oximeter equipment.*

1) For *portable ME equipment* that is only intended to be used within a protective case, this requirement may be met while the *ME equipment* is inside the case.

NOTE 1 Additional requirements for ingress of water or particulate matter into the *enclosure* of *cerebral tissue oximeter equipment* intended for use in the *home healthcare environment* are found in IEC 60601-1-11 and in the *emergency medical services environment* are found in IEC 60601-1-12.

NOTE 2 See also 201.8.7.4.7.

Check conformance according to the tests of IEC 60529:2013 with the cerebral tissue oximeter equipment placed in the least favourable position of normal use and by inspection. After these procedures, confirm that basic safety and essential performance are maintained.

201.11.6.7 *Sterilization* of *ME equipment* or *ME system*

Amendment (add note before conformance test):

NOTE Additional requirements are found in 11.6.6 of IEC 60601-1:2005+AMD1:2012.

Addition:

201.11.8.101 Additional requirements for interruption of the power supply/*supply mains* to *ME equipment*

201.11.8.101.1 *Technical alarm condition* for power supply failure

a) If *cerebral tissue oximeter equipment* is equipped with an *alarm system* that detects a *physiological alarm condition*, the *alarm system* shall provide at least a *medium priority technical alarm condition* to indicate when the power supply falls outside the values specified for normal operation.

NOTE After the loss of power, the *alarm system* is not expected to repeat *alarm signals* indefinitely.

b) If the function of the *cerebral tissue oximeter equipment* is maintained by the switchover to an *internal electrical power source*, the supply failure *medium priority technical alarm condition* shall not be activated.

1) Any such switchover to an *internal electrical power source* shall be indicated by an *information signal* or a *low priority technical alarm condition*.

Check conformance by functional testing.

201.11.8.101.2 Settings and data storage following short interruptions or automatic switchover

When the *supply mains* to the *cerebral tissue oximeter equipment* is interrupted for less than 30 s or automatic switchover to an *internal electrical power source* occurs:

a) no change of clinical *operator* settings shall occur, including the mode of operation; and

b) all stored *patient* data shall remain available.

NOTE 1 The *cerebral tissue oximeter equipment* does not have to continue to operate during the interruption of the *supply mains*.

NOTE 2 Settings include *operator settings*, *responsible organization* settings, and the mode of operation.

Check conformance by observing the cerebral tissue oximeter equipment settings and stored patient data and then interrupting the supply mains for a period of between 25 s and 30 s by disconnecting the power supply cord. After reestablishment of power, the above settings and stored data shall be the same.

201.11.8.101.3 Operation following long interruptions

a) The instructions for use shall disclose the operation of the *cerebral tissue oximeter equipment* after the *supply mains* has been interrupted when the “on-off” switch remains in the "on" position and is restored after a period of time longer than 30 s.

b) A *cerebral tissue oximeter* shall provide a *technical alarm condition* at least 5 min prior to the time that it can no longer function in accordance with the *manufacturer’s* specification when powered from the *internal electrical power source*.

Check conformance by inspection of the instructions for use.

201.12 Accuracy of controls and instruments and protection against hazardous outputs

Clause 12 of the general standard applies, except as follows:

Addition:

201.12.1.101 * *StO_2 accuracy* of *cerebral tissue oximeter equipment*

201.12.1.101.1 * Specification

a) The *StO_2 accuracy* of *cerebral tissue oximeter equipment* shall be determined as a root-mean-square difference over the *declared range* of 50 % to 85 % of the *reference haemoglobin oxygen saturation*, S_R.

b) *StO_2 accuracy* shall be less than or equal to 10,0 % *StO_2* over the *declared range* of 50 % to 85 % S_R.

1) *StO_2 accuracy* specifications over additional ranges may be provided as long as the range is greater than 20 %.

EXAMPLE A specified *StO_2 accuracy* of 8 % for 50 % to 85 % S_R and 7 % for 50 % to 80 % S_R.

c) The instructions for use of *cerebral tissue oximeter equipment* shall disclose:

1) the *StO_2 accuracy*; and

2) its *declared range*.

d) *StO_2 accuracy* information shall be accompanied by a note reminding the reader that, because *cerebral tissue oximeter equipment* measurements are statistically distributed, only about two-thirds of *cerebral tissue oximeter equipment* measurements can be expected to fall within $\pm A_{rms}$ of the reference measurement over the *declared range*.

e) The instructions for use may additionally disclose *StO_2* trend accuracy.

1) If provided, the *StO_2* trend accuracy shall be reported over the *declared range* of 50 % to 85 % S_R.

f) When a *cerebral tissue oximeter monitor* is suitable for use with a variety of *cerebral tissue oximeter probes*, *StO_2 accuracy* information shall be made available for each type of *cerebral tissue oximeter probe* indicated in the instructions for use.

g) The following results of the *accuracy* performance studies shall be provided in the instruction for use:

1) a scatter plot, i.e. *StO_2* versus S_R, and the parameters (slope, intercept, correlation coefficient) of a regression line calculated within the limits of the *declared range;*

i) The plot should contain grid lines and a line of identity (y=x);

2) a Bland and Altman plot [i.e., (*StO_2* - S_R) versus (*StO_2* + S_R)/2].

h) In case of in-vivo *verification*, population *mean bias* (μ_0), between-subject variance (σ_μ^2), within-subject variance (σ^2), and upper 95 % and lower 95 % limits of agreement shall be provided as outlined in Section 3 of Reference [28].

1) In case the plots show noticeable outliers, the following shall be provided:

i) a discussion of the state of health, subject characteristics, test setup, test *procedure*, and any other factors that might have affected these data points; and

ii) a discussion of how the outlier(s) do not raise safety and performance concerns regarding the *accuracy* of the *cerebral tissue oximeter*.

i) Three statistical metrics (*accuracy*, A_{rms}, *mean bias, B,* ± standard deviation of the bias) and the plots shall be provided:

1) for all subjects pooled (in case of *verification* by a *controlled desaturation study*); and

2) for all required *ctHb* values pooled (in case of phantom desaturation).

j) The *accuracy* statements (*accuracy*, A_{rms}, *mean bias, B,* ± standard deviation of the bias) and the plots shall be provided for each combination of *cerebral tissue oximeter probe* and *cerebral tissue oximeter monitor* listed in the instructions for use.

Check conformance by following the requirements of 201.12.1.101.2 and by inspection of the accompanying document as well as the information that is available to the responsible organization upon request.

201.12.1.101.2 * Data collection for determination of StO_2 accuracy

a) The claims of StO_2 *accuracy* and trend accuracy, if provided, shall be supported by a *controlled desaturation study* or *tissue haemoglobin phantom* measurements taken over the full *declared range* of the reference S_R or between +3 % of the lower value and −3 % of the upper value for which StO_2 *accuracy* is claimed.

NOTE 1 In a *controlled desaturation study*, the $SavO_2$ is not controlled directly, so for a desaturation of 100 % to 70 % SaO_2, the $SavO_2$ range will vary from subject to subject.

1) The range of human demographics represented in the *controlled desaturation study* shall be disclosed, including anatomy, physiology and pathophysiology.

2) Data points should be recorded with comparable density over the full *declared range*.

EXAMPLE 1 A *controlled desaturation study* supporting a *declared range* of StO_2 *accuracy* from 55 % $SavO_2$ to 80 % $SavO_2$ can be supported with $SavO_2$ data collected over the range of 58 % $SavO_2$ to 77 % $SavO_2$.

b) The *controlled desaturation study* shall conform with the requirements of ISO 14155:2020.

c) The *residual risk* inherent in a controlled hypoxia study on healthy adult volunteers, can be reduced to a non-significant level by following recommended additional *procedures*[30].

d) The *accuracy* of *cerebral tissue oximeter equipment* for paediatric *patients* shall be supported via:

1) a convenience sample study on the intended population; or

2) a desaturation study on a *tissue haemoglobin phantom* constructed to represent the targeted paediatric population.

NOTE 2 The *accuracy* of *cerebral tissue oximeter equipment* for paediatric *patients* cannot be supported via a *controlled desaturation study* of adult subjects.

NOTE 3 Additional information is found in Annexes AA, DD and EE.

e) Any types of interference known to influence or affect the StO_2 *accuracy*:

1) need not be stated as part of the StO_2 *accuracy* specification; but

2) shall be disclosed in the instructions for use.

EXAMPLE 2 Ambient light (including photodynamic therapy); physical movement (*patient* and imposed motion); diagnostic testing; electromagnetic interference; HF surgical equipment; dysfunctional haemoglobin; presence of certain dyes; inappropriate positioning of the *cerebral tissue oximeter probe*; low *total haemoglobin concentration*; excessive thickness of extracerebral tissue.

f) A summary of the test methods used to establish the *StO_2 accuracy* claims shall be disclosed:

1) in the technical description; and

2) the instructions of use.

201.12.1.101.3 * Data analysis for determination of *StO_2 accuracy*

a) For each *declared range* specified, *StO_2 accuracy* of the *cerebral tissue oximeter equipment* shall be stated in terms of the root-mean-square (rms) difference between measured values (StO_{2i}) and reference values (S_{Ri}), as given by Formula (1), for the number of paired samples (n).

$$A_{rms} = \sqrt{\frac{\sum_{i=1}^{n} \left(StO_{2i} - S_{Ri} \right)^2}{n}} \qquad (1)$$

b) For each *declared range* specified, *StO_2* trend accuracy, if provided, of the *cerebral tissue oximeter equipment* shall be disclosed by the *manufacturer* along with the method of determination.

NOTE 1 At the time of this document, there is no consensus on the methods for reporting trend accuracy.

NOTE 2 The concepts of bias and precision as given in ISO 3534-2:2006[6] and ambiguity[80] also have value in representing the *accuracy* of *ME equipment*. The decision to require the form of *StO_2 accuracy* stated above is based on the belief that it will be more widely understood by the general community of clinical *operators* and on the recognition that in some cases it represents the overall *StO_2 accuracy* of *cerebral tissue oximeter equipment* better than do bias and precision.

NOTE 3 Attention is also drawn to ISO/IEC Guide 99 (VIM)[9] and ISO/IEC Guide 98-3 (GUM)[10] as well as the documents of ISO/TC 69, *Applications of statistical methods*, for determination of accuracy and precision.

c) In case of in-vivo *verification* by a *controlled desaturation study*, the standard reference for the *StO_2 accuracy* as read by *cerebral tissue oximeter equipment* shall be traceable to *Sav*O_2 values obtained from *CO-oximeter* analysis of simultaneously drawn arterial and jugular venous blood.

1) The assumption on the ratio of arterial and venous compartment sizes, R, shall be disclosed in the instructions for use.

NOTE 4 See definition 201.3.220, Note 2 to entry.

2) The *CO-oximeter* shall have a specified performance of 1 % (1 standard deviation) or better over the range for *Sa*O_2 and *Sjv*O_2 blood draws.

3) Quality assurance, including maintenance and *procedures* for assessing *CO-oximeter* performance that are required in laboratories reporting clinical data shall be utilized for the *CO-oximeter*.

NOTE 5 Additional information is found in Annex EE.

d) In case of in-vitro *verification* (phantom), the reference method for the assessment of *StO_2 accuracy* shall be disclosed in the instructions for use.

1) The performance of the reference method shall be appropriately *verified*.

NOTE 6 Additional information on phantoms is found in Annex DD.

201.12.1.101.4 Characteristics of the study used for determination of *StO₂ accuracy*

a) If in-vivo methods are used, the summary of the clinical study report used to assess *StO₂ accuracy* shall:

   1) state whether the test subjects were sick or healthy;

   2) describe their skin colour, age and gender; and

   3) be disclosed in the *accompanying document*.

b) If in-vitro methods are used, the summary of the phantom study used to assess *StO₂ accuracy* shall state the main characteristics of the experiment as listed in DD.4.2.

Check conformance by inspection of the accompanying document.

201.12.4 Protection against hazardous output

Addition:

201.12.4.101 * *Data update period*

a) There shall be an indication that *StO₂* is not current when the *data update period* is greater than 30 s.

   NOTE The *data update period* can be shorter than 30 s.

b) If the *cerebral tissue oximeter equipment* is equipped with an *alarm system* that detects any *physiological alarm conditions*, the *alarm system* shall provide at least a *low priority alarm condition* to indicate when the *data update period* exceeds 30 s.

c) *Cerebral tissue oximeter equipment* that is not equipped with an *alarm system* that detects any *physiological alarm condition* shall indicate when the *data update period* exceeds 30 s.

   1) The indication shall be described in the instructions for use.

d) If the *cerebral tissue oximeter equipment* is equipped with a *functional connection* (see 201.102), an indication that the *data update period* exceeds 30 s shall be included in the data stream.

Check conformance by inspection.

201.12.4.102 * Signal inadequacy

a) An indicator of signal inadequacy shall be provided to the *operator* when the displayed *StO₂* value is potentially incorrect.

   1) Symbol ISO 7000-0435 (see Table 201.D.1.101, Symbol 1) may be used for this indication.

   2) The *accompanying document* shall include a description:

      i) of the indicator; and

      ii) of its function.

   EXAMPLE Signal inadequacy indicated by a visual *information signal* or a *low priority alarm signal*.

b) If the *cerebral tissue oximeter equipment* is equipped with a *functional connection* (see 201.102), then signal inadequacy shall be included in the data stream (see Table HH.201).

Check conformance by inspection.

201.13 *Hazardous situations* and fault conditions for *ME equipment*

Clause 13 of the general standard applies, except as follows:

Addition:

201.13.101 Detection of *probe faults* and *probe cable extender* faults

a) If the *cerebral tissue oximeter equipment* is equipped with an *alarm system* to detect any *physiological alarm conditions*, the *alarm system* shall provide a *technical alarm condition* to indicate when any wire in the *cerebral tissue oximeter probe* cable or *probe cable extender* is opened or shorted to any other wire in the *cerebral tissue oximeter probe* cable; that compromises *basic safety* or *essential performance*.

b) *Cerebral tissue oximeter equipment* that is not equipped with an *alarm system* that detects any *physiological alarm conditions* shall visually indicate the presence of *probe faults*.

1) The indication shall be described in the instructions for use.

EXAMPLE Indication of abnormal operation by blank display.

Check conformance with the following test:

c) Disconnect the cerebral tissue oximeter probe from the cerebral tissue oximeter equipment and place it in series with a circuit with which each cerebral tissue oximeter probe wire can be opened or shorted to any other cerebral tissue oximeter probe wire. Do not test unused wires in the cerebral tissue oximeter probe cable or probe cable extender.

d) Repeat for any probe cable extender.

e) Confirm either that a probe fault is indicated by the cerebral tissue oximeter monitor or that the cerebral tissue oximeter equipment continues normal operation.

201.14 *Programmable electrical medical systems* (*PEMS*)

Clause 14 of the general standard applies.

201.15 Construction of *ME equipment*

Clause 15 of the general standard applies, except as follows:

Addition:

201.15.3.5.101 * Additional requirements for rough handling

201.15.3.5.101.1 * Shock and vibration (robustness)

a) *Cerebral tissue oximeter equipment* or its parts shall have adequate mechanical strength when subjected to mechanical stress caused by *normal use*, pushing, impact, dropping and rough handling.

b) *Stationary* equipment is exempt from the requirements of this subclause.

c) After the following tests, the *cerebral tissue oximeter* shall:

1) maintain *basic safety* and *essential performance*; and

2) conform with the requirements of 201.12.1 and 201.12.4.

NOTE 1 A *cerebral tissue oximeter* tested and conforming with a more severe requirement is considered to conform with the corresponding requirement of this subclause.

Check conformance with the following tests:

d) Shock test in accordance with IEC 60068-2-27:2008[1], using the following conditions:

NOTE 2 This represents IEC/TR 60721-4-7:2001[11], Class 7M2.

1) *test type: Type 1, or*

— *peak acceleration: 150 m/s² (15 g),*

— *duration: 11 ms,*

— *pulse shape: half-sine,*

— *number* of shocks: 3 shocks per direction per axis (18 total);

or

2) *test type: Type 2*

— *peak acceleration: 300 m/s² (30 g),*

— *duration: 6 ms,*

— *pulse shape: half-sine,*

— *number of shocks: 3 shocks per direction* per axis (18 total).

e) Broad-band random vibration test in accordance with IEC 60068-2-64:2008+AMD1:2019, using the following conditions:

NOTE 3 This represents IEC/TR 60721-4-7:2001+ AMD1:2003[11], Classes 7M1 and 7M2.

1) acceleration amplitude:

— *10 Hz to 100 Hz: 1,0 $(m/s^2)^2$/Hz;*

— *100 Hz to 200 Hz: –3 dB per octave;*

2) duration: 10 min per perpendicular axis (3 total).

f) Confirm that basic safety and essential performance are maintained following the tests.

201.15.3.5.101.2 * Shock and vibration for a *transit-operable cerebral tissue oximeter* during operation

a) A *cerebral tissue oximeter* and its parts, including applicable *accessories*, intended for *transit-operable* use (during *patient* transport inside a healthcare facility) shall have adequate mechanical strength when subjected to mechanical stress caused by *normal use*, pushing, impact, dropping and rough handling while operating.

b) For this test, the *cerebral tissue oximeter* and its parts, and applicable *accessories*, shall be mounted using the mounting *accessories* indicated in the *accompanying documents*.

NOTE 1 If more than one mounting system is described in the *accompanying documents*, multiple tests are required.

NOTE 2 A *cerebral tissue oximeter* tested and conforming with a more severe requirement is considered to conform with the corresponding requirement of this subclause.

c) During the following test, a *cerebral tissue oximeter* shall maintain *basic safety* and *essential performance* and shall not exhibit an StO_2 deviation greater than ±4 %. Do not confuse maximum deviation with *accuracy*, A_{rms}, of the *cerebral tissue oximeter*. The maximum deviation allowed during this test is usually considerably smaller than the value of A_{rms}.

d) During this testing, *alarm limits* for StO_2 shall be set to their least sensitive levels.

Check conformance by performing the following tests:

e) *Shock test in accordance with IEC 60068-2-27:2008[11], using the following conditions:*

1) test type: Type 1,

— *peak acceleration: 50 m/s² (5 g);*

— *duration: 6 ms;*

— *pulse shape: half-sine;*

— *number of shocks: 3 shocks per direction per axis (18 total);*

f) *Broadband random vibration test in accordance with IEC 60068-2-64:2008+AMD1:2019, using the following conditions:*

1) acceleration amplitude:

— *10 Hz to 100 Hz: 0,33 $(m/s^2)^2$/Hz;*

— *100 Hz to 500 Hz: –6 dB per octave;*

2) duration: 30 min per perpendicular axis (3 total).

g) *Free fall in accordance with IEC 60068-2-31:2008, using Procedure 1 and the following conditions:*

1) fall height:

i) for mass ≤1 kg, 0,25 m

ii) for mass >1 kg and ≤10 kg, 0,1 m

iii) for mass >10 kg and ≤50 kg, 0,05 m

iv) for mass >50 kg, 0,01 m

2) number of falls: 2 in each specified attitude.

h) *Confirm that following these tests, basic safety and essential performance are maintained.*

201.15.101 Mode of operation

Cerebral tissue oximeter equipment shall be suitable for *continuous operation.*

NOTE 1 Moving the *cerebral tissue oximeter probe* to a new site on the body is *normal use* and is considered *continuous operation*.

NOTE 2 Intermittent use of *cerebral tissue oximeter equipment* on one *patient* or among *patients* is *normal use* and is considered *continuous operation*.

Check conformance by functional testing.

201.16 *ME systems*

Clause 16 of the general standard applies.

201.17 Electromagnetic compatibility of *ME equipment* and *ME systems*

Clause 17 of the general standard applies.

