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Deliverable 7.7

First Annual Ethics Report

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1 Introduction

Within the RASimAs project, two trials are planned to be conducted for the evaluation of the simulator and the assistant system for Regional Anaesthesia (RA).

For the evaluation of the simulator providing a model-based training of RA, a training trial will be performed. Unexperienced anaesthesia trainees will be recruited for this trial and will be randomized either to a training or a control group, with or without receiving training sessions with the RASimAs simulator, respectively. Afterwards, all trainees will perform RA during the standard care and under supervision of a senior anaesthesiologist according to the traditional way of RA training in the clinics.

Regarding the assistant system, a clinical trial with a non-approved medical device will be conducted. Therefore, patients that are eligible for RA will be recruited and an experienced senior anaesthesiologist will perform the RA under the guidance of the assistant system that provides additional information on the physiological structures of the patient.

Both of the trials are involving human subjects and hence, they will be conducted according to the administrative regulations and specific laws that apply in the different countries of the RASimAs partners.

In the following, we first describe the general requirements on medical trials involving humans and then derive the ethical constraints for the RASimAs project.

2 Research Involving Human Subjects

2.1 Historical Overview

The main historical milestones on the way of the establishment of unique regulations and quality standards regarding experiments in human beings are summarized at the example of the development in Germany.

1900 Prussian Decree

First codification of informed consent in Germany.

1947 Nuremberg Code

Experiments with human beings during the National Socialist period were the reason for the establishment of the Nuremberg Code consisting of a set of ethical research principles for conduction of clinical trials.

1961 Germany founded Health Agency

As last member state of the European Economic Community (EEC) Germany founded a Health Agency with a sub division for drugs and adopted a law which provided a legal framework for the registration of drugs.

1964 Declaration of Helsinki

The Declaration of Helsinki was established by the World Medical Association (WMA) and developed ten ethical principles that were first stated in the Nuremberg Code. It is internally regarded as a milestone document for the human research ethics.

The legal bindingly instruments that should follow in the later years to be installed for conduction of clinical trials are strongly inspired by the Declaration of Helsinki as ethical quality standard. The seventh and last revision of the declaration was in 2013.

1966 National Institute of Health (NIH) called for insurance and information

Henry Beecher (1904 – 1976), American anaesthesiologist, published an article on unethical practices in medical experimentations within the New England Journal of Medicine that inspired the development of guidelines on informed consent and on the conclusion of an insurance for the trial subjects.

1972 German Research Association (DFG) calls for ethical review of clinical research projects

1975 German Health Agency founded department for medicinal products

1976 German Drug Law

The national drug law of 1961 was reformed and the first version of the today`s German