Additional clauses:

201.101 * *Cerebral tissue oximeter probes* and *probe cable extenders*

201.101.1 General

a) All *cerebral tissue oximeter probes* and *probe cable extenders* shall conform with the requirements of this document, whether they are produced by the *manufacturer* of the *cerebral tissue oximeter monitor*, by another entity ("third party manufacturer" or healthcare provider) or are *remanufactured*.

b) *Manufacturers* of *remanufactured cerebral tissue oximeter probes* and *probe cable extenders* shall perform testing to ensure that all *cerebral tissue oximeter equipment* specifications are met with each model of *cerebral tissue oximeter monitor* with which the *cerebral tissue oximeter probe* or *probe cable extender* is intended to be used.

c) The *accompanying document* of *remanufactured cerebral tissue oximeter probes* and *probe cable extenders* shall list all *cerebral tissue oximeter monitors* with which compatibility is claimed.

d) It is the responsibility of the *manufacturer* to validate their *processes* to ensure that any new or *remanufactured* product conforms with the requirements of this document.

Check conformance by the tests of this document.

201.101.2 Labelling

a) The *model or type reference* of at least one *cerebral tissue oximeter monitor* shall be included in the *accompanying document* provided with each *cerebral tissue oximeter probe*, conforming with 201.101.1.

b) Statements shall be included in the *accompanying document* of each *cerebral tissue oximeter probe* or *probe cable extender* to the effect that:

1) probes are designed for use with specific monitors;

2) the *responsible organization* and *operator* are responsible for checking the compatibility of the monitor, probe and cable before use; and

3) incompatible components can result in degraded performance.

NOTE Additional information is found in 201.101.1.

Check conformance by inspection of the accompanying document.

201.102 *Functional connection*

201.102.1 General

Basic safety and *essential performance* shall be maintained:

a) during failure of equipment connected to the *cerebral tissue oximeter equipment*; or

b) because of disruptions to the *functional connection* of *cerebral tissue oximeter equipment*.

Check conformance by functional testing.

201.102.2 * Connection to an electronic health record or *integrated clinical environment*

a) *Cerebral tissue oximeter equipment* should be equipped with a *functional connection* that permits data transmission from the *cerebral tissue oximeter equipment* to an electronic health record or *integrated clinical environment*.

1) If so equipped, the transmission shall conform with Annex HH.

b) The data transmission should be capable of being provided with a *network/data coupling* in accordance with AAMI 2700-1.

201.102.3 Connection to a *distributed alarm system*

a) For *cerebral tissue oximeter equipment* that is equipped with an *alarm system* that detects a *physiological alarm condition,* the *alarm system* should be equipped with a *functional connection* that permits connection to a *distributed alarm system*.

b) The data transmission should be capable of being provided with a *network/data coupling* in accordance with AAMI 2700-1:2019.

202 Electromagnetic disturbances — Requirements and tests

IEC 60601-1-2:2014+AMD1:2020 applies except as follows:

202.4.3.1 Configurations

Amendment (replace the second dash of 4.3.1 with):

aa) setting the StO_2 within the *declared range*, to be at least the StO_2 *accuracy* different from that of a noise-induced value (and within *display range* and at least the StO_2 *accuracy* away from the boundaries of the *cerebral tissue oximeter equipment display range*).

1) This shall apply to *immunity* testing of *cerebral tissue oximeter equipment.*

bb) The StO_2 signal may be derived from a *functional tester* (Annex FF) for these tests.

202.5.2.2.1 Requirements applicable to all *ME equipment* and *ME systems*

Amendment (add note to list element b)):

NOTE The requirements of this document are not considered deviations or allowances.

Addition:

202.8.1.101 Additional general requirements

a) Under the *immunity test levels* specified in IEC 60601-1-2:2014, 8.9, *cerebral tissue oximeter equipment* shall be able to provide *basic safety* and *essential performance*.

b) The following degradations, if associated with *basic safety* or *essential performance* shall not be allowed:

1) component failure(s),

2) change(s) in programmable parameters or settings,

3) reset to default settings, and

4) change of operating mode.

c) The *cerebral tissue oximeter equipment* may exhibit temporary degradation of performance (e.g. deviation from the performance indicated in the instructions for use during *immunity* testing) that does not affect *basic safety* or *essential performance* providing the *cerebral tissue oximeter equipment* recovers from any disruption within 30 s without *operator* intervention.

d) *Cerebral tissue oximeter equipment* shall not exhibit an StO_2 deviation greater than ±4 %.

202.8.2 *Patient* physiological simulation

Replace the third paragraph with the following:

a) The StO_2 signal may be derived from a *functional tester* for these tests.

b) The amplitude of the simulated *patient* signal provided by a *functional tester*, shall be representative of the signal characteristics which trigger the signal inadequacy indicator, yet high enough so that the outcome of the test is not penalized by the statistics of detection and the noise floor of the detection circuitry.

Replace the NOTE with:

NOTE 100 Current technology of solid phantoms used for *functional testers* during EMC testing does not provide precise signal characteristics. Based upon this limitation, this document does not specify exact levels for the required simulated *patient* signals.

NOTE 101 See Annex FF for more information.

206 Usability

IEC 60601-1-6:2006+AMD1:2012+AMD2:2020 applies except as follows:

For *cerebral tissue oximeter equipment*, the following shall be considered *primary operating functions*:

a) setting the *operator*-adjustable controls:

   1) setting *alarm limits* if applicable;

   2) inactivating *alarm signals* if applicable;

   3) switching between different modes;

b) observing monitored parameters;

c) applying the *cerebral tissue oximeter probe* to the *patient*;

d) starting the *cerebral tissue oximeter equipment* from power off; and

e) connecting and disconnecting the *distributed alarm system*, if provided.

208 General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems

IEC 60601-1-8:2006+AMD1:2012+AMD2:2020 applies except as follows:

Addition:

208.6.1.2.101 * Additional requirements for *alarm condition* priority

If the *cerebral tissue oximeter equipment* is equipped with an *alarm system* that detects a *physiological alarm condition*, the *alarm system* shall provide at least a *medium priority alarm condition* for low StO_2 level.

Check conformance by inspection.

208.6.5.4.101 * Additional requirements for *default alarm preset*

Unless the low StO_2 *alarm limit* is displayed continuously, if the *cerebral tissue oximeter monitor* is equipped with an *alarm system* to detect a low StO_2 level *physiological alarm condition*, the *alarm limit* in the *operator*-configured *alarm preset* for the StO_2 level *physiological alarm condition* shall not be less the *manufacturer*-specified low *alarm limit*.

Check conformance by functional testing.

208.6.8.5.101 Additional requirements for *alarm signal* inactivation states, indication and access

The *manufacturer*-configured default *audio paused* or *alarm paused* interval of *cerebral tissue oximeter equipment* shall not exceed 2 min.

Check conformance by functional testing.

211 Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

For *cerebral tissue oximeter equipment* intended for use in the *home healthcare environment*, IEC 60601-1-11:2015+AMD1:2020 applies except as follows:

Addition:

The tests of IEC 60601-1-11:2015+AMD1:2020, Clause 10, and
IEC 60601-1:2005+AMD1:2012+AMD2:2020, 15.3, shall be performed on the same sample of the *cerebral tissue oximeter equipment* following any *remanufacturing* established for this equipment.

212 Requirements for medical electrical equipment and medical electrical systems used in the emergency medical services environment

For *cerebral tissue oximeter equipment* intended for use in the *emergency medical services environment*, IEC 60601-1-12:2014+AMD1:2020 applies except as follows:

Addition:

The tests of Clause 10 of IEC 60601-1-12:2014, and 15.3 of
IEC 60601-1:2005+AMD1:2012+AMD2:2020 shall be performed on the same sample of the *cerebral tissue oximeter equipment* following any *remanufacturing* established for this equipment.

Annexes of the general standard apply, except as follows.

Annex C
(informative)

Guide to marking and labelling requirements for *ME equipment* and *ME systems*

Annex C of IEC 60601-1:2005+AMD1:2012+AMD2:2020 applies, except as follows:

Addition:

201.C.1 Marking on the outside of *ME equipment*, *ME systems* or their parts

Additional requirements for marking on the outside of *cerebral tissue oximeter equipment* or their parts or *accessories* are found in Table 201.C.101.

Table 201.C.101 — Marking on the outside of *cerebral tissue oximeter equipment* or its parts or *accessories*

Description of marking	Subclause
Follow instructions for use of *safety sign*	201.7.2.3
If applicable for a *remanufactured cerebral tissue oximeter probe*, so indicated	201.7.2.101 b)
If applicable, IP classification of carrying case	201.7.2.9 b) 2)
If applicable, keep dry	201.7.2.9 d)
If not provided with a low StO_2 limit *alarm condition*, so indicated	201.7.2.101 a)
IP classification of the *enclosure*	201.7.2.9 a) 201.7.2.9 b) 1)
Units of measure of oxygen saturation	201.7.4.3

201.C.2 *Accompanying documents*, general

Additional requirements for general information to be included in the *accompanying documents* of *cerebral tissue oximeter equipment* or its parts or *accessories* are found in Table 201.C.102.

Table 201.C.102 — *Accompanying documents*, general

Description of disclosure	Subclause
Description of signal inadequacy indicator and its function	201.12.4.102 a)
For *cerebral tissue oximeter probes* or *probe cable extenders*, incompatible components can result in degraded performance	201.101.2 b) 3)
For *cerebral tissue oximeter probes* or *probe cable extenders*, *probes* are designed for use with specific monitors	201.101.2 b) 1)
For *cerebral tissue oximeter probes* or *probe cable extenders*, the *responsible organization* and *operator* are responsible for checking compatibility prior to use	201.101.2 b) 2)
For *cerebral tissue oximeter probes*, a compatible *cerebral tissue oximeter monitor*	201.101.2 a)
For in-vitro *verification*, the summary of the phantom study including the main characteristics of the experiment as listed in DD.4.2	201.12.1.101.4 b)
For in-vivo *verification*, summary of the clinical study report	201.12.1.101.4 a)
For *remanufactured cerebral tissue oximeter probes* or *probe cable extenders*, list of compatible *cerebral tissue oximeter monitors*	201.101.1 c)

201.C.3 *Accompanying documents*, instructions for use

Additional requirements for information to be included in the instructions for use of *cerebral tissue oximeter equipment,* its parts or *accessories* are found in Table 201.C.103.

Table 201.C.103 — *Accompanying documents*, instructions for use

Description of disclosure	Subclause
± standard deviation of the bias	201.7.9.2.1.101 n)
A statement to the effect that performance assessment based on in-vivo and in-vitro methods are not equivalent	201.7.9.2.1.101 j)
Accuracy	201.7.9.2.1.101 l)
Bland and Altman plot	201.12.1.101.1 g) 2)
Range of *alarm limit* adjustment	201.7.9.2.9.101 e)
Declared ranges of StO_2 *accuracy* of *cerebral tissue oximeter equipment*	201.12.1.101.1 c) 2)
Description of the meaning of any IP classification	201.7.9.2.9.101 c) 2)
Description of the signal adequacy indicator	201.7.9.2.9.101 a)
Displayed ranges of StO_2	201.7.9.2.1.101 f)
Effect of any selectable operating mode on 1) to 4)	201.7.9.2.1.101 e) 5)
Effect of data averaging on displayed and transmitted StO_2 values	201.7.9.2.1.101 e) 1)
Effect of the *alarm condition delay* on displayed and transmitted StO_2 values	201.7.9.2.1.101 e) 3)
Effect of the *alarm signal generation delay* on displayed and transmitted StO_2 values	201.7.9.2.1.101 e) 4)
Effect of the *data update period* on displayed and transmitted StO_2 values	201.7.9.2.1.101 e) 2)
For *cerebral tissue oximeter equipment* not provided with an *alarm system* that includes the capability to detect *physiological alarm conditions*, means of indicating a *probe fault*	201.13.101 b) 1)
For *cerebral tissue oximeter probes* or *probe cable extenders*, a warning that probes are	201.7.9.2.2.101 a)

Description of disclosure	Subclause
designed for use with specific monitors	
For *cerebral tissue oximeter probes* or *probe cable extenders*, a warning that the *responsible organization* or *operator* is responsible for checking compatibility prior to use	201.7.9.2.2.101 b)
For *cerebral tissue oximeter probes* or *probe cable extenders*, a warning that misapplication of a probe with excessive pressure for prolonged periods can induce pressure injury	201.7.9.2.2.101 c)
For *cerebral tissue oximeter probes*, the list of compatible *cerebral tissue oximeter monitors* and *probe cable extenders*	201.7.9.2.14.101 a)
For each *cerebral tissue oximeter equipment* and *cerebral tissue oximeter probe*, whether replacement or repositioning requires baseline re-establishment	201.7.9.2.1.101 a)
For each *cerebral tissue oximeter equipment* and *cerebral tissue oximeter probe*, the specified use	201.7.9.2.1.101 a) 1)
For each *cerebral tissue oximeter monitor*, the list of compatible *cerebral tissue oximeter probes* or *probe cable extenders*	201.7.9.2.1.101 h)
For each *cerebral tissue oximeter probe*, optical output power	201.7.9.2.1.101 d)
For each *cerebral tissue oximeter probe*, range of peak wavelengths	201.7.9.2.1.101 c)
For in-vitro *verification,* the reference method for the assessment of StO_2 *accuracy*	201.12.1.101.3 d)
For in-vivo *verification* where the scatter plot StO_2 vs. S_R has outliers, a discussion of the state of health, subject characteristics, test setup, test *procedure*, and any other factors that may have affected these data points	201.12.1.101.1 h) 1) i)
For in-vivo *verification* where the scatter plot StO_2 vs. S_R has outliers, a discussion of how the outlier(s) do not raise safety and performance concerns regarding the *accuracy* of the *cerebral tissue oximeter*	201.12.1.101.1 h) 1) ii)
For in-vivo *verification*, population *mean bias*	201.12.1.101.1 h)
For in-vivo *verification,* the assumption on the ratio of arterial and venous compartment sizes	201.12.1.101.3 c) 2)
For *probe cable extenders*, the list of compatible *cerebral tissue oximeter monitors* and *cerebral tissue oximeter equipment*	201.7.9.2.14.101 b)
If no StO_2 *alarm conditions*, so indicated	201.7.9.2.1.101 g)
If not equipped with an *alarm system* that includes the capability to detect *physiological alarm conditions*, description of the indication that the *data update period* exceeds 30 s	201.12.4.101 c) 1)
If the *applied part* temperature can exceed 41 °C, instructions emphasizing the importance of proper application	201.7.9.2.9.101 d)
If the *applied part* temperature can exceed 41 °C, specific instructions for any changes in recommended maximum application time	201.7.9.2.9.101 d) 1)
If the *applied part* temperature can exceed 41 °C, a statement to the effect that a patient with susceptible skin requires special attention	201.11.1.2.2 dd)
If the *applied part* temperature can exceed 41 °C, the sequence of *operator* actions needed to activate	201.11.1.2.2 bb)
Information to indicate that StO_2 values from different *cerebral tissue oximeters* might not be directly comparable	201.7.9.2.1.101 k)
Interference known to influence the StO_2 *accuracy*	201.12.1.101.2 e) 2)
IP classification and its meaning for the carrying case, if applicable	201.7.9.2.9.101 c) 1)
IP classification and its meaning for the *enclosure*	201.7.9.2.9.101 c)

Description of disclosure	Subclause
Mean bias	201.7.9.2.1.101 m)
Operation of *cerebral tissue oximeter equipment* following *supply mains* interruption longer than 30 s	201.11.8.101.3
Recommended maximum application time for each type of *cerebral tissue oximeter probe* at a single site	201.7.9.2.9.101 b)
Specified combinations of *cerebral tissue oximeter equipment*	201.4.103 b)
Statistical metrics information provided for each type of *probe* indicated in the instructions for use	201.12.1.101.1 j)
Statistical metrics of *accuracy*, A_{rms}, *mean bias*, B, ± standard deviation of the bias, and the plots	201.12.1.101.1 i)
StO_2 *accuracy* information provided for each type of *probe* indicated in the instructions for use	201.12.1.101.1 f)
StO_2 *accuracy* of *cerebral tissue oximeter equipment*	201.12.1.101.1 c) 1)
StO_2 trend accuracy shall be reported over the *declared range* of 50 % to 85 % S_R, if provided	201.12.1.101.1 e) 1)
StO_2 versus S_R scatter plot	201.12.1.101.1 g) 1)
Summary of the test methods used to establish the StO_2 *accuracy*	201.12.1.101.2 f) 2)
That the *cerebral tissue oximeter equipment* displays *functional oxygen saturation*	201.7.9.2.1.101 b)
The method used to determine trend accuracy, if provided	201.7.9.2.1.101 o)
The *verification* method used to assess the *accuracy*	201.7.9.2.1.101 i)
Within the *declared range* only 2/3 of measurements are expected to fall within the StO_2 *accuracy*	201.12.1.101.1 d)

201.C.4 *Accompanying documents*, technical description

Additional requirements for the technical description of *cerebral tissue oximeter equipment* or its parts or *accessories* are found in Table 201.C.104.

Table 201.C.104 — *Accompanying documents*, technical description

Description of disclosure	Subclause
Functional tester cannot be used to assess *accuracy*	201.7.9.3.1.101
If the *applied part* temperature can exceed 41 °C, the method used to measure *applied part* temperature	201.11.1.2.2 ff)
Summary of methods used to establish StO_2 *accuracy*	201.12.1.101.2 g) 1)

Annex D
(informative)

Symbols on marking

Annex D of IEC 60601-1:2005+AMD1:2012+AMD2:2020 applies, except as follows:

Addition:

Table 201.D.1.101 — Additional symbols on marking

No	Symbol	Reference	Title and description
1		ISO 7000-0435	Assistance; query (Malfunction) To indicate malfunction or to identify the control by which the *operator* can ask for assistance (help button).
2		ISO 7000-0626	Keep away from rain (Keep dry) On transport packaging. To indicate that the package must be kept in dry conditions. Indicates a medical device that needs to be protected from moisture.
3		IEC 60417-5319	Alarm inhibit To identify the alarm inhibit on control equipment. On medical *alarm systems* this graphical symbol is used as follows: When used with a negation cross of solid lines: *alarm off* To identify the control for *alarm off* or to indicate that the *alarm system* is in the *alarm off* state. NOTE 1 The *alarm condition* may be indicated inside, below, or beside the triangle. NOTE 2 As far as there is no danger of confusion, this symbol may also be used to identify equipment that has no *alarm system*.

Additional Annexes:

Annex AA
(informative)

Particular guidance and rationale

AA.1 General guidance

Cerebral tissue oximetry has been commercially available since the 1990s, with initial clinical usage occurring mainly in the cardiac anaesthesia arena. With improvements in *cerebral tissue oximeter* technology and cost, coupled with data from clinical research, usage has spread to include monitoring during vascular, trauma and neurosurgery, along with surgery in the beach chair position and other areas where brain perfusion can be at *risk*.[43],[49],[57],[59],[63] Guidelines from learned societies have begun to recommend use or consideration of cerebral tissue oximetry monitoring where brain perfusion is at *risk*, although a number of them have taken an equivocal stance whilst awaiting further data to support firm recommendations.

It was considered by the committees that information to support clinicians in making informed decisions about how and when to use *cerebral tissue oximeters* based on *manufacturers'* equipment characteristics and comparative differences would be clinically valuable and enhance the utility of *cerebral tissue oximeters*. Information should be readily accessible to the *operator* at point of care (e.g. printed on *probe* packaging or laminated card, accessible via a link or button on the *operator interface*, QR [Quick Response] code).

Information for clinicians which is relevant to appropriate use and *cerebral tissue oximeter* selection can include:

— the approximate typical tissue depth which the *probe* is expected to interrogate;

— sufficient information for the *operator* to determine if the *cerebral tissue oximeter* is suitable in relation to *patient* age and weight;

— appropriate *probe* application to minimize the *risk* of erroneous values or tissue damage (pressure or thermal injury) resulting from excess pressure over the *probe* (e.g. from surgical drapes, other equipment, *patient* lying on *probe* or cable);

— the potential for artefactual values to be generated when *probe*-to-skin application is insufficient;

— known limitations for use in both paediatric and adult populations (e.g. potential for erroneous values in the presence of anaemia, some types of skin pigmentation and intense ambient lighting, and excessive cerebrospinal fluid, air sinuses, or extracerebral tissue thickness);

— duration of *probe* use as dictated by *probe* adhesive or gel properties, physiological or mechanical limitations, or programmed time limits;

— the response time or averaging time required before StO_2 values are updated on the *cerebral tissue oximeter monitor* display;

— information to indicate that StO_2 values from different *cerebral tissue oximeters* cannot be directly comparable. Possible reasons for this difference can include algorithm differences, probe construction, and differences in calibration methods.

— trend accuracy has been associated with positive clinical outcomes and represents clinical use and interventions based on a *patient*'s change in StO_2 from baseline level. Because definitions of trend accuracy can be different between *manufacturers*, clinicians should be cautioned against comparing the trend accuracy results from one *manufacturer* to another.

Information which is desirable and, where available, should be included.

— Methods of *accuracy* performance *verification* for displayed StO_2 values and trends thereof (e.g. phantom, clinical trials, *controlled desaturation study*).

— Known potential bias of the displayed *cerebral tissue oxygenation* value (StO_2) due to contamination by extracerebral tissue (e.g. skin, skull) which can result where a substantial difference exists between *patient* cerebral tissue and scalp oxygen saturations. This is important for clinical situations where one tissue layer can be subject to ischaemia not affecting the other. Some clinical studies have assessed artefactual changes which occur in displayed cerebral tissue oximetry values during application of a scalp tourniquet; if mathematical modelling using the *manufacturer's cerebral tissue oximeter* algorithms could predict these effects it can be of value in determining suitability for an extended range of clinical situations.

— If there are known interactions with other equipment, which can be used on adjacent tissue (e.g. depth of consciousness monitoring electrodes or pulse oximeter probe).

— Any specific uses for which regulatory clearance has been granted or professional medical society guidelines exist (country- or region-specific).

— The typical range of StO_2 values expected in healthy subjects for a specific *manufacturer's cerebral tissue oximeter*. This information is requested in acknowledgement of the situation where occasional users of the technology encounter different *manufacturers' cerebral tissue oximeters* in clinical practice but cannot be aware of the known bias, which has been found in clinical studies comparing different *manufacturers' cerebral tissue oximeters*.

— Appropriate placement of the *cerebral tissue oximeter probe* on the upper forehead to avoid as far as possible the presence of air sinuses, sagittal sinus, birthmarks, hair, or tattoos beneath the *probe*.

This document allows two methodologies for *the* assessment of *accuracy* performance of *cerebral tissue oximeters*, namely desaturation measurements on *tissue haemoglobin phantoms* (in vitro, see Annex DD) and controlled desaturation studies on healthy adult subjects (in vivo, see Annex EE). The latter rely on taking arterial and jugular venous blood samples and determining SaO_2 and $SjvO_2$ by means of a *CO-oximeter*. *Accuracy* performance *verification* against a *cerebral tissue oximeter* (StO_2) instead of a *CO-oximeter* (SaO_2 and $SjvO_2$) during spontaneous and possibly pathological variation of StO_2 is theoretically possible. For certain *patient* groups and certain populations (e.g. children) non-invasive and non-interventionist methods can provide more applicable results than *verification* based upon healthy adult subjects and are much less constrained by ethical concerns than a *controlled desaturation study*. As of this writing, no standard *procedures* for such experiments have been proposed to address *accuracy*; such studies can be of value to demonstrate the similarity of *cerebral tissue oximeters*. Such studies can also demonstrate the plausibility of the direction and magnitude of changes in StO_2 given changes in other physiological variables or in *patient* state.

The methods for performance assessment described in this document do not allow the selectivity with which the measurement of a given *cerebral tissue oximeter* records StO_2 from the brain to be evaluated. This selectivity depends, among other factors, on the source-detector separation, the extracerebral tissue thickness and the algorithm implemented in the device. From a clinical perspective, the following example of a physiological plausibility test of responsiveness to a modulation of the blood flow in the brain was suggested. A stimulus known to change cerebral blood flow to a certain degree (i.e. a 15 %

change in $EtCO_2$ [from hyper- to hypo-ventilation around a normal baseline of 40 mmHg]) should be reflected by parallel changes in (cerebral) StO_2. The degree to which extent StO_2 changes upon this stimulus might be determined from reference oximeters.

AA.2 Rationale for particular clauses and subclauses

Subclause 201.1 — Scope

Equipment used in research applications is often experimental or intended primarily for non-medical uses. Imposition of the requirements of this document on equipment used for research might unduly limit development of beneficial new techniques or equipment.

Subclause 201.3.218 — *Remanufacturing*

The term *remanufacturing* was chosen, instead of terms such as reprocessing or refurbishing, because the committees were looking for the widest possible term. Any activity, outside the instructions given by the *manufacturer*, for subsequent reuse is considered *remanufacturing*. This includes cleaning and reuse of a single use *cerebral tissue oximeter probe*, as well as taking a used single use *cerebral tissue oximeter probe* as the raw material for a *remanufacturing process* to create a "new" *cerebral tissue oximeter probe* for use. The term reprocessing is a deprecated term for this definition.

Subclause 201.4.3.101 – Additional requirements for *essential performance*

Sufficient *accuracies* of StO_2 are necessary for *cerebral tissue oximeter equipment* to be suitable for its intended purpose and are required to prevent adverse *patient* events, as is expected by the *essential principles of safety and performance*. When limit *alarm conditions* are provided, *operators* rely on the proper operation of limit *alarm conditions* to alert them to take appropriate actions based on the condition of the *patient*.

Cerebral tissue oximeter equipment is expected to maintain these capabilities or indicate to the *operator* that it cannot perform these tasks. The general standard requires that the *risk* associated with loss or degradation of *essential performance* be reduced to acceptable levels in both *normal condition* and *single fault condition*. This includes any failure, e.g. of any component or power source. This document identifies some specific *risk control* measures that address this issue, but in general it is the responsibility of the *manufacturer* to ensure adequate *risk control* measures in *single fault condition*. The most common *risk control* measure for the *risk* associated with loss or degradation of *essential performance* is to generate an *alarm condition*, which also includes *alarm conditions* not specified by this document, to notify the *operator* that the expected *essential performance* might not be maintained. See 4.3 and 4.7 of the general standard.

Subclause 201.7.9.3.1.101 — Additional general requirements

The appropriate application of *functional testers* has been misunderstood by some *operators* or *responsible organizations*. See Annex FF for a discussion of this issue.

Subclause 201.11.6.5.101 — Additional requirements for ingress of water or particulate matter into the *ME equipment* or *ME system*

Fluids commonly found in the care environment include saline, blood and body fluids. Maintaining *basic safety* and *essential performance* following reasonably foreseeable encounters with fluids protects *operators* and *patients* from unacceptable *risks*.

Subclause 201.12.1.101 — *StO_2 accuracy* of *cerebral tissue oximeter equipment*

StO_2 accuracy is affected by the combination of the *cerebral tissue oximeter monitor*, any cable, the *cerebral tissue oximeter probe* and human tissue.

Subclause 201.12.1.101.1 — Specification

There was considerable discussion about the minimum acceptable *StO_2 accuracy* specification of *cerebral tissue oximeter equipment*. Ideally, *cerebral tissue oximeter equipment* would deliver high *StO_2 accuracy* (<4 %) with all *cerebral tissue oximeter probes* and application sites. However, due to well-known limitations in current cerebral tissue oximetry technology and the uncertainty inherent in the reference measurements, that level of *StO_2 accuracy* is not routinely achievable[31].

Therefore, the committees had to consider the following question: "What is the minimum acceptable *StO_2 accuracy* for safe and effective use of *cerebral tissue oximeter equipment*?"

Due to the diverse applications of *cerebral tissue oximeter equipment*, minimum performance requirements are not universal. Two general categories of use can be described as monitoring and diagnosis.

— Monitoring utilizes temporal changes in *StO_2*, e.g., through *alarm limits* for *StO_2* or trends in *StO_2*.

— Diagnosis — or diagnostic use — can be defined as measurement of *StO_2* as an estimate of *functional oxygen saturation* of haemoglobin under the probe to facilitate diagnosis or guide therapy.

Regardless of the specified *StO_2 accuracy*, arterial and jugular bulb venous blood samples can still be needed.

Based on clinical experience and the historical use of *cerebral tissue oximeter equipment*, *StO_2 accuracy* better (numerically less) than 10 % is acceptable for many monitoring applications. Clinicians on the committees expressed concern that *cerebral tissue oximeter equipment* specified with *StO_2 accuracy* in excess of 10,0 % at 1 standard deviation (20,0 % at 2 standard deviations) might lead to mistreatment in clinical practice. Even though better (numerically lower) *StO_2 accuracy* is usually more desirable, and frequently attainable, this figure represents a clinically acceptable trade-off.

The committees agreed that it is important to provide a uniform basis for comparing different *cerebral tissue oximeter equipment.* After reviewing the *controlled desaturation study* results[31], the minimum *declared range* was put at 50 % to 85 % *SaO_2* since the data for a human *controlled desaturation study* from 70 % to 100 % *SaO_2* will give an approximately equal density of measurements across this range. Outside of this range the density of data decreases significantly.

For some clinical applications, trend performance can be insufficient. For emergency care, and whenever the first *cerebral tissue oxygenation* reading is obtained in a diseased state, the value that is obtained needs to be trustworthy and *operators* need to be able to interpret this value in a context of 'normality' and of *risk* of brain injury or neurological damage. In some clinical applications, this is not necessary. For cerebral monitoring during elective anaesthesia and surgery, and whenever the probe is placed at a time when the *patient* is in their normal state, any subsequent change of value needs to be trustworthy (i.e. trend accuracy is necessary) and the *operator* needs to be able to interpret this change in a context of 'normality' and of *risk* of brain injury or neurological damage. For prediction of brain injury and neurological damage either clinical studies that relate values of *cerebral tissue oxygenation* in relevant *patients* directly to those pathologies, or a broader pathophysiological framework including animal research with direct measures of tissue oxygenation can be used.

Subclause 201.12.1.101.2 — Data collection for determination of *StO_2 accuracy*

Both the in-vivo and in-vitro *accuracy verification* methods proposed for inclusion in this document are imperfect. In-vitro (phantom) testing is a laboratory approach that provides high quality *StO_2* referencing, enables testing over physiological ranges that would be unethical in human studies, and enables evaluation of biological variables (e.g. *ctHb*, thickness of extracerebral layers) to estimate inter-*patient* variations in a controlled manner. However, phantoms are simplified models that lack many biological details and, at present, only simulate the most basic aspects of human anatomy.

The in-vivo *controlled desaturation study* captures inter-subject variability, but is limited to healthy adult volunteers, is restricted to narrow *ctHb* and *StO_2* ranges, cannot identify interference from extracerebral tissues, and a gold standard reference for *StO_2* is not available. Convenience sampling of arterial and venous blood specimens from infants and children can complement the results of a *controlled desaturation study* but lack the distribution range of *ctHb* and reference for *StO_2* values. Users should be aware of these differences in the *verification* of *cerebral tissue oximeter accuracy* performance. A comparison of the two assessment methods is provided in Annex II. See 201.7.9.2.1.101 i) and j).

During a *controlled desaturation study*, it is often difficult to achieve a target *Sav*O_2, particularly at the lower end of the *SavO_2* range. Attempts should be made at least to achieve a measured *Sav*O_2 within 3 % *StO_2* of the stated range of *StO_2 accuracy*, the sample size should be statistically justified with at least 200 data points[75]. The *StO_2 accuracy* of *cerebral tissue oximeter equipment* depends strongly on the optical interaction of the *cerebral tissue oximeter probe's* emitted and collected light with the *patient's* blood-perfused tissues. The correlation of the measured change in light transmission through blood-perfused tissues and the underlying tissue oxygenation depends, among other things, on the spectral content of the *cerebral tissue oximeter probe's* emitted light and on the interaction between the *cerebral tissue oximeter probe* optics and the skin surface. Since these complex wavelength-dependent interactions are not assessed nor reproduced by *cerebral tissue oximeter equipment functional testers* and simulators, such equipment does not currently characterize or validate the *accuracy* of the *cerebral tissue oximeter probe/cerebral tissue oximeter monitor* combinations. *Functional testers* can be used to confirm the *basic safety* and *essential performance* of *cerebral tissue oximeter monitors* and *cerebral tissue oximeter probes*. (See also Annex FF.)

Over the last 30 years, public and private laboratories have conducted hypoxia studies on more than 10 000 subjects with zero serious adverse events from either the hypoxia *procedure* or the arterial lines. Based on these data, the *risk* of even minor adverse events is less than 0,03 %. Data from these hypoxia laboratories corroborate this information. Studies measuring cerebral venous blood from the jugular bulb showed no abnormally low brain saturations[52]; studies evaluating neurologic function during hypoxia using pupillary dilation and visual tracking demonstrated the absence of any neurologic dysfunction[30]. Many of the healthy adult volunteer subjects (physicians, scientists, etc.) in the above hypoxia studies returned over a period of several years to take part in these studies with follow-up medical evaluations, all of whom report normal function in their occupation with no limitations.

Based on evidence presented and discussed at its meetings, the committees felt that more detail in the recommended methods (EE2.3) regarding use of hypoxia and arterial/venous lines in healthy adult volunteers will support continued safety. These are:

a) Time in low *SaO_2* saturation plateaus (i.e., 60 % - 70 %, 70 % - 80 %, and 80 % - 90 %) should be limited to the minimum amount of time required to obtain stable test/reference data as tolerated by the subject. The committees recommend that saturation plateaus be limited in duration, as indicated in (EE.2.3.3, i)).

b) Inclusion: Age 18 y to 50 y, ASA category 1 and positive Allen's Test.

c) Exclusion: pregnancy.

d) Monitoring and observation with arterial pressure, ECG, heart rate, $EtCO_2$, respiratory rate and FiO_2[30].

e) Arterial and venous lines should be placed by a clinician using jurisdictional guidelines for blood vessel puncture.

f) Aftercare should include 5 min to 15 min pressure, pressure bandage >1 h, instructions for limited activity and Principal Investigator's contact information.

The References [30] [31] and experience of laboratories that have done tissue oximetry performance assessment studies shows that the *risks* inherent in a controlled hypoxia study and arterial and jugular venous catheter placement in healthy adult volunteers can be mitigated to a safe level[30][78].

Subclause 201.12.1.101.3 — Data analysis for determination of *StO_2 accuracy*

CO-oximeters have an inherent uncertainty that will influence *StO_2 accuracy* assessment[46]. To reduce *cerebral tissue oximeter equipment* uncertainty, the uncertainty of the reference *CO-oximeter's* measurement of SaO_2 and $SjvO_2$ needs to be controlled.

The committees are not aware of a practical or traceable *procedure* that allows a *manufacturer* or *responsible organization* to confirm the SO_2 accuracy of a *CO-oximeter*. To minimize the influence of the *CO-oximeter* uncertainty in the A_{rms} measurement, careful attention should be paid to ensure that the *CO-oximeter* is performing within its specified performance capability. *Verification* of correct operation by use of the *CO-oximeter manufacturer's* recommended maintenance *procedures* is necessary, but is not sufficient to ensure a traceable, accurate measurement. Further quality assurance *procedures* for the *verification* of *CO-oximeter accuracy* are needed.

NOTE Sources of quality assurance *procedures* can be found in References [7] and [14].

Subclause 201.12.4.101 — *Data update period*

Cerebral tissue oximeter equipment is required to provide an indication that the displayed *StO_2* value is not current if the *data update period* of *StO_2* exceeds 30 s. Subclause 201.7.9.2.1.101 includes a requirement to disclose the *data update period* in the *accompanying documents*. However, there is no requirement that limits the duration of the *data update period*. The additional requirement that "there shall be an indication that the displayed value is not current" was added by the committees based on potentially significant delays that can occur between an event that activates an *alarm condition* (such as *patient* desaturation), and the actual generation of the *alarm signals*. The displayed *StO_2* value does not reflect changes in the measured *StO_2* value until completion of each update period. If an event that activates an *alarm condition*, such as *patient* desaturation, occurs just after the display is updated, a significant delay could occur between the event and the generation of the *alarm signals*. This could create a *hazardous situation* for the *patient* if the *data update period* is long.

To mitigate this potentially *hazardous situation*, the committees believe it is important for the *cerebral tissue oximeter equipment* to provide an indication to the *operator* when the displayed *StO_2* value has not been updated in the last 30 s and as such, can be invalid. This provides the *operator* timely information to assess the *patient's* condition and take appropriate action, if necessary.

Subclause 201.12.4.102 — Signal inadequacy

Clinicians assume that StO_2 *accuracy* degrades under various physiological (e.g. anaemia, tissue oedema) and environmental conditions, and they wish to see an indicator of performance degradation.

In fact, many factors contribute to degradation of signal adequacy with potential loss of *accuracy*. Changes can be sensitive to noise and changes in signal strength. These factors can include, but are not limited to: signal strength, noise frequency and amplitude, ambient light intensity, probe positioning and alignment.

Ideally, it would be beneficial to provide a means for assessment of signal adequacy as it relates to general performance, including confidence in measurement *accuracy*. This could best be accomplished by a comprehensive real-time assessment of signal adequacy and a visual indication of said status.

Subclause 201.15.3.5.101 — Additional requirements for rough handling

ME equipment, including *cerebral tissue oximeter equipment,* in *normal use,* used for professional transport of a *patient* outside a professional healthcare facility will be subjected to these mechanical stresses (e.g. vibration, shock, bump, and drop) and could randomly be subjected to additional stresses. Therefore, *ME equipment* intended to be used for professional transport of a *patient* outside a professional healthcare facility needs to be robust enough to withstand the mechanical strength testing described by IEC 60721-3-7, class 7M3[15]. IEC 60721-3-7 indicates that in addition to the conditions covered by class 7M2, class 7M3 applies to use at and direct transfer between locations with significant vibrations, or with high-level shocks. Rough handling and transfer of *ME equipment* is expected in these environments.

There are no established generalized test programmes that exactly reproduce the variety of vibration and shock conditions that *ME equipment* can meet when installed in a range of land vehicles and aircraft. Therefore, the dynamic tests specified in this subclause have been chosen because *ME equipment* tested to these levels are likely to withstand the dynamic disturbances routinely seen during use in the range of vehicles and aircraft (including helicopters) likely to be used to transport *patients*.

The use of *ME equipment* in road ambulances, fixed-wing and rotary wing aircraft, naval vessels, etc. can require additional tests and *verification* of safety when used in these different environments.

For free-fall testing described in IEC 60068-2-31, the committees used the rationale for the various levels to gauge the severity of the test based on Table AA.1. The category of the test level chosen for *portable ME equipment* was *portable* cases. The committees agreed that *cerebral tissue oximeter equipment* should be required to meet a level of drop testing for the professional transport environment. The committees also agreed that much *cerebral tissue oximeter equipment* can be supplied with a protective or carrying case for use in transport environments. The committees agreed that it would be an adequate test for *portable ME equipment* to be dropped while in their carrying cases, as this would be most like the real-world environment. For *mobile ME equipment*, a less severe level was chosen since wheeled *ME equipment* is typically heavier.

Table AA.1—Qualitative assessment of *cerebral tissue oximeter equipment* shock and vibration environment

***ME equipment* category**	**Location**											
	Standard environments						**Transport vehicles**					
	Home			**Healthcare facility**			**Wheels**			**Wings/Rotary**		
Mobile	D1	S1	V1	D1	S2	V1	D1	S3	V2	D1	S3	V3
Portable	D1	S2	V0	D1	S2	V1	D1	S3	V2	D1	S3	V3
Hand-held	D3	S1	V0	D3	S2	V1	D3	S3	V2	D3	S3	V3
Stationary	None			None			Not applicable					

S: shock

V: vibration

D: drop

Rating: 0 = no test, 1 = least severe or 7M1[a]; 2 = moderate severity or 7M2; 3 = most severe or 7M3

[a] The 7Mx designations are defined in IEC 60721-3-7:2002[15]

Confirming that the *ME equipment* is functioning within the *manufacturer's* specifications while the vibration (random and sinusoidal) tests are being conducted was not believed necessary. This line of thought was considered, and it was decided that the test done in this manner would be overly burdensome and would only add a minimum additional level of safety to the *ME equipment* that would not outweigh the costs. Confirming proper functioning after completion of the tests is believed adequate.

Subclause 201.15.3.5.101.1 — Shock and vibration

ME equipment, including *cerebral tissue oximeter equipment*, in *normal use*, used within a professional healthcare facility will be subjected to these mechanical stresses (e.g. vibration, shock) and could randomly be subjected to additional stresses. Therefore, *ME equipment* intended to be used in the professional healthcare facility needs to be robust enough to withstand the vibration and shock testing described by IEC 60721-3-7 level 7M2[15]. IEC 60721-3-7 indicates that this class applies to use at, and direct transfer between, locations with only low-level vibrations, or with medium-level shocks. Careful handling and transfer of products is expected in these environments.

Subclause 201.101 — *Cerebral tissue oximeter probes* and *probe cable extenders*

Cerebral tissue oximeter probes and *probe cable extenders* are as important in establishing the safety and *accuracy* of the complete *cerebral tissue oximeter equipment* as is the *cerebral tissue oximeter monitor* itself. 201.101 establishes that the *manufacturer* of the *cerebral tissue oximeter probe* or *probe cable extender* (including a *manufacturer* of a *remanufactured cerebral tissue oximeter probe* or *probe cable extender*) is responsible for the separately testable properties (e.g. biocompatibility) of their components as well as for the affected combined properties. This *manufacturer* is responsible for testing the affected combined properties for their *cerebral tissue oximeter probe* or *probe cable extender* when used with any *cerebral tissue oximeter equipment* they have specified as compatible. The affected combined properties include at least *accuracy*, electromagnetic compatibility (EMC), electrical safety, and protection against excessive temperature at the *cerebral tissue oximeter probe*-tissue interface. As an example of a possible effect of *processing* on biocompatibility, some surface-cleaning agents can result in impregnation of the material with solvent that, if not sufficiently removed by subsequent *processing*, can cause a chemical burn when that *process* is not described (and therefore validated) in the *accompanying documents*.

Subclause 201.102.2 — Connection to an electronic health record or *integrated clinical environment*

The Society for Technology in Anesthesia (STA) proposed the following horizontal guidance:

A medical device electronic data interface (EDI) shall be capable of communicating the following.

— Medical device identification data including *manufacturer*, model number, serial number and software/firmware version number.

— All data available for display to the *operator*, including numeric values, waveforms and *alarm conditions*.

— The mode of operation and the state of *operator*-configurable equipment settings (e.g. signal filters, signal averaging time, *alarm limits*).

— Medical device clock time and last clock time update, time zone.

— *Patient* ID if stored in the medical device.

This document applies these general requirements to *cerebral tissue oximeter equipment*.

Cerebral tissue oximeter equipment should be equipped with a *functional connection* that permits integration into an *integrated clinical environment*. If the *cerebral tissue oximeter equipment* is equipped with data transmission, Annex HH contains requirements regarding the data transmission.

The transmission of *cerebral tissue oximeter equipment* data to other *ME equipment*, *ME systems* or health software systems for purposes including decision support, control and data logging is problematic due to the use of proprietary interfaces and protocols. It is the intent of this document, as a safety and performance standard, to define a minimum set of measured parameters, equipment identification parameters and equipment settings that should be available for transmission if the *cerebral tissue oximeter equipment's* external data interface is intended to be incorporated into an *integrated clinical environment* (ICE). The standardization of a minimum set of parameters and settings allows greater interoperability between *cerebral tissue oximeter equipment* and *ME systems*, thus enabling new applications and paradigms that can increase *patient* safety and improve *patient* care such as part of an infusion delivery system.

It is not intended to define a specific device information model for *cerebral tissue oximeter equipment* communication. The ISO/IEEE 11073 series[16] defines one such model and includes for specific equipment such as *pulse oximeter equipment*, a device specialization document (ISO/IEEE 11073-10404). Another approach divides the healthcare space into domains. One such domain, the IHE *Patient* Care Device (PCD)[3] domain through the use of existing documents such as HL7®[4] and clinical language vocabularies such as LOINC®[5][6], is described as providing a framework for integrating medical devices into the healthcare enterprise. AAMI 2700-1:2019 on the *integrated clinical environment* (ICE)

[3] IHE – Integrating the Healthcare Enterprise, available at https://www.ihe.net/*Patient*_Care_Devices/

[4] HL7® is a trademark of Health Level Seven International. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO.

[5] LOINC® is the registered trademark of Regenstrief Institute, Inc. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO.

[6] Logical Observation Identifiers Names and Codes, https://loinc.org/

describes the need for an "ICE" model to take into consideration interactions with the connected *ME equipment*, workflow and *patient* state to support the coordinated use of medical devices for improved *patient* safety.

Cerebral tissue oximeter equipment in clinical use has provided parameters, identification data and settings through the *functional connection.* However, these data have been transmitted primarily using proprietary interfaces and protocols. To help foster interoperability of *cerebral tissue oximeter equipment* in the medical device ecosystem, increased standardization of this interface is desirable. This document has sought logically to categorize the data that can be transmitted or received as parameters, identification data, settings data, configuration data, specification data, service monitoring data and *alarm system*-related data. In addition to these categories and types of data, *manufacturers* are encouraged to leverage the *functional connection* to allow the *cerebral tissue oximeter equipment* greater capabilities, including the use of intelligent algorithms that can reside in the *cerebral tissue oximeter equipment* and which can adjust their algorithm or display settings based upon information received externally. This includes, for example, location, status and data from other sensors.

With the proliferation of *cerebral tissue oximeter equipment* with varying performance and features, it is becoming increasing important for clinical care to determine the *cerebral tissue oximeter equipment's* suitability for a particular clinical application. At the present time, this is solely determined by caregivers based on their knowledge of the equipment and requirements of the application. Given that the requirements for an application such as closed-loop control (whether it be autonomous or with a clinician providing the titration) depend on *cerebral tissue oximeter equipment* specifics such as averaging time, *accuracy* of attached *cerebral tissue oximeter probe*, time response and delays in the *cerebral tissue oximeter equipment*, the determination of applicability of the *cerebral tissue oximeter equipment* can be challenging for the average caregiver. However, if the *cerebral tissue oximeter equipment* provides this information through the *functional connection,* the determination of applicability can be made by querying the equipment settings, configuration and specifications.

Subclause 208.6.1.2.101 — Additional requirements for *alarm condition* priority

The committee members and their advisors had discussions as to just what were the circumstances in which low StO_2 do not require *physiological alarm conditions* at all. The committees agreed that *operators* and *responsible organizations* should know when they require a *cerebral tissue oximeter monitor* to have *physiological alarm conditions*, so that a useful contribution of this document would be to ensure that *cerebral tissue oximeter monitors* having no *physiological alarm conditions* are labelled appropriately (see 201.7.2.101 and 201.7.9.2.1.101 f)), and that if such *alarm conditions* are included, there is an *alarm condition* for the parameter that is usually most important, i.e. low StO_2.

Some *cerebral tissue oximeter monitors* can have *technical alarm conditions* for *cerebral tissue oximeter equipment*-related variables, such as low battery, but no *physiological alarm conditions*. Such *cerebral tissue oximeter monitors* are not required to have a low StO_2 level *alarm condition*.

Subclause 208.6.5.4.101 – Additional requirements for *default alarm preset*

There is an unacceptably low StO_2 for most clinical situations where a low *alarm limit* should be set; however, lower *alarm limits* can be desirable in particular clinical conditions[54][55]. The *operator* is permitted to set lower *alarm limits* during *normal use*.

The committees recognize that there are competing clinical requirements when selecting the lower *alarm limit*. One requirement was that *cerebral tissue oximeter equipment* should act as an early indicator of distress in a *patient* with relatively normal oxygenation. The second requirement is to avoid frequent *alarm signals* not necessarily requiring clinical intervention, which might "desensitize" caregivers to *alarm signals* (i.e., cause 'alarm fatigue'). In this case, one might argue for a default *alarm*

limit low enough to guarantee that most *alarm conditions* would be meaningful by anyone's measure. It was recognized that in both clinical situations, many, if not most, *operators* were likely to rely on the default low StO_2 *alarm limit*.

Another factor that the committees considered is that many examples of *cerebral tissue oximeter equipment* intended for continuous monitoring allow *responsible organization*-configured or *operator*-configured default *alarm limits* and that for specific monitoring settings, default *alarm limits* that were more closely tailored to the needs of the *patient* and *operator* in that the setting could be selected.

Annex BB
(informative)

Skin temperature at the *cerebral tissue oximeter probe*

BB.1 Surface temperature limits

A literature review relating to temperature requirements leads to the conclusion that it is appropriate and conservative to retain the 41 °C limit for infants (*patients* up to 1 year of age) and to apply the limits of 42 °C for 8 h and 43 °C for 4 h for older *patients*.

BB.2 Literature review

See ISO/IEC 80601-2-61[3]. The committees feel the references related to pulse oximetry are applicable since both technologies use light-emitting equipment that can generate heat at the skin interface.

BB.3 Test methods

This document does not require a particular method of measuring the skin temperature beneath the *cerebral tissue oximeter probe*. There are many different widely known and accepted methods of measuring surface temperatures. Different *cerebral tissue oximeter probe manufacturers* have evolved their own methods of measuring temperature, using either human test subjects or thermo-mechanical simulators. It would be impractical today to find a single universally acceptable test method, and the excellent thermal safety record of pulse oximetry suggests that such a method is not necessary. *Cerebral tissue oximeter probe* designers who wish to take advantage of the higher temperatures should keep the following cautions in mind.

— Measurement tolerances are required to be evaluated carefully. The *manufacturer* should know the accuracy of temperature measurement when designing *cerebral tissue oximeter probes* for use at temperatures above 41 °C since a higher temperature reduces the margin of safety.

— Temperature sensors are required to be small enough so as not to distort the measurement. The largest temperature sensors that have been found acceptable have characteristic dimensions near 0,5 mm (e.g. the bead of a thermocouple welded from 0,25 mm wire). Often still smaller temperature sensors are used.

— The temperature sensor is required to not reduce the measured peak temperature by conducting a significant amount of heat away from the measurement region. Thus, it would usually be inappropriate to use the copper-constantan type T thermocouples that are common in medical investigation, since the high thermal conductivity of the copper wire could cause a falsely low temperature measurement.

— Experimental methods are required to be adequate to ensure that recommended temperature limits are met under “reasonable worst case” conditions. As an example, reasonable worst case for neonatal *cerebral tissue oximeter probes* might include the following conditions:

  — The light-emitting diodes (LEDs) in the *cerebral tissue oximeter probe* are driven at the maximum current which the *cerebral tissue oximeter monitor* is capable of providing during normal operation (this condition can occur when the *patient* has very dark skin).

  — An active heat source is in use to artificially raise the baby's temperature.

It is not the intention to require that every model of *cerebral tissue oximeter probe* be tested directly on "worst-case" *patients*. The *manufacturer* should select methods for evaluation of the thermal performance of the *cerebral tissue oximeter probe* that lead to confident prediction of thermal safety on such *patients*.

Annex CC
(informative)

Determination of *accuracy*

CC.1 General

This annex discusses both the formulas used to evaluate the quality of *cerebral tissue oximeter equipment* measurements, and the names that are assigned to those formulas. This information has been adopted and modified from ISO 80601-2-61:2017[3] (pulse oximeters) for use on *cerebral tissue oximeter equipment.*

It has been common for the StO_2 *accuracy* and StO_2 trend accuracy specifications of *cerebral tissue oximeter equipment* to be stated in terms such as "10,0 %, one standard deviation, respectively." In this document, the committees have chosen a different name for the recommended StO_2 *accuracy* measure, while retaining essentially the same formula (a value of n - 1 is replaced with n) that has been in common use. Definitions are recommended for *local bias*, *mean bias*, and *precision* that are consistent with common engineering usage, but slightly different from the meanings of these terms, as they have sometimes been used in the cerebral tissue oximetry literature. The reasons for these recommendations are explained in this annex.

CC.2 *Accuracy*, bias and *precision*

CC.2.1 Definitions from other standards

The terms accuracy, bias and precision have all been used in a variety of ways. The committees have chosen specific definitions that are consistent with the general definitions appearing in ISO 3534-2:2006[6]:

CC.2.1.1 Accuracy

The definition of accuracy from ISO 3534-2:2006 is: closeness of agreement between a test result or measurement result and the true value.

NOTE 1 In practice, the accepted reference value is substituted for the true value.

NOTE 2 The term "accuracy", when applied to a set of test or measurement results, involves a combination of random components and a common systematic error or bias component.

NOTE 3 Accuracy refers to a combination of trueness and precision.

CC.2.1.2 Bias

The definition of bias from ISO 3534-2:2006 is: difference between the expectation of a test result or measurement result and a true value.

NOTE 1 Bias is the total systematic error as contrasted to random error. There might be one or more systematic error components contributing to the bias. A larger systematic difference from the true value is reflected by a larger bias value.

NOTE 2 The bias of a measuring instrument is normally estimated by averaging the error of indication over an appropriate number of repeated measurements. The error of indication is the "indication of a measuring instrument minus a true value of the corresponding input quantity".

NOTE 3 In practice, the accepted reference value is substituted for the true value.

CC.2.1.3 Precision

The definition of precision from ISO 3534-2:2006 is: closeness of agreement between independent test/measurement results obtained under stipulated conditions.

NOTE 1 Precision depends only on the distribution of random errors and does not relate to the true value or the specified value.

NOTE 2 The measure of precision is usually expressed in terms of imprecision and computed as a standard deviation of the test results or measurement results. Less precision is reflected by a larger standard deviation.

NOTE 3 Quantitative measures of precision depend critically on the stipulated conditions. Repeatability conditions and reproducibility conditions are particular sets of extreme stipulated conditions.

CC.2.2 Effects of offset and linearity errors

The committees' choice of definitions was influenced by considering three synthesized data sets, which might have resulted from a *controlled desaturation study*, and can be referenced in ISO 80601-2-61:2017[3] (pulse oximeters) for an explanation of these effects of offset and linearity errors.

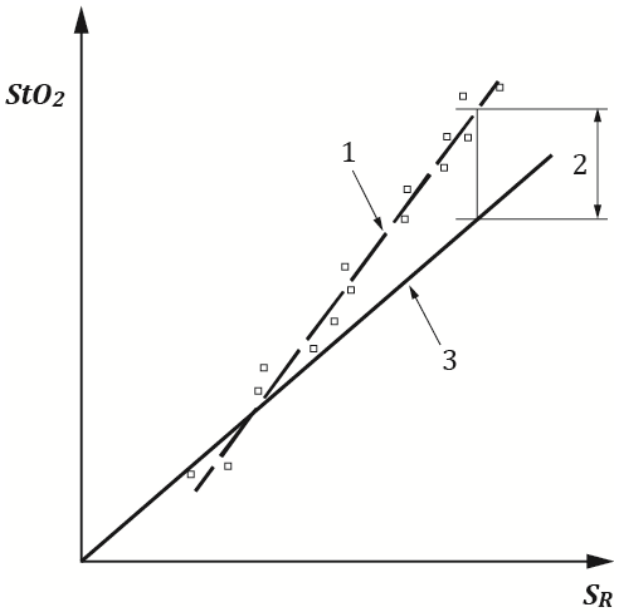
CC.2.3 Bias (see Figures CC.1 and CC.2)

Local bias (indicated here by *b*) at a given value of *x*, is the difference between the *y*-value of the regression line at that coordinate and the *y*-value of the line of identity, and is calculated by Formula (CC.1). See Figure CC.1.

$$b_i = StO2_{\text{fit},\,i} - S_{Ri} \quad \text{for} \quad i = 1 \ldots n \tag{CC.1}$$

Mean bias is a single number (indicated here by *B*), representing the whole data set. It is the mean difference of the test and reference values, preserving sign, and is calculated by Formula (CC.2). See Figure CC.2.

$$B = \frac{\sum_{i=1}^{n} (StO2_i - S_{Ri})}{n} \tag{CC.2}$$



Key

StO_2 oxygen saturation displayed by the *cerebral tissue oximeter*

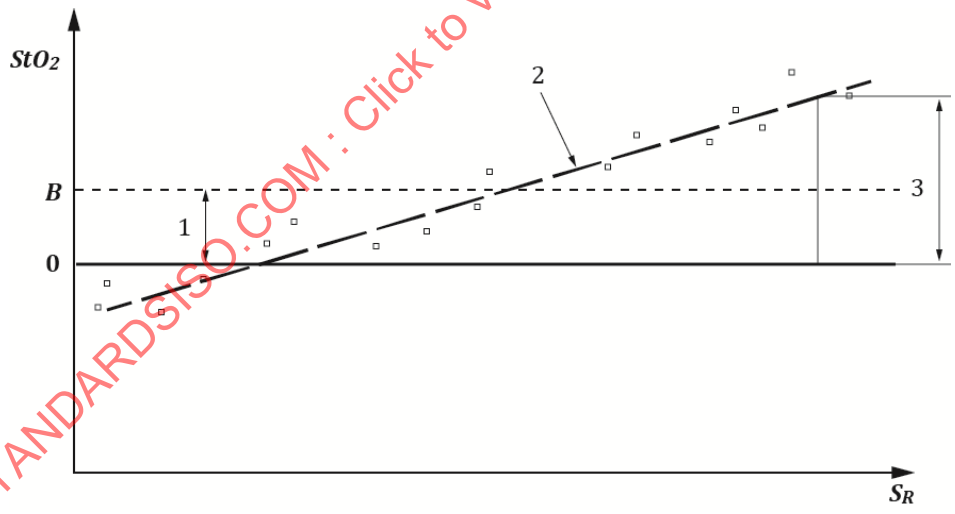
S_R reference oxygen saturation

1 regression line

2 *local bias*

3 line of identity

Figure CC.1 — Graphical representation for the definition of *local bias* (Test *probe* StO_2 as a function of reference S_R)



Key

StO_2 oxygen saturation displayed by the *cerebral tissue oximeter*

S_R reference oxygen saturation

1 *mean bias*

2 regression line

3 *local bias*

Figure CC.2 — Graphical representation for the definition of *local bias* and *mean bias* (Test *probe* StO_2 as a function of reference S_R)

When defined in this way, *mean bias* is, as it should be, the average of all *local bias* values, as shown in Formula CC.3.

$$B = \frac{\sum_{i=1}^{n} (StO_{2i} - S_{Ri})}{n} = \frac{\sum_{i=1}^{n} \left[(StO_{2i} - StO_{2fit,i}) + (StO_{2fit,i} - S_{Ri}) \right]}{n} = 0 + \frac{\sum_{i=1}^{n} b_i}{n} \quad \text{(CC.3)}$$

The zero term on the right-hand side results from the regression that defines StO_{2fit}, and the second term simply recognizes the definition of b_i in Formula CC.1.

CC.2.4 Precision

The committees support defining precision as the standard deviation of the residuals (s_{res}), given by Formula CC.4[29]:

$$s_{res} = \sqrt{\frac{\sum_{i=1}^{n} \left(StO_{2i} - StO_{2fit,i} \right)^2}{(n-2)}} \quad \text{(CC.4)}$$

where

n is the number of data pairs in the sample;

$StO_{2i} - StO_{2fit,i}$ is the difference between the i^{th} StO_2 datum and the value of the fitted curve corresponding to the i^{th} reference value, S_{Ri}.

s_{res} can intuitively be recognized as the scatter of data points about the best-fit calibration curve. It is a measure of the scatter to be expected in multiple measurements made with the same *cerebral tissue oximeter equipment* at a given oxygen saturation, taking into account both variations among *patients* and repeatability of the *ME equipment* electronics and software.

CC.2.5 *Accuracy*

As suggested by the definition that appears in ISO 3534-2:2006[6], the committees wish *accuracy* to represent a combination of the systematic and random components of error. The definition which has long been used by many *manufacturers* is the root-mean-square (rms) difference between measured values (StO_{2i}) and reference values (S_{Ri}), as given by Formula (CC.5):

$$A_{rms} = \sqrt{\frac{\sum_{i=1}^{n} (StO_{2i} - S_{Ri})^2}{n}} \quad \text{(CC.5)}$$

A_{rms} is a way of averaging the absolute values of errors over the *declared range(s)*.

NOTE The use of n in the denominator of the expression for A_{rms} rather than $n - 1$, which would be used if A_{rms} were a standard deviation. The difference in the numerical value is typically trivial. The appearance of $n - 1$ in the definition of standard deviation arises from the fact that only $n - 1$ of the samples that comprise the standard deviation can be freely chosen (statisticians say that there are "$n - 1$ degrees of freedom"). The nth sample is constrained in value because the definition of standard deviation includes the difference from a mean, implying that the nth sample is chosen so that the mean has the known value. There is no such constraint on the calculation of A_{rms}, because the expression does not include any predetermined parameter, such as a mean.

Understanding that A_{rms} is not a standard deviation is important in avoiding error in calculating oximeter *StO_2 accuracy*. If one were to create a spreadsheet column containing all the differences, $StO_{2i} - S_{Ri}$, and instruct the spreadsheet software to calculate the standard deviation of the data, the result would not be A_{rms} (in fact, as noted below, it would be P_s, a measure of precision[80]). Standard deviation, for any variable x, is indicated in Formula CC.6.

$$s_x = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n-1}} \tag{CC.6}$$

where $\bar{x}$ is the mean of all the values of x_i.

Comparing this to the expression for A_{rms}, one can see that in A_{rms} there is no subtraction of a mean value. A_{rms} does not measure scatter about a mean value. It measures the difference between test values and reference values. A_{rms} is affected both by random scatter and by *mean bias* and *local bias*.

CC.2.6 Analysis

The relationship between the definitions used above and the terms used by two respected sources that have been influential in the clinical literature of pulse oximetry is discussed. Bland and Altman[29] campaigned effectively against the misuse of correlation coefficients in comparing two methods of measurement and introduced a useful graphical method of examining the data from comparison experiments. Severinghaus *et al*.[80] introduced definitions of bias and *precision* that were based on the Bland and Altman method, and also defined the new term, ambiguity, as the sum of precision and bias.

In the following paragraphs, the same symbols B_s and P_s are used for the definitions of bias and *precision* that were used by Severinghaus. He defined bias as the mean difference of the test and reference values, preserving sign[80] as indicated in Formula CC.7:

$$B_S = \frac{\sum_{i=1}^{n}(StO_{2i} - S_{Ri})}{n} \tag{CC.7}$$

By no coincidence, this is identical to our definition of *mean bias*. We adopted Severinghaus' language for the definition, with the additional recognition that *cerebral tissue oximeter equipment* studies sometimes exhibit variation of bias with saturation, so that it is useful to distinguish between *local bias* and *mean bias*.

Severinghaus *et al*[79]. defined *precision* as the "standard deviation of the bias" Formula CC.8:

$$P_S = \sqrt{\frac{\sum_{i=1}^{n}(StO_{2i} - S_{Ri} - B_S)^2}{n-1}} \tag{CC.8}$$

This measure is different from our recommended definition of *precision*. One perspective is that P_S is the root-mean-square (rms) deviation of differences from *mean bias*, while s_{res} is the rms deviation of differences from *local bias*. Formula CC.8 is presented as it relates to the Bland and Altman plot in its measure of *precision* of the *mean bias* and has been historically included in published *cerebral tissue oximeter equipment* studies as "precision". The committees believe however, *precision* as defined in

Formula CC.4 remains accurate as defined for pulse oximetry. Clinical accuracy results can still be presented as widely accepted in terms of $B_s \pm P_s$ but the second term should be identified as "standard deviation of the bias" or "standard deviation of the error".

CC.2.7 Trend accuracy

There is no consensus on the definition of the term trend accuracy.

CC.2.8 Statistical Considerations

There is no gold standard for tissue oximetry. Any in-vivo calibration or *verification* depends on comparison to another imperfect measure of 'tissue oxygenation'. Tissue oxygenation is a 'latent' variable, i.e. a concept that can be meaningful, and clearly described in terms of predicted relationships to other physiological and pathophysiologic variables. To the degree that indirect and imperfect measures of tissue oxygenation have been proved to 'behave' as the latent variable should behave, these measures can be relevant in clinical monitoring.

In the situation of *verification* in the healthy adult during controlled hypoxaemia, the measurement of reference is a weighted average of the haemoglobin-oxygen saturation in blood drawn from an artery and from the superior jugular bulb and measured by CO-oximetry. While the uncertainty of the *CO-oximeter* is negligible in this context, and arterial oxygen saturation is a well-defined physiological quantity in normal healthy persons, jugular venous blood cannot accurately represent the local venous blood in the brain tissue that is 'seen' by the *probe*. Furthermore, the standard weighting factor of the relative contributions of arterial and venous blood to the tissue oxygenation signal (the a/v-ratio) can be dynamic.

In providing additional statistical assessment of *cerebral tissue oximeter accuracy,* the committees recommend the following points should be considered. Standard linear regression fit should be initially performed. Further analyses should take into consideration the longitudinal correlation of data within test subjects (repeated measurement data are not independent within test subjects) and error in the reference (independent) variable. However, the standard linear regression can be inappropriate on its own, as the unaccounted-for error in the independent variable will lead to a bias towards zero on the regression coefficient. It is recommended to consider error in variables analysis to account for this limitation.

Annex DD
(informative)

Characteristics of a *tissue haemoglobin phantom* for the *verification* of the *accuracy* of *cerebral tissue oximeter equipment*

DD.1 General

This annex is provided as a guideline for the construction and use of phantoms that can be applied by *manufacturers* to assess the performance and, in particular, the *verification* of StO_2 *accuracy* of *cerebral tissue oximeter equipment* in a standardized and reproducible manner. For a detailed comparison of in-vivo and phantom-based *verification* approaches see Annex II.

Haemoglobin-containing turbid phantoms have been used by a number of research laboratories for decades, to validate equipment and algorithms in diffuse optical spectroscopy, in particular in the context of tissue oximetry[45][54][58][60][85]. Such phantom measurements have also been part of evidence for regulatory considerations of *cerebral tissue oximeters* in Europe, Japan and the US. The main component of a *tissue haemoglobin phantom* is a turbid liquid that contains, in particular, erythrocytes and a scattering material. The level of haemoglobin oxygen saturation in the *tissue haemoglobin phantom*, $SphanO_2$, can be adjusted over a wide range, in principle from 0 to 100 %. Oxygen saturation and total concentration of haemoglobin in the phantom can be accurately known. Anyone who uses the recipe described in clause DD.2 can reproducibly build a *tissue haemoglobin phantom* with equal characteristics.

The *tissue haemoglobin phantom* is a simplified model of the human head in terms of diffuse light propagation which is governed by tissue geometry and the wavelength-dependent optical properties reduced scattering coefficient (μ_s'), absorption coefficient (μ_a), and refractive index (n).

a) Geometry: Two possible implementations of a homogenous semi-infinite *tissue haemoglobin phantom* are described in this Annex: one implementation with the *probe* of the *cerebral tissue oximeter equipment* immersed in the liquid, originally based on Reference [84], and a more recent and advanced implementation with a thin solid turbid interface layer between *probe* and liquid based on Reference [54]. The homogeneous phantom with or without a thin (i.e. 2,5 mm) superficial layer can be considered a reasonably adequate model for the head of very preterm neonates (gestational age <28 weeks). Applying such a homogeneous phantom for tests of *probes* for infants (extracerebral tissue thickness 4 mm to 10 mm) or adults (extracerebral tissue thickness 8 mm to 20 mm) can be regarded as a basic test, mimicking a situation where *total haemoglobin concentration* (related to relative blood volume) and oxygenation are the same in the cerebral and extracerebral compartments. This condition resembles the situation during *controlled desaturation studies*, where oxygenation of each tissue layer is changed synchronously. Current research towards more realistic phantoms with complex geometries that are not yet included in the proposed implementation is discussed in this Section further below.

b) Optical properties: The scattering coefficient and the *total haemoglobin concentration* of the homogeneous liquid can be adapted in a wide range to specific target values for the various *patient* populations.

Potentially, the phantom approach provides the flexibility to modify geometry and optical properties to optimally estimate performance for major *patient* groups, including neonates, children and adults, and high and low skin pigmentation. It would be desirable to build a model that simulates the layered tissue

structure and optical properties in the individual tissue compartments of the head with more detail. Such a model would enable assessment of the impact of the superficial compartment on measured signals attributed to the cerebral compartment — an issue that previous clinical studies have reported[38][81]. However, a model with oxygenation and concentration of haemoglobin changing separately in two or more compartments is a substantial technical challenge and presently the subject of active research studies. Additionally, there are many more degrees of freedom compared to a homogeneous phantom to adjust the properties of the individual layers. To date there is no adequate in-vivo database available regarding the details of the dependence of blood volume and oxygenation in the individual compartments (scalp, brain) during hypoxia. Nevertheless, a simple test case to help assess whether cerebral hypoxia is being missed would be brain at normal *ctHb* and low oxygenation, but skin at normal *ctHb* and normal oxygenation.

Meanwhile, the influence of superficial tissue compartments on the measurement of StO_2 has been investigated with hybrid solid-liquid phantoms. The impact of a superficial fat layer in the case of muscle oximetry was studied with a solid turbid interface layer of varying thickness between *probe* and liquid[67]. An advanced type of phantom for cerebral oximetry that relies on a 3D-printed cerebrovascular module with channels containing whole blood with tuneable oxygenation has several advantages over liquid phantoms[22]. This phantom has also been equipped with superficial layers, here mimicking skull/scalp and cerebrospinal fluid layer, and various commercial *cerebral tissue oximeters* and *probes* have been tested[22]. Such tests can provide valuable insights into the capability of a device to reach the brain through a certain thickness of extracerebral tissues. Both studies found, for some devices, a substantial decrease of sensitivity to changes in oxygenation in the lower liquid layer with increasing superficial thickness in the lower liquid layer. This finding is supported by simulations for a similar situation[73]. However, at the time of writing of this document, such types of hybrid phantoms cannot be recommended in general for *accuracy* determination due to the lack of a final, well-validated approach. The aforementioned two studies used carbon-based absorbers in the superficial layer which does not allow full haemoglobin (Hb) spectra to be mimicked in this layer. Ideally, the simulated optical property values should more accurately represent the oxygenation and *ctHb* of superficial perfused tissues.

Another element of more realistic phantoms is the impact of skin pigmentation, which has been shown to have an effect on measurements of some oximeters[31][35]. First tests of *cerebral tissue oximeters* have been reported with a thin pigmented superficial layer on a channel array *tissue haemoglobin phantom*[23]. Both the aforementioned clinical and phantom tests tend to show a negative bias in StO_2 for high pigmentation levels.

It should also be mentioned that valuable insights into the dependence of measurement results on various factors for complex geometries and sets of optical properties can be obtained efficiently from computer simulations of light propagation in tissue (e.g. Reference [78]). However, knowledge of the analysis algorithm of the particular *cerebral tissue oximeter equipment* under consideration is needed to convert the simulated light intensities into estimates of haemoglobin oxygenation and other parameters such as *total haemoglobin concentration*.

DD.2 Features of the *tissue haemoglobin phantom*

DD.2.1 General

Near infrared light emitted from the source of the *cerebral tissue oximeter probe* reaches the detector with its intensity reduced owing to scattering in the living tissue and absorption by haemoglobin and other chromophores such as water, cytochrome oxidase, fat, melanin and myoglobin (in muscles). The main functional component of the *tissue haemoglobin phantom* is a turbid liquid that simulates major characteristics of light scattering and absorption in the living tissue. It contains natural haemoglobin, for which the oxygen saturation can be controlled over a clinically relevant range.

DD.2.2 Safety precautions regarding blood or blood components

Personnel handling blood are at *risk* for occupational exposure to bloodborne pathogens, including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Personnel working with blood should follow simple rules to assure safety and minimize the *risk* of exposure to pathogens. Gloves, a lab coat, and safety glasses should be worn to prevent any contamination. When taking blood from a blood bag or any recipient, if syringes and needles are required, one should use blunt tip needles. This prevents *hazard* from sharp needles. Lastly, the clean and dirty (contaminated) areas in the lab should be kept separated and no equipment should be touched by gloves that have been in contact with blood. Regarding the disposal of the blood, a disinfectant such as "Trigene" or "Virkon" should be added to the waste blood for an appropriate time before pouring it to a drain. Moreover, all equipment needs to be thoroughly cleaned with a disinfectant and/or 70 % alcohol (usually industrial methylated spirit (IMS) or methanol). Finally, blood containers, gloves, tissues, or any material in contact with blood should be disposed of in dedicated clinical waste bags, apart from the needles and other sharp items which should be disposed of in sharps bins. For further information see regulations such as Human Tissue Act (UK, 2004), Bloodborne Pathogens Standard (29 CFR 1910.1030, Occupational Safety and Health Administration – OSHA, US), European Directive 2002/98/EC setting standards of quality and safety for the collection, testing, *processing*, storage and distribution of human blood and blood components (2003).

DD.2.3 Composition of the *tissue haemoglobin phantom* liquid

The turbid liquid of the *tissue haemoglobin phantom* consists of the following materials.

a) Haemoglobin component: Erythrocyte concentrate from a blood bank or blood taken from veins of healthy volunteers. The *total haemoglobin concentration* (in g/dl) in the blood or in the erythrocyte concentrate is measured before preparing the *tissue haemoglobin phantom* by means of a blood gas analyser which makes it possible to exactly determine the *total haemoglobin concentration* after dilution with scattering materials and physiological buffered saline as described below. The *total haemoglobin concentration* (in µmol/l, or µM) in the *tissue haemoglobin phantom* should match typical values for the target tissue type and *patient* population (e.g. neonates, children, adolescents, adults) under consideration for which a *cerebral tissue oximeter monitor-probe* combination is intended. To assess the capability of the *cerebral tissue oximeter* to measure accurately when this parameter varies, at least two different *total haemoglobin concentrations* (including a normal and a low value) should be used. If venous blood sampled from a healthy volunteer is used, care is needed to prevent clotting by using, e.g. a heparinized syringe.

   NOTE 1 Human blood is preferred. However, Zijlstra[91] states that animal blood, for example bovine blood or free haemoglobin solutions can be an alternative to human blood after proving that their absorption spectra in the relevant wavelength range match those of human erythrocytes sufficiently well. In case of blood of non-human species, the respective safety guidelines should be observed.

   NOTE 2 For target values of *ctHb* see Table DD.1.

   NOTE 3 The absorption of the *tissue haemoglobin phantom* as described here in the near-infrared spectral range is given primarily by the absorption of oxy- and deoxyhaemoglobin and of water.

b) Scattering component: Commercially available fat emulsions for intravenous nutrition based on soybean oil [87][66][44] to adjust the reduced scattering coefficient to be typical for the living tissue under consideration. As these emulsions are designed for intravenous use, they are designed to mix with blood. The relationship between the (wavelength-dependent) reduced scattering coefficient and concentration should be determined in advance for the particular fat emulsion chosen. Most

commonly, Intralipid®[7] is used[82]. Intralipid 20 % was shown to exhibit high stability over years when kept in the original closed containers and small batch-to-batch variations (observed deviations from average max. 2.2 %)[39]. The intrinsic reduced scattering coefficient of Intralipid 20 % was also determined in a multi-centre study with an uncertainty of about 2 % or better[82]. The wavelength dependence of scattering of Intralipid[39] and of the relevant tissues in adults[65] as well as neonates[25] is in reasonable agreement. Since there are reports about the degradation of Intralipid scattering when used in a *tissue haemoglobin phantom*, it is recommended to keep the total duration of an experiment below 2 h and to monitor periodically the stability of the scattering coefficient because of the propensity of lipid aggregation. A deviation in μ_s' of up to about 15 % can be tolerated[74].

NOTE 4 For target μ_s' values, see Table DD.1.

NOTE 5 Erythrocytes or whole blood provide a minor contribution to scattering.

c) Diluting agent: Physiological buffered saline for diluting the blood or erythrocyte concentrate to adjust the total *haemoglobin concentration* to a typical value for the living tissue under consideration and to maintain the stability of the erythrocytes[40]. Its osmotic pressure and pH have been so adjusted as to prevent haemolysis and to maintain a pH of ~7.4, respectively[40]. A pH range of 6.8<pH<8 of the phantom seems acceptable. Stricter criteria can apply in case the reference method is pH-dependent.

DD.2.4 Design of the *tissue haemoglobin phantom* setup

DD.2.4.1 Liquid-*probe* interface

The *tissue haemoglobin phantom* is based on a homogeneous liquid that resembles the in-vivo situation in terms of scattering, total Hb concentration and water content and the opportunity to vary oxygenation. The semi-infinite geometry (half-space with a flat air-tissue boundary) is adopted. Several technical solutions for the interface between the *probe* and liquid are feasible. In the preferred implementations, the *probe* is either immersed in the liquid[84][50][32] or attached to a thin turbid interface layer[54]. Usually source and detector are embedded in a flat black pad which is substantially larger than the source-detector separation. Then, it is irrelevant from point of view of light propagation whether there is air or liquid on the back (averted from tissue) of the *probe*, so the semi-infinite geometry is also valid in this case. If a material is used in between the *probe* and turbid liquid such as a wrap to avoid liquid ingress, it has to be checked that this material does not alter the reading of the *cerebral tissue oximeter* (e.g. due to a light-guiding effect). It has been shown that transparent adhesive membrane dressing is suitable. The most advanced technical solution of *probe* attachment uses windows in the container that are made of a turbid silicone layer with optical properties resembling those of neonatal skull[54]. From experiments in which the thickness of the first layer was varied[67], it can be inferred that the influence of a thin first layer (2,5 mm) is negligible.

DD.2.4.2 Container

The container should have black walls and the *probe* of the *cerebral tissue oximeter* under test should be placed far from any boundaries to avoid their influence on light propagation from the source to detector optodes. The container needs to be large enough to fulfil the following criterion: The distance between boundaries and source as well as between boundaries and detector should be greater than or equal to the largest source-detector separation that is realized in the *cerebral tissue oximeter probe* under test. This requirement applies to both lateral directions, while in depth direction the homogeneous liquid should extend to at least twice the source-detector separation.

[7] Intralipid® is a registered trademark of Fresenius Kabi AB. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named.

The temperature in the container should be kept at a constant level in the range (37 ± 2) °C. Temperature should be monitored at least at the beginning and end of each oxygenation-deoxygenation cycle. Temperature stabilization can be achieved by a heater plate in thermal contact with the liquid[54], a heating sheet wrapped around the container[56] or a water bath[84][71].

A magnetic stirrer ensures the homogeneity of the solution, in particular when changing oxygenation, as well as temperature homogeneity. The homogeneity of oxygenation should be tested by a pO_2 sensor or any other sensor measuring oxygenation locally in a volume <1 cm^3 that can be moved to various locations in all directions inside the liquid.

It is recommended that a lid be used to shield the liquid from ambient air. In this way, atmospheric oxygen exchange can be minimized and $SphanO_2$ values down to zero can be achieved. For maximum desaturation effect, it is advantageous to flush the space above the liquid with nitrogen immediately after reaching the high target $SphanO_2$.

DD.2.4.3 *Probe* arrangement

DD.2.4.3.1 Immersed *probe*

The *cerebral tissue oximeter probe* is held in the container so that its measuring side is in contact with the liquid and not faced to the wall of the container.

a) Precaution in the case of separated *probes*

Some of the *cerebral tissue oximeter probes* are separated into illuminating and receiving elements. These separated probes are properly unified with the holder when attached on the surface of the *patient*. Separated *probes* should be thus inserted into the *tissue haemoglobin phantom* in this unified state specified by the instructions for use of the *cerebral tissue oximeter*.

b) Waterproofing of the *probe* including *extension cable*

Some of the *cerebral tissue oximeter probes* consist of only optical components while others include electronics on the *probe*. The former can be inserted in the *tissue haemoglobin phantom* as they are, but the latter can be waterproofed if deemed necessary. Methods such as following have been used.

— Adhesive waterproof sheet: The *cerebral tissue oximeter probe* is covered with an adhesive waterproof sheet where needed. It should be confirmed in advance that there is no significant difference (compared with the range of data fluctuation) in the measurement data between when covered with sheet and not covered by using an appropriate method (e.g. measurement on a solid phantom).

— Waterproof jelly: The *cerebral tissue oximeter probe* is coated with waterproof jelly. It should be confirmed in advance that there is no significant difference in the measurement data between when coated with jelly and not coated by using an appropriate method (e.g. measurement on a solid phantom).

The direction from source to detector should be arranged horizontally to avoid the influence of a possible (vertical) oxygenation gradient in the liquid. The *tissue oximeter probe* and the reference probe should be mounted at the same vertical height (within about 1 cm).

DD.2.4.3.2 *Probe* attached to turbid window

All parts of the *probe* should be in tight contact with the turbid silicone window material which is achieved in the following way: The mount is spring-loaded or contains an elastic element (e.g. a layer of soft silicone), which is compressed during the mounting *process* and applies a gentle force on the *probe*

pointing towards the window boundary to avoid an air gap between the *probe* and window material. This is intensified by the fluid pressure bending the windows outwards in case they are made from elastic material (e.g. from turbid silicone) as well. The shape of the mounting element might have to be adapted to the rear shape of the source-detector pad to obtain a flat *probe*-window interface.

The direction from source to detector should be arranged horizontally to avoid the influence of a possible (vertical) oxygenation gradient in the liquid. The *tissue oximeter probe* and the reference probe should be mounted at the same vertical height (within about 1 cm).

DD.2.5 Methods to change oxygenation

The measurement is started at complete oxygenation, i.e. $SphanO_2$ = 100 %. The *verification* measurement, i.e. recording of oxygenation by the *cerebral tissue oximeter* to be *verified* and by the reference instrument is performed while slowly decreasing saturation. The control of oxygenation can be performed in different ways:

Oxygenation as well as deoxygenation of the phantom liquid can be induced by an extracorporeal membrane oxygenator (artificial lung)[50]. The *tissue haemoglobin phantom* is circulated with a pump between the container and an oxygenator. A mixture of O_2, N_2 and CO_2 (5 %) gases is delivered into the oxygenator. To change the $SphanO_2$ (i.e., haemoglobin oxygen saturation of *tissue haemoglobin phantom*), the ratio of O_2 and N_2 contents in a mixed gas is changed while keeping the CO_2 content nearly constant (5 %) to maintain pCO_2 of the *tissue haemoglobin phantom* around 40 mmHg which is a typical condition in living tissues. With this method, $SphanO_2$ can be changed precisely over a wide range. However, the equipment is expensive, and deoxygenation is rather slow.

If this option is chosen, special care has to be taken to ensure homogeneity of the *tissue haemoglobin phantom* liquid. The outlet tube of the artificial lung should be placed far away from the *cerebral tissue oximeter probe* and the reference instrument probe, in order to minimize the influence of the related local inhomogeneity. Homogeneity of the liquid should be *verified* in at least two states at which a gradient is most likely: (i) at high $SphanO_2$ = 100 %, within the first 5 minutes after having started the deoxygenation at the maximum intended deoxygenation speed and (ii) when the lower target $SphanO_2$ (see Table DD.1) is reached. The homogeneity test is to be performed with a pO_2 sensor or another instrument capable of determining small volume (<1 cm^3) differences in $SphanO_2$ in real time. The measurement locations should be representative of the volume probed by the *tissue oximeter* and by the reference instrument. The homogeneity test should be repeated as soon as the speed of stirring or other relevant parameters are changed.

Without use of an artificial lung, complete oxygenation can be achieved by exposing the liquid to ambient air or bubbling oxygen gas into the liquid. The latter option enables a much faster increase of $SphanO_2$. With the gas bubbling approach, it is advantageous to use a fine bubble diffuser to minimize the bubble size, haemolysis and mechanical stress to the components of the suspension.

Deoxygenation can be performed by bubbling nitrogen gas through the liquid[53][60] or adding yeast[84][48][60].

When bubbling nitrogen, the homogeneity of $SphanO_2$ should be *verified* by measurements at representative positions within the liquid, once per experiment, at high $SphanO_2$ where the gradient is expected to be highest. One needs to ensure that the measurement is not compromised by gas bubbles running through the volume sampled by the *cerebral tissue oximeter* under test as well as reference instrument probes, e.g. by repeatedly turning off the gas flow and observing changes in readings. Also, one needs to ensure that no gas bubbles adhere to the *probe*-liquid interface, by testing in clear liquid and, if necessary, wiping off bubbles from the interface before the measurement.

When yeast is used for deoxygenation, its respiration (i.e., metabolism) consumes oxygen thereby decreasing the oxygen concentration and thus *SphanO₂*. Yeast is a single-celled fungus that uses cellular respiration, which converts glucose and oxygen into carbon dioxide and adenosine triphosphate (ATP). Dry and fresh yeast are equally suitable. The method based on yeast is preferable because oxygen is extracted homogenously within the liquid, improving homogeneity of *SphanO₂*. Further advantages compared to deoxygenation by nitrogen gas are increased and adjustable speed of the experiments and improved phantom stability, in particular of the lipid component. A disadvantage of deoxygenation by yeast is that the liquid becomes acidic with time due to production and accumulation of CO_2. The drift towards acidity can be slowed down by adding more buffer (e.g. solution of sodium bicarbonate) to the liquid (see DD.3.2.2) but can still be an issue in case of a pH-sensitive reference method. It should be noted that deoxygenation by yeast is a continuous *process* that does not easily allow targeting of multiple plateau levels of *SphanO₂*. It should be ensured that the speed of deoxygenation is slow enough to enable the liquid to deoxygenate homogeneously and the recordings by the *cerebral tissue oximeter* and the reference equipment to be performed synchronously.

DD.2.6 Reference measurement for *SphanO₂*

Reference measurement values S_R of the Hb oxygen saturation of the *tissue haemoglobin phantom* can be obtained in different ways. However, at present none of the methods described below represents a gold standard without restrictions.

The most desirable method would be the use of a blood gas analyser[38][48] or *CO-oximeter*[50]. However, not all such equipment is capable of reliably measuring *SphanO₂* in the given liquid mixture with relatively low concentrations of haemoglobin and high turbidity compared to human whole blood.

Several alternative options that are based on diffuse optical spectroscopy exist. One option is visible light spectroscopy (VLS) at short source-detector separation that makes use of different distinct maxima in the absorption spectra of oxy- and deoxyhaemoglobin[26][48][54][68]. Several algorithms were compared in a phantom[69]. To date, there is no commercial VLS equipment available.

Another option is the use of frequency-domain or time-domain near infrared spectroscopy instrumentation that is capable of separating absorption and scattering. Hb concentrations and oxygenation can be derived from the absorption coefficients measured at various wavelengths. These methods have the additional advantage of allowing the reduced scattering coefficient to be monitored during the experiment as an indicator of stability of the scattering component.

In principle, *StO₂* of the *tissue haemoglobin phantom* can also be determined exploiting the haemoglobin-oxygen dissociation curve. *SphanO₂* can be calculated from the measured values of the partial O_2 pressure and pH of the *tissue haemoglobin phantom*[71][79][34]. There are even more sophisticated approaches to calculating *SphanO₂* from simultaneous measurements of pO_2, pH, pCO_2, temperature and concentration of 2,3-diphosphoglycerate (DPG)[37]. If any of the variables cannot be measured, a reasonable span of values should to be considered and justified. A technical problem can be the stability and *accuracy* of the probe readings under phantom conditions (e.g. due to proteins)[54]. It might be feasible to conduct intermittent measurements or continuous measurements with more suitable probes.

For any of the methods chosen, the uncertainty of the measured reference values should be estimated and disclosed.

DD.3 *Procedures* for *verification* of *cerebral tissue oximeter equipment* with the *tissue haemoglobin phantom*

DD.3.1 Purpose of the *verification*

The primary purpose of the *verification* of the *cerebral tissue oximeter equipment* with the *tissue haemoglobin phantom* is for the *verification* of the measurement *accuracy* of the *cerebral tissue oximeter equipment* regarding the measurand StO_2.

DD.3.2 Test *procedure* of the *verification*

The test measurement is performed while decreasing $SphanO_2$. The following steps of the test *procedure* refer to deoxygenation by yeast. If other means of deoxygenation are used (see DD.2.4), the *procedure* should be adapted accordingly.

a) The experiment is started with pre-tempered saline buffer solution in the container with temperature control and stirring.

b) Intralipid is added by a syringe.

c) Erythrocyte concentrate or blood is added.

d) The initial state with complete oxygenation ($SphanO_2$ of 100 %) is prepared by bubbling oxygen gas through the liquid for a period of a few minutes.

e) The measurement is started.

f) Yeast dissolved in a small quantity of saline buffer is added to the liquid. Respiration of yeast gradually reduces $SphanO_2$.

NOTE 1 Glucose solution with a relative concentration (mass ratio) of <1 % can be added to increase the speed of deoxygenation without increasing the amount of yeast. The limit of 1 % to set to avoid an influence on scattering and refractive index of the turbid liquid.

g) During the following desaturation, the oxygen saturation of the tissue haemoglobin phantom, $SphanO_2$, is measured simultaneously with the reference equipment ($SphanO_{2,ref}$) and with the *ME equipment* ($SphanO_2$). The measurements should either be performed continuously or intermittently in steps of 5 % or the maximum practically achievable rate, whichever is higher. $SphanO_2$ should be decreased to at least the lower limit of the *declared range* of *accuracy*.

NOTE 2 The phantom can allow $SphanO_2$ to decrease down to 20 % or lower.

The required accuracy of synchronization between both measurements (including sampling times and delays) depends on the speed of deoxygenation. The recommended duration of the desaturation phase is between 10 min and 30 min. It can be adjusted by the amount of yeast and glucose added.

h) When a plateau at the low saturation limit is reached, further cycles of oxygenation and deoxygenation can be performed, either repeating the measurement with the same phantom composition or increasing *ctHb* by adding further erythrocyte concentrate or blood. Repeat steps d) to g).

DD.4 Specifications of the *tissue haemoglobin phantom*

DD.4.1 Target parameters of the *tissue haemoglobin phantom*

Depending on the target population of the particular *probe* under test, different values of *ctHb* and μ_s' should be used in the *tissue haemoglobin phantom*. The performance of the *ME equipment* should be evaluated not only at normal, but also at low *ctHb* that can be present in critically ill *patients*.

The concentration of the components in Table DD.1 was defined based on the following considerations:

1) *Total haemoglobin concentration* of the *tissue haemoglobin phantom*: The measurement of cerebral blood volume (CBV) has been studied in the human brain tissue using near-infrared spectroscopy or positron emission tomography (PET). The values of CBV (blood volume per tissue mass) lie in the range of 2 to 5 ml/(100 g)[33], but lower values were also reported[51]. The *ctHb* can be inferred from these values and typical Hb concentrations in blood. Alternatively, literature data are available for *ctHb* derived from measurements of near-infrared absorption coefficients for neonates[51][42][25] and infants[72].

2) Scatterer concentrations of the *tissue haemoglobin phantom*: The reduced scattering coefficient of brain tissue in-vivo has been measured by time domain or frequency domain diffuse optical spectroscopy methods[51][85][25], for neonates[51][90][25] and adults[89][47][41].

NOTE The values given in Table DD.1 represent average values obtained from a comprehensive literature survey. The literature values are spread over a substantial range, e.g. extreme values of μ_s' for neonates of 2.3 and 12 cm^{-1} were found.

Table DD.1 — Target parameters of the *tissue haemoglobin phantom*

Property	Quantity	Unit	Target population	
			Neonates	Adults
Target *total haemoglobin concentration* (brain tissue)	*ctHb*	µM	25, 45, 70	50, 70
Target reduced scattering coefficient (brain tissue) at 800 nm	μ_s'	cm^{-1}	6	10
Target Hb oxygenation range	$SphanO_2$	%	20 to 95	20 to 95

To illustrate the practical implementation, two examples of *tissue haemoglobin phantoms* that have been employed to test and compare *tissue oximeter equipment* are presented. Note that the μ_s' and *ctHb* values realized in these previous implementations were not exactly the same as the values given in Table DD.1.

Phantom A, based on earlier work published in[84], was realized with a black cylindrical container in which the *probe* was immersed. For temperature control, the container was surrounded by a water bath. The *ctHb* and μ_s' values were chosen to represent typical values of adults, i.e. 70 µM and 11 cm^{-1} (at 800 nm), respectively. The liquid consisted of 1,81 l of saline buffer solution (PBS), 130 ml of Intralipid 20 %, and 60 ml of fresh human blood (Hb concentration 150 g/l). Oxygenation was achieved by O_2 bubbling, deoxygenation by adding 2,7 g of dry yeast. $SphanO_2$ varied from 95 % down to 40 %.

Phantom B[54] was realized with a dedicated 3D-printed container with 4 windows, a gas-tight lid and a bottom heater plate for temperature control. The μ_s' value was chosen to be typical of neonates, i.e. 5,5 cm^{-1}, while *ctHb* was varied to cover the range that occurs in *patients*, i.e. 25, 45 and 70 µM. The

liquid consisted of 2.5 l of saline buffer solution (PBS) and 15, 25, and 35 ml, respectively, of sodium bicarbonate buffer, 74 ml of Intralipid 20 %, and 20, 33,5 and 53,5 ml, respectively, of erythrocyte concentrate from a blood bank (Hb concentration 220 g/l). Oxygenation was achieved by O_2 bubbling, deoxygenation by adding 3 g of fresh yeast. *SphanO*$_2$ varied from approximately 100 % down to nearly 0 %.

DD.4.2 Properties of the *tissue haemoglobin phantom* to be disclosed

Apart from the target parameters chosen according to DD.4.1, the test results should be accompanied by the following disclosures:

— type and amount of haemoglobin component and its total Hb concentration;

— type and amount of scattering component;

— type and amount of diluting agent;

— other chemicals added;

— type of container;

— volume of liquid;

— *probe* arrangement (*probe*-liquid interface: immersed or turbid window);

— *probe*-liquid interface layer (thickness and optical properties);

— method of oxygenation;

— method of deoxygenation (in case of yeast: type and amount);

— reference method for determining *SphanO*$_2$.

Annex EE
(informative)

Guideline for evaluating and documenting *StO₂ accuracy* in human subjects

EE.1 General

This annex is provided as a guideline for evaluating and documenting the *StO₂ accuracy* of *cerebral tissue oximeter equipment*. The methods described in this annex are applicable to both new *cerebral tissue oximeter equipment* and modified *cerebral tissue oximeter equipment* or parts whenever human testing is performed.

201.12.1.101.2 requires that any human study conducted to evaluate the *StO₂ accuracy* of *cerebral tissue oximeter equipment* conforms with ISO 14155:2020. See discussion of safety aspects in Reference [30].

This annex describes testing methods for assessing the *StO₂ accuracy* of *cerebral tissue oximeter equipment*. It does not prescribe medical practice. Proper safety *procedures*, institutional review board (IRB), and ethics committee (EC) *processes* should be appropriately observed. All subjects should consent to participate in the study.

EE.2 *Procedure* for laboratory testing on healthy volunteers

EE.2.1 Purpose of a *controlled desaturation study*

The general purpose of a *controlled desaturation study* is for the *verification* of the *StO₂ accuracy* of *cerebral tissue oximeter equipment* in comparison to *SavO₂* values obtained on the basis of *functional oxygenation saturation* measurements *SaO₂* and *SjvO₂* by a *CO-oximeter*. This is achieved through paired observations of *StO₂* and *SavO₂* values over a specified range (e.g. 70 % to 100 % *SaO₂*) of the *cerebral tissue oximeter equipment* on a group of healthy adult volunteers. The fraction of inspired oxygen (FiO_2) delivered to test subjects is varied to achieve a series of targeted steady-state saturation periods. Arterial and jugular venous blood samples are periodically taken from indwelling arterial and jugular venous catheters for use in the comparison. Maintaining the subject in a normocarbic state (i.e., a partial pressure of CO_2 in arterial blood ($PaCO_2$) between 35 to 45mmHg, 4,7 to 6,0kPa) is important during the *controlled desaturation study* to reduce variability in the subject's cerebral blood flow. Continuous measurement of end-tidal carbon dioxide ($EtCO_2$) can help assess for a normocarbic state but *verification* that the $PaCO_2$ is within the normocarbic range should happen with each arterial blood specimen.

The method described below involves *procedures* that need to be supervised by qualified personnel. Subjects have an artery cannulated and jugular venous bulb catheter and then are exposed to inspired oxygen concentrations lower and higher than room air. Accordingly, this study method always requires protocol approval by an IRB or EC, including informed consent of the subjects.

EE.2.2 Scope of a *controlled desaturation study*

This *controlled desaturation study* method is used for the *verification* of the *StO₂ accuracy* of *cerebral tissue oximeter equipment* under well controlled, optimal laboratory conditions on healthy adult subjects.

EE.2.3 Methods

EE.2.3.1 Study population

The following parameters should be considered.

1) Number and source of subjects

The study should include a sufficient number of subjects to attain the statistical significance necessary to demonstrate a specified *StO_2 accuracy*.

— Subjects should be healthy adult volunteers.

— For the broadest application to the largest group of patients, the subjects should vary in their physical characteristics to the greatest extent possible.

NOTE The characteristics of the subjects can be limited due to safety reasons or availability.

2) Subject inclusion and exclusion criteria

— The study protocol should define the inclusion/exclusion criteria.

— Subjects participate in the study on a voluntary basis.

— All subjects should be in good health at the time of the study. Unless specified otherwise in the protocol, the following values could be applied: COHb < 3 %, MetHb < 2 %, *ctHb* > 10 g/dl; these values are not intended to be a comprehensive determination of "good health".

— Inclusion criteria should serve the purpose of the study. (Examples are not intended to be comprehensive.)

EXAMPLE 1 Both male and female subjects.

EXAMPLE 2 Differing skin pigmentation.

EXAMPLE 3 Healthy adult subjects capable of undergoing controlled hypoxaemia to the levels called for in the protocol with minimal medical *risk*.

— Examples of exclusion criteria (not intended to be comprehensive).

EXAMPLE 4 Smokers or individuals exposed to high levels of carbon monoxide that result in elevated carboxyhaemoglobin levels, unless specific dyshaemoglobins are called for in the study protocol.

EXAMPLE 5 Individuals subject to conditions that result in elevated levels of methaemoglobin, unless specific dyshaemoglobins are called for in the study protocol.

EXAMPLE 6 Subjects who would be placed at undue medical *risk* associated with any *procedures* called for in the protocol (e.g. blood vessel cannulation and hypoxia).

EXAMPLE 7 Age.

3) Criteria for study termination

— Study protocol should define circumstances and/or subject response to the *procedure* that becomes grounds for study termination.

EXAMPLE 8 The subject is discovered to meet one of the pre-defined exclusion criteria (e.g. elevated methaemoglobin level).

EE.2.3.2 Apparatus

EE.2.3.2.1 *CO-oximeter* for measuring SaO_2, $SjvO_2$ and *procedures* and supplies recommended by the *CO-oximeter manufacturer*.

EE.2.3.2.2 Materials for arterial catheterization, jugular venous bulb catheter and blood sampling.

EE.2.3.2.3 Means for recording StO_2 values (device under test), which can be manual or automated.

EE.2.3.2.4 *Cerebral tissue oximeter equipment* to be tested. See also EE.2.3.4 c).

EE.2.3.2.5 Means for delivering a medical grade oxygen-nitrogen mixture of varying FiO_2 levels to the subject (e.g. pre-mixed high-pressure cylinders or gas-mixing equipment).

EE.2.3.3 *Procedure*

To perform a *controlled desaturation study*:

a) The study protocol should describe the specific conditions of the test (e.g. optimal laboratory conditions).

b) After the catheters are placed in the artery and jugular bulb, the *probes* to be evaluated are attached to the subject's forehead.

NOTE 1 Further detail of the proper techniques and maintenance of the arterial line and jugular bulb catheter are beyond the scope of this document. The radial artery is typically used.

c) The protocol should specify criteria and methods for determining stability of the StO_2 at the *cerebral tissue oximeter probe* site.

EXAMPLE 1 A stable plateau on the *cerebral tissue oximeter equipment* under test.

EXAMPLE 2 A stable plateau on a reference *cerebral tissue oximeter equipment*.

EXAMPLE 3 A real-time measurement of expired respiratory gases.

d) The breathing circuit is fitted to the subject and the subject breathes a mixture of oxygen and nitrogen. Carbon dioxide can be added to the inspired gas mixture to maintain normal carbon dioxide levels and to prevent respiratory alkalosis secondary to hyperventilation caused by hypoxia.

e) FiO_2 is reduced or increased to bring the subject near target levels. Desaturation to the lowest level (e.g. 70 % SaO_2) is conducted in a stepwise *process* targeting a number of saturation plateaus (periods in which the saturation is relatively stable). The number of saturation plateaus finally accepted as valid is represented by a value M. SpO_2 can be used to monitor the settling of each plateau as it is a continuous estimate of SaO_2.

f) When combined across subjects, these M plateaus should result in a distribution of collected and pooled data pairs spanning the specified $SavO_2$ range. See also EE.2.3.4 b) and EE.2.3.4 f).

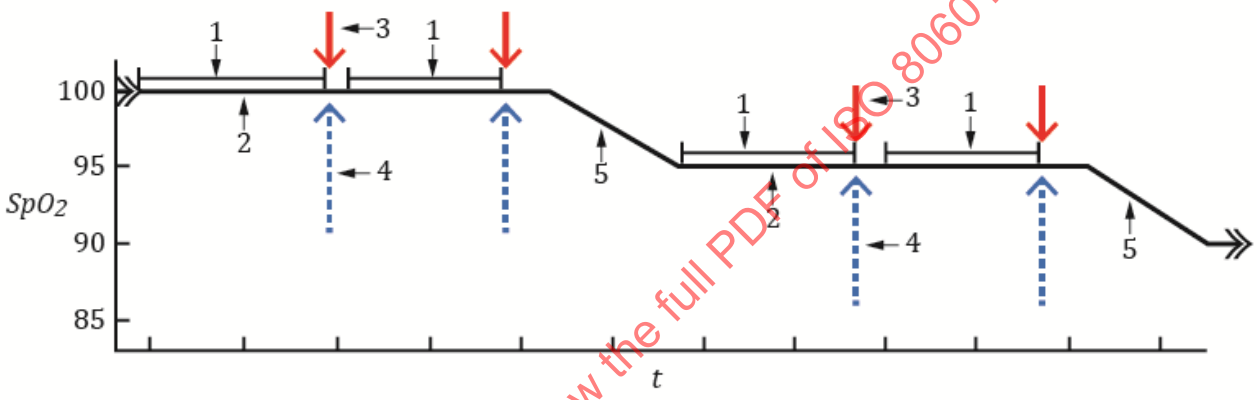
g) Within each saturation plateau level, draw N samples of the arterial and jugular venous blood and pair with the corresponding StO_2 values.

It is important to have the jugular venous blood sampled over a slow period of at least 30s. If the jugular draw is done faster there is a *risk* of pulling superficial blood from other areas. The arterial blood should be taken within the same interval as the jugular sample.

EXAMPLE 4 A study design is shown in Table EE.1 and Figure EE.1. In this example, $M = 5$ and $N = 2$. The values in this example are not intended to be limiting in the number of plateaus or numbers of samples per plateau.

Table EE.1 — Example of target plateaus and ranges

SpO_2 plateau range %	Target number of samples
100 to 97	2
96 to 92	2
91 to 85	2
84 to 78	2
77 to 70	2
Total	10



Key

SpO₂ measured in per cent

1 time interval where *SpO₂* is stable for >90 seconds

2 *SpO₂* Plateau

3 sample arterial specimen (deadspace purge and sampling can be rapid) – solid arrow

4 sample venous specimen (deadspace purge and sampling needs to be at least 30 s each) – dashed arrow

5 desaturation

Arrow points are when blood is sampled.

Figure EE.1 — Example of desaturation-time profile

h) For each subject, $M \times N$ blood draws provide (SaO_2, *SjvO₂*, *StO₂*) data triplets for analysis [see EE.2.3.4 f)]. These data triplets are either acquired simultaneously or correlated in time to accommodate physiological and *cerebral tissue oximeter equipment* delays.

NOTE 2 The values of M and N can vary by subject, given the ability to reach and maintain the targeted plateau levels.

i) When the reference system's blood saturation stabilizes (for example, by visually assessing the display of *SpO₂* and *StO₂*) at an acceptable plateau level, blood sampling can begin. After a change in plateau level, readings should be allowed to stabilize between 90 s and 180 s to allow SaO_2 to reach equilibrium at the *cerebral tissue oximeter probe* sampling site.

j) Care should be taken for the sampling, handling and analysis of blood to ensure the SaO_2 and $SjvO_2$ *accuracy* of the *CO-oximeter* measurement. *Procedures* for the sampling, handling and analysis of blood are found elsewhere[21].

k) The protocol should define the time interval between successive samples within a plateau to ensure that samples are independent. In determining this interval, consideration should be given to

allowing the blood circulation to flush and replace the haemoglobin at the *cerebral tissue oximeter probe* site and to the averaging time of the *cerebral tissue oximeter equipment*.

EE.2.3.4 Data analysis

A *controlled desaturation study* data analysis is performed as follows.

a) Paired StO_2 and $SavO_2$ data points are pooled for all subjects and the A_{rms} is calculated using the formula given in 201.12.1.101.3.

b) Pooled data values are required to include $SavO_2$ levels within 3 % of the endpoints of the StO_2 *accuracy* range, e.g. 55 % to 80 %. StO_2 *accuracy* calculations are required to include data pairs with $SavO_2$ values that span at least 58 % to 77 % (per 201.12.1.101.2.).

c) For *cerebral tissue oximeter equipment* that places an upper limit on displayed StO_2 (e.g. 95 %), the data analysis should ensure that A_{rms} is not influenced by cutting measured values.

EXAMPLE 1 Include only observations where StO_2 readings are less than the upper display limit.

EXAMPLE 2 Statistically down-weight those values with $StO_2 = 95$ % (e.g. treat observations of 95 % as censored, as is done in the analysis of survival data).

EXAMPLE 3 Configure the data-collection system to record values of $StO_2 > 95$ %.

NOTE A_{rms} describes the combined bias and *precision* of StO_2 readings, and by limiting display values, the assumptions of a normal distribution are violated.

d) Data pairs can be rejected if, determined retrospectively, they were taken during conditions that were outside of the scope of the testing as defined in the protocol.

EXAMPLE 4 An unstable StO_2 plateau.

EXAMPLE 5 If the clinical study record indicated that there were difficulties with the blood draw (e.g. excessive bubbles).

EXAMPLE 6 The *CO-oximeter* experienced error conditions.

e) The total number of acceptable data pairs acquired during the study needs to be sufficient to demonstrate statistically the specified StO_2 *accuracy*.

f) The distribution of $SavO_2$ values in the pooled data set needs to be made with comparable density over the full *declared range*. For example, approximately 1/4 of the data should fall within each of the following ranges: 55 % to 60 %, 61 % to 66 %, 67 % to 72 % and 73 % to 80 % $SavO_2$.

g) If sufficient statistical power can be achieved using study inclusion criteria, then a multiple regression is performed to determine influence of skin pigmentation, sex and age of the subjects on measured variables.

EE.3 Testing on *patients*

EE.3.1 *Procedure*

The StO_2 *accuracy* of *cerebral tissue oximeter equipment* is measured by comparing StO_2 readings of the *cerebral tissue oximeter equipment* to functional oxygenation values of $SavO_2$ determined by a *CO-oximeter*.

In a clinical environment, the primary responsibility is *patient* care. StO_2 measurements from *patients* in that environment when compared to measurements from a *CO-oximeter* in that environment can be

degraded because data collection cannot always be well controlled. Both measurements are better controlled under laboratory conditions.

In a clinical environment, measurements from *cerebral tissue oximeter equipment* and *CO-oximeters* are often subject to non-optimal conditions and are difficult to match reliably due to circulatory instabilities or dynamics.

The *patient's* clinical condition should be considered when placing any *cerebral tissue oximeter probe* in relation to the arterial and jugular venous sampling site. Whenever possible, the *cerebral tissue oximeter probe* should be observing blood that is part of the same circulatory stream as the artery and jugular vein from which blood is taken.

NOTE Blood samples can be withdrawn either as a needed part of clinical care or solely for the purposes of the study, as specified in an approved study protocol.

The total number of acceptable data pairs acquired during the study needs to be sufficient to statistically demonstrate the specified *StO_2 accuracy* which can require a large number of *patients*. The distribution of reference values in the pooled data set needs to be made with comparable density over the full *declared range*. Specific numbers of samples and subjects as well as the analysis technique need to be justified using statistical methods.

Annex FF
(informative)

Functional testers for *cerebral tissue oximeter equipment*

FF.1 General

A variety of equipment and methods can be used to test *cerebral tissue oximeter equipment* but there needs to be a distinction between equipment and methods used to assess the *accuracy* of *cerebral tissue oximeter equipment* versus equipment and methods that are limited to testing only the functionality of the *cerebral tissue oximeter equipment*. While *functional testers* are useful in various applications, they are not designed to be fully representative of *cerebral tissue oximeter equipment* use on *patients* and cannot be used to assess the *accuracy* of *cerebral tissue oximeter equipment*.

At the time of writing this Annex, the availability of *functional testers* for *cerebral tissue oximeter equipment* was very limited. Functional testers were not commercially available from independent *manufacturers*. These *functional testers* were being used primarily by the *manufacturers* of *cerebral tissue oximeter equipment* and by research laboratories. However, it is assumed that *functional testers* for *cerebral tissue oximeter equipment* will become more available and the committees recognized that the *responsible organizations* need to be informed of their possible limitations.

201.7.9.3.1.101 requires the instruction manuals of *cerebral tissue oximeter equipment* to state that *functional testers* cannot in general be used to measure the StO_2 *accuracy* of *cerebral tissue oximeter probes* and *cerebral tissue oximeter monitors*. This annex is intended to clarify the reasons for this requirement as well as semantic issues. Terms such as simulator, calibrator and tester have several common meanings, which can contribute to misunderstanding of the actual capability of a particular item. We have recommended specific uses of the term "*functional tester*" when this term applies to cerebral tissue oximetry. This annex explains the possible limitations of *functional testers* and suggests the appropriate use of *functional testers*. It also explains why it is inappropriate to use measurements made with *functional testers* to support StO_2 *accuracy* claims for *cerebral tissue oximeter probes* or *cerebral tissue oximeter monitors*.

FF.2 What is a simulator?

In conventional usage, a simulator is test equipment that stands in for the human *patient*. For example, simulators for invasive and non-invasive blood pressure and for electrocardiograph signals are well accepted substitutes for a *patient.* The measurement *accuracy* for testing *ME equipment* using a simulator can be expected to be comparable to that seen monitoring *patients.* A finite possibility of some additional uncertainty exists due to errors in the simulator.

There is, at the time of writing, no simulator for *cerebral tissue oximeter equipment* that reproduces the optical properties of a broad range of *patients* well enough to warrant its use by the *responsible organization* in determining the StO_2 *accuracy* of any *cerebral tissue oximeter monitor* and *cerebral tissue oximeter probe* combination.

FF.3 What is a *functional tester*?

At the time of writing, there are no commercially available *functional testers* for *cerebral tissue oximeter equipment*. However, *manufacturers* and researchers use *functional testers* for specific engineering purposes related to development and testing of *cerebral tissue oximeter equipment*. Additionally,

manufacturers can specify or sell *functional testers* to *responsible organizations* for their use in confirming the functionality of their *cerebral tissue oximeter equipment*. Two principal characteristics of *functional testers* are as follows.

An appropriate *functional tester* allows the *responsible organization* to determine whether the *cerebral tissue oximeter equipment* is performing as the *manufacturer* designed it to perform, without in any way determining whether the design was correct.

An accurate reading of StO_2 on a *functional tester* never implies that the *cerebral tissue oximeter equipment* is accurate on human beings. All that is being evaluated by the tester is the *cerebral tissue oximeter equipment*'s ability to reproduce the calibration curve or mathematical model that the *manufacturer* designed into it; this calibration curve or mathematical model might not be accurate.

FF.4 Types of *functional testers* and their uses

Some *functional testers* can be designed to connect to a *cerebral tissue oximeter probe*. In this type of design, the *functional tester* is providing a simulation of some characteristics of the *patient*.

Current *functional testers* cannot test all aspects of *cerebral tissue oximeter equipment*. The *operators* and *responsible organizations* that use a *functional tester* need to be aware of its capabilities and limitations to ensure it is appropriate for its intended use (see Table FF.1).

Table FF.1 — Limitations of *functional testers* for use with *cerebral tissue oximeters*

Characteristic of *Functional tester*	Possible Limitation	Possible Concern
Probe to *patient* interface	Is light shunting (allowing light to pass directly from the *probe* emitter to the *probe* detector without passing through the *functional tester*) prevented in a manner, similar to use on a *patient*?	Excessive light shunting can affect the ability to obtain an StO_2 reading or the stability or value of the reading.
	Is ambient light prevented from reaching the *probe* photo-detectors, similar to use on a *patient*?	Excessive ambient light can affect the ability to obtain an StO_2 reading or the stability or value of the reading.
	Does the surface of the *functional tester* allow the light to enter and exit the *functional tester*, similar to *probe* use on a *patient*? The surface of the *functional tester* cannot adequately simulate *patient* skin, resulting in *probe* light output not entering the *functional tester* or light output from the *functional tester* not reaching the *probe* photo-detectors.	This can cause a reduction in signal strength received at the *cerebral tissue oximeter probe*, resulting in an inability to obtain an StO_2 reading, or affecting the stability or value of the reading.

Characteristic of *Functional tester*	Possible Limitation	Possible Concern
Patient superficial layer	Does the *functional tester* simulate the superficial layer of a *patient*?	Homogeneous light absorption and scattering does not test how well the *cerebral tissue oximeter equipment* measures the oxygenation of the brain tissue, rejecting the effects of oxygenation of the superficial layer and the effect of the skull.
Level and/or range of optical absorbance and scattering	Does the *functional tester* simulate the full range of absorbance and scattering, resulting in signal strength, similar to use on a *patient*?	If the signal strength is higher than a *patient's* signal strength the *cerebral tissue oximeter equipment* can operate on the *functional tester* but performance on a *patient* can be inadequate.
Range of simulated StO_2	A *functional tester* can simulate only a single StO_2 value or a limited range of StO_2 values.	The *functional tester* might not provide simulation across the *declared range* of the *cerebral tissue oximeter equipment*.
Ability to test the effects of the *probe's* light output power, its spectral characteristics, or its photo-detector sensitivity.	A *functional tester* can be designed in a manner such that the *probe's* light output is not returned to the *probe's* photo-detector. This type of *functional tester* uses the *probe's* light output for triggering purposes and generates light at the appropriate timing to send to the *probe's* photo-detector.	Characteristic of the *cerebral tissue oximeter probe* related to light output power, optical sensitivity and spectra affect its performance but are not tested with this type of *functional tester*.

Some *functional testers* can be designed to connect to the *cerebral tissue oximeter monitor* in place of the *cerebral tissue oximeter probe*. In this design the *functional tester* is providing a simulation of some characteristics of the *cerebral tissue oximeter probe* and some characteristic of the *patient*. This type of *functional tester* only tests the *cerebral tissue oximeter monitor,* as the *probe* is not included in the test.

While this type of *functional tester* can appear to be testing all aspects of the *cerebral tissue oximeter monitor* this cannot be the case. The *operators* and *responsible organizations* that use *functional testers* need to be aware of their capabilities and limitations to ensure they are appropriate for their *intended use*.

While *functional testers* have limitations, they are appropriate for some uses such as:

A *manufacturer* can need the *cerebral tissue oximeter equipment* to be operating for development purposes or during environment tests such as temperature and EMC testing. During these tests the *manufacturer* should only be concerned that the *functional tester* simulates some characteristics of *patient* signals at predictable levels. The characteristics of the simulated signals (i.e. repeatability, reproducibility, stability, low signal amplitude, specific StO_2 value, etc.) can be optimized for the specific test being performed.

The *responsible organization* can need the *cerebral tissue oximeter equipment* to be operating during functional and safety testing performed by a biomedical engineer.

Annex GG
(informative)

Concepts of *ME equipment* response time

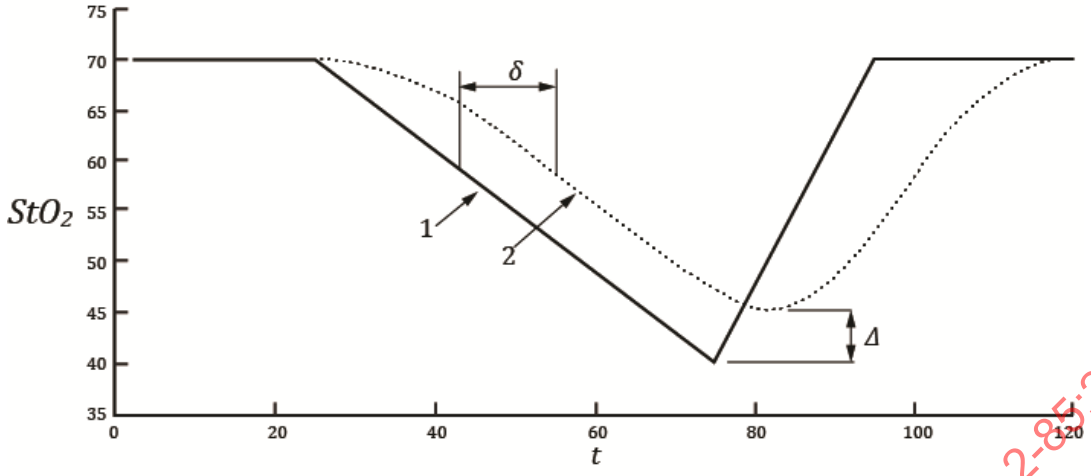
GG.1 General

There can be trade-offs between accurately tracking the magnitude of changes in StO_2 and minimizing the effects of noise. In general, faster response times can cause *cerebral tissue oximeter equipment* to be more vulnerable to noise but can allow them to follow the actual physiological change more closely[86]. The response of some *cerebral tissue oximeters* can be optimized for particular clinical situations. There are two important concepts in describing *cerebral tissue oximeter equipment* response. One is the fidelity in tracking StO_2 changes. The other is the delay from the time that an event occurs (the $SavO_2$ changes at the measurement site) until the display indicates the change or the generation of *alarm signals*. "Fidelity" and "delay" are influenced by *cerebral tissue oximeter equipment* design and *operator settings*. *Cerebral tissue oximeter equipment* design can include signal processing and conditioning times and data transmission delays. Adjustable controls (e.g. averaging time and *alarm signal generation delay)* can be set.

Cerebral transit time as well as the response time of cerebral vessels to change to stimuli are on the order of several seconds. Furthermore, the deleterious effects of hypoxia develop over minutes. Therefore, a response time/time resolution of less than 10 s is not relevant for clinical purposes. For cerebrovascular research faster response times/time resolution can be relevant. For research studying fast responses, it is important for the researcher to know the origin of the instantaneous values that are displayed/stored/measured as a time range of the optical signal and/or any applied filter function.

GG.2 Fidelity

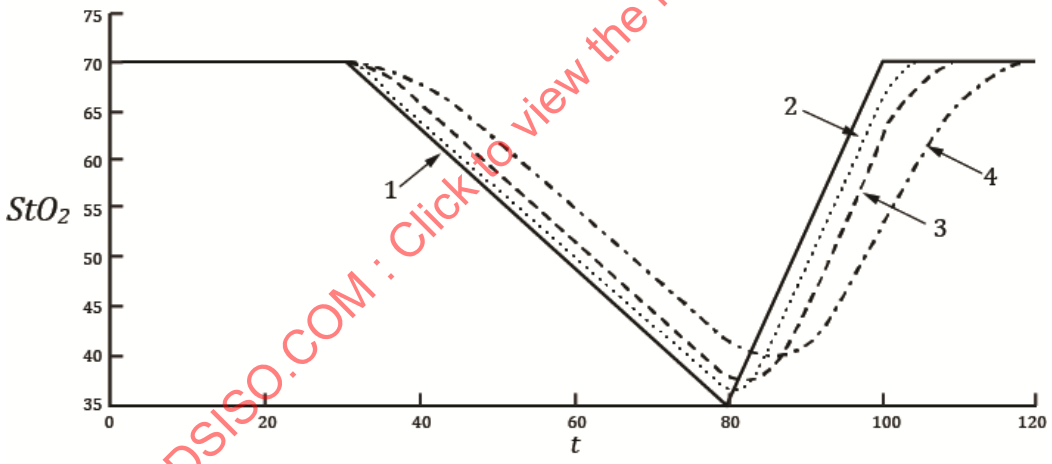
Fidelity can be described graphically by showing the range of responses of the *cerebral tissue oximeter equipment* to a change in saturation. Figure GG.1 illustrates a simulated response of *cerebral tissue oximeter equipment* to a change in saturation. Figure GG.2 illustrates the simulated effect of different averaging times on the response of the *cerebral tissue oximeter equipment*.



Key

1	S_R	Δ	saturation deviation
2	displayed StO_2	δ	time delay
		StO_2	saturation in %
		t	time in seconds

Figure GG.1 — Illustration of fidelity of *cerebral tissue oximeter equipment* performance in tracking saturation changes



Key

StO_2 saturation in %
t time in seconds
1 S_R
2 displayed StO_2, faster averaging
3 displayed StO_2, normal averaging
4 displayed StO_2, slower averaging

Figure GG.2 — Illustration of effect of different averaging times on fidelity

The symbols δ and Δ in Figure GG.1 do not refer to any particular requirement in this document. They are illustrated here as possible points of interest, in that these are the likely areas of StO_2 *accuracy* that can be affected by different averaging or filtering techniques response curves. The span depicted by the symbol δ represents a time lag before changes in saturation are reflected in the processed StO_2 value. This lag can be caused by, for example, the time required for data acquisition, signal conditioning, and

algorithm processing. The deviation denoted by Δ illustrates a lack of fidelity in reproducing the degree of change in a transient desaturation. Δ is generally affected by, for example, signal averaging or the *data update period*.

The importance of the errors, δ and Δ, introduced by the processing of the StO_2 parameter as well as the detection of *alarm conditions* and the subsequent generation of *alarm signals* that the purchasers of *cerebral tissue oximeter equipment* need to consider for the applications in their clinical practice [see 201.7.9.2.1.101 e)], are well illustrated in Reference [62].

GG.3 Effects of delays

Delays can be described graphically, for example, by showing the response of the *cerebral tissue oximeter equipment* using Figure GG.3. The time from t_1 to t_2 is the *alarm condition delay* and the time from t_2 to t_3 is the *alarm signal generation delay*.

A possible *procedure* to measure the sum of the *alarm condition delay* and *alarm signal generation delay* of *cerebral tissue oximeter equipment* is described below.

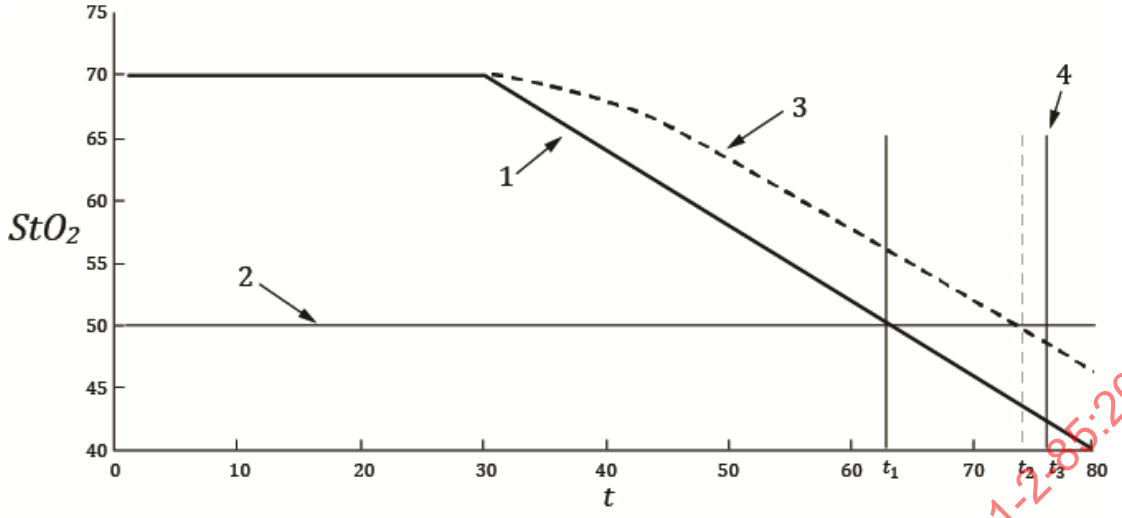
— A *functional tester* is set to start at a saturation level of e.g. 70 %.

— This level should be simulated for a period of time that is sufficient to allow stabilization of the *cerebral tissue oximeter equipment* under test.

— The *functional tester* then changes the saturation level in a linear ramp function with a predefined slope (or any other predefined function) down to a given end value (e.g. 5 % below the *alarm limit*).

— The sum of the *alarm condition delay* and *alarm signal generation delay* is defined as the time from having the simulated saturation passing the *alarm limit* (e.g. 50 % or the default low saturation *alarm limit*) to the time the *alarm system* generates the appropriate *alarm signal*.

Figure GG.3 illustrates the components of *alarm signal generation delay*.



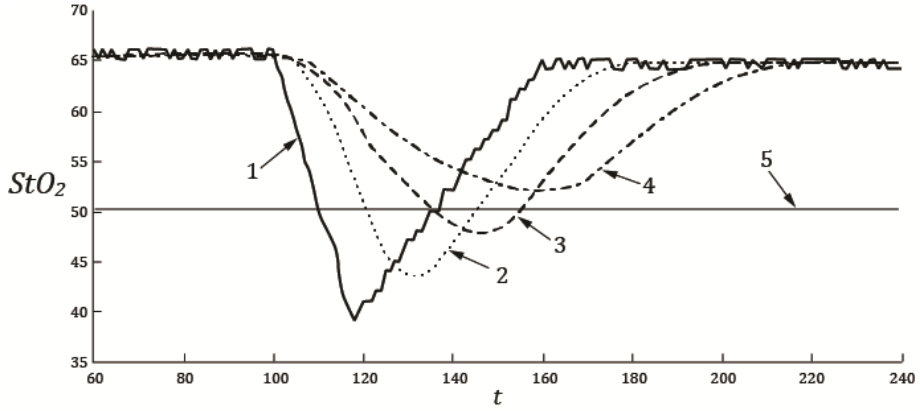
Key

StO_2	saturation in %
t	time in seconds
t_1, t_2, t_3	see GG.3
1	S_R
2	*alarm limit*
3	displayed *StO2* in %
4	*alarm signal* generation

Figure GG.3 — Graphic representation of components of *alarm system* delay

The delay due to the *cerebral tissue oximeter equipment* processing and averaging is $t_2 - t_1$, the *alarm condition delay*. The interval $t_3 - t_2$, the *alarm signal generation delay*, is attributed to the *alarm system* strategy and the communication time to the *alarm signal* generation communicator or *distributed alarm system* (e.g. *patient* monitor or central station). Thus, the overall *alarm system* delay time is $t_3 - t_1$.

Figure GG.4 represents a faster desaturation slope and a more realistic, noisier saturation signal. Curves 3 and 4 underestimate the depth of the fall in saturation. Curve 2, faster averaging, can cross a low saturation *alarm limit* sooner than curve 3, normal averaging, or curve 4, slower averaging, which might not cause an *alarm condition* at all. The benefit of normal and slower averaging is to smooth out the otherwise noisy signal and reduce the number of *false positive alarm conditions*.



Key

StO_2 saturation in %

t time in seconds

1 unprocessed StO_2

2 displayed StO_2, faster averaging

3 displayed StO_2, normal averaging

4 displayed StO_2, slower averaging

5 *alarm limit*

Figure GG.4 — Illustration of the effects of different averaging times on a more rapid and noisier desaturation signal

Annex HH
(normative)

Data interface requirements

HH.1 Background and purpose

Cerebral tissue oximeter equipment in clinical use has typically provided data transmitted using proprietary interfaces and protocols. To help foster interoperability of *cerebral tissue oximeter equipment* in the medical device ecosystem, increased standardization of this interface is desirable. This document has sought to logically categorize the data that can be transmitted or received as parameters, identification data, settings data, configuration data, specification data, service monitoring data and *alarm system* data via a *functional connection*.

The following categories of data are defined.

— **Parameters and units of measurement:** Parameters and units of measurement used within the *cerebral tissue oximeter equipment*.

— **Equipment identification:** Information identifying the *cerebral tissue oximeter equipment*.

— **Equipment settings:** Settings relating to the control and operation of the *cerebral tissue oximeter equipment*.

— **Equipment configuration:** *operator settings* that can be remotely configured.

— **Equipment specifications:** Relevant specifications to be transmitted.

— **Service monitoring:** Indicators relating to preventative or corrective maintenance of the *cerebral tissue oximeter equipment* and its *accessories*.

All *cerebral tissue oximeter equipment* with a *functional connection* should provide the information to enable identification of the *cerebral tissue oximeter equipment* and the required parameters in Table HH.1.

HH.2 Data definition

If *cerebral tissue oximeter equipment* parameter data are transmitted via a *functional connection*, the *cerebral tissue oximeter equipment* parameter data shall include at a minimum the parameters listed as required in Table HH.1. In addition to these parameters, the metadata, which includes signal quality indicators and *manufacturer*-specific indices, should be transmitted.

Table HH.1 — Parameters and units of measurement

Parameter	Required	Description	Type
StO_2	Yes	StO_2 value as determined by the *cerebral tissue oximeter equipment* (see 201.3.225)	Value: (%)
Signal inadequacy	Yes	Signal when the displayed StO_2 is potentially incorrect (see 201.12.4.102)	As described by *manufacturer*
Signal quality indicator	Optional	A measure of the signal quality (e.g. noise indicator)	As described by *manufacturer*

If *cerebral tissue oximeter equipment* identification data are transmitted via a *functional connection*, the *cerebral tissue oximeter equipment* identification data shall include the parameters listed in Table HH.2. These data can be provided by the combination of the *model or type reference*, serial number and the software unique identifier of the *cerebral tissue oximeter equipment*, or by a unique device identifier (UDI).

Table HH.2 — Equipment identification

Parameter	Required	Description	Type
Manufacturer	Yes	Identification of the *manufacturer* of the equipment	Text string
Model	Yes	Identification of the product or model number of the equipment	Text string
Serial number	Optional	The identification number of the equipment	Text string
Software or Firmware version[a]	Optional	Identification of the software version implemented in the equipment	Text string

[a] More than one software or firmware version can need to be communicated from the equipment.

NOTE The United States Food and Drug Administration UDI, consisting of a device identifier (DI) and a production identifier satisfies the requirements of Table HH.202.

If *cerebral tissue oximeter equipment* settings data are transmitted via a *functional connection*, the *cerebral tissue oximeter equipment* settings data shall include the parameters listed in Table HH.3.

Equipment settings can be made available through a *functional connection* continually or through a query-response. If equipment settings are communicated by query-response, a change to equipment settings shall be immediately indicated via the *functional connection*.

Equipment specifications for settings that are not *operator*-adjustable should be made available via the *functional connection*.

Table HH.3 — *Operator*-adjustable equipment settings

Parameter	Required	Description	Type
Data update period	Optional	Interval in which the *cerebral tissue oximeter equipment* algorithm provides new valid data to the display or the *functional connection* (see 201.3.204)	Value: (s)
Averaging Time	Yes	*Operator* settable or preset averaging window used to calculate a parameter	List of text strings (*manufacturer*-defined)
Alarm signal inactivation state present	Optional	List of text strings (*alarm off*, *alarm paused*, *audio off*, *audio paused*, *acknowledged*)	List of text strings
High StO_2 *alarm condition*	Optional	Setting of the high StO_2 *alarm limit*	Value: (%)
Low StO_2 *alarm condition*	Optional	Setting of the low StO_2 *alarm limit*	Value: (%)
Active *technical alarm conditions*	Optional	Currently active *alarm conditions* Examples of *alarm conditions* include the *cerebral tissue oximeter probe* is not connected to the *cerebral tissue oximeter equipment*, the *cerebral tissue oximeter probe* is not detected, detection of an artefact, no signal detected, low quality of signal, display error, *cerebral tissue oximeter equipment* inoperative, low battery, defective *cerebral tissue oximeter probe* or *probe cable extender*, unrecognized *cerebral tissue oximeter probe*, incompatible *probe cable extender*, line frequency interference, ambient light interference, inadequate display	List of text strings (*manufacturer*-defined)
Probe location	Optional	Location of the *probes*	Text string

If *cerebral tissue oximeter equipment* configuration data can be queried through a *functional connection*, the *cerebral tissue oximeter equipment* configuration data should include the parameters listed in Table HH.4.

Table HH.4 — Equipment configuration

Parameter	Required	Description	Type
cerebral tissue oximeter probe type connected or *cerebral tissue oximeter probe* model number connected	Optional	Type of *cerebral tissue oximeter probe* can imply applicable *patient* group (e.g. neonate, paediatric, adult) or other *cerebral tissue oximeter probe* information (large or small area), including methods of securing, e.g. adhesive v. non-adhesive, or usage type, e.g. do not reuse v. reusable.	Text string
cerebral tissue oximeter probe lot or serial number	Optional	If applicable, the specific *cerebral tissue oximeter probe* lot or serial number connected to the *cerebral tissue oximeter equipment*	Text string
Active *probe* channels	Optional	Number of the channel of the active *probe*	Text string

If *cerebral tissue oximeter equipment* specifications data are transmitted via a *functional connection*, the *cerebral tissue oximeter equipment* specifications data should include at least the parameters listed in Table HH.5.

Table HH.5 — Equipment specifications

Parameter	Required	Description	Type
StO_2 accuracy	Optional	*StO_2 accuracy*, A_{rms}, as defined in 201.12.1.101.1 of this document	Value: (%)
Declared ranges of *StO_2* and *StO_2 accuracy*	Optional	*Declared range* of *StO_2* and *StO_2 accuracy* over the *declared range,* as defined in 201.12.1.101.1 of this document	Value triple [upper limit, lower limit, *accuracy*] (%)
StO_2 accuracy under conditions of low signal	Optional	*StO_2 accuracy* under conditions of low signal as defined in 201.12.1.103 of this document	Value: (%)
Method for performance specification	Optional	Whether the performance was determined based on a phantom or in-vivo testing	Text

If *cerebral tissue oximeter equipment* service monitoring indicators data are transmitted via a *functional connection*, the *cerebral tissue oximeter equipment* service monitoring indicators data should include the parameters listed in Table HH.6.

Table HH.6 — Service monitoring indicators

Parameter	Required	Description	Type
Remaining *cerebral tissue oximeter probe* life	Optional	Remaining *cerebral tissue oximeter probe* life	Value: (e.g. hours, days)
Next periodic maintenance date	Optional	Date service is required	ISO 8601 Date (YYYY-MM-DD)

Check conformance by inspection.

HH.3 Clinical context

The *StO_2* measurement is a non-invasive estimate of *functional oxygen saturation* of haemoglobin in cerebral tissue below the *probe*. Oxygen saturation is used alone for *patient* assessment and can be used as an input to open-loop and closed-loop systems relating to oxygenation and ventilation. There is significant clinical value to providing data from *cerebral tissue oximeter equipment* for use in systems such as an *integrated clinical environment*. Annex B of AAMI 2700-1 provides examples of detailed clinical scenarios that illustrate adverse events that could have been averted with the use of such integrated *ME systems*. These scenarios include the use of safety interlocks (with and without *ME equipment* synchronization), *process* control, smart *alarm systems*, clinical decision support, and physiological closed-loop control[17].

Annex II
(informative)

Comparison of methods of performance evaluation

II.1 General

Cerebral tissue oximetry is aimed at measuring haemoglobin oxygen saturation in cerebral tissue beneath the *probe*. This document allows *manufacturers* of *cerebral tissue oximeter equipment* to report the *accuracy* performance of their *cerebral tissue oximeter* using either human desaturation studies (in-vivo testing, see Annex EE for details) or phantom desaturation testing (in-vitro testing, see Annex DD for details). Regulatory bodies of particular countries can require a specific method of *accuracy* performance *verification* for the *manufacturer* to substantiate their *cerebral tissue oximeter's* claims.

This document requires that *manufacturers* specify the method used for the *verification* of the *accuracy* performance of their *cerebral tissue oximeter* and the method for estimating *accuracy*. This Annex is intended to review the advantages and limitations of the in-vivo and in-vitro testing methods.

Cerebral tissue oximeter equipment from differing *manufacturers* have claimed similar *accuracy*, yet their StO_2 measurements could be substantially different in *patients*. For the clinician or the *responsible organization* to understand how a particular *cerebral tissue oximeter* can perform on *patients*, it is necessary to understand how the *cerebral tissue oximeter* was validated, the limitations of the chosen method of *accuracy* performance *verification*, and how the stated *accuracy* claims can relate to use on *patients*. Tables II.501 and II.502 list some advantages and limitations of both methods.

As *cerebral tissue oximeter equipment* and methods for *accuracy* performance *verification* continue to mature, a goal for *cerebral tissue oximeter* performance should include accurate readings over the intended range of use for the declared *patient* population. This goal should be independent of the method used for *accuracy verification*.

II.2 Rationale for multiple methods of *accuracy* performance *verification*

During the drafting of this document, concerns arose regarding the requirement of human desaturation studies for *accuracy verification*. Some expressed concern about human desaturation testing being the most appropriate method and whether such testing was safe or ethical. In some countries, human desaturation studies were not allowed for the purpose of *cerebral tissue oximeter verification*. Conversely, some deemed human desaturation studies not only safe but necessary to demonstrate that the *cerebral tissue oximeters* performed as designed on humans. However, in some *patient* groups (e.g. preterm infants, neonates and children) it is not possible to conduct *controlled desaturation studies* and the data obtained from healthy human adults are not considered representative of paediatric *patients*.

For these reasons both methods were included in this document.

II.3 Desire for improvement of methods for *accuracy* performance *verification*

Manufacturers of *cerebral tissue oximeter equipment* have *accuracy* claims for their *cerebral tissue oximeter*. While these *accuracy* claims from differing *manufacturers* are typically very similar, their *cerebral tissue oximeters* can produce quite different StO_2 measurements on the same *patient*. This situation can cause the clinician to question which *cerebral tissue oximeter* is most accurate on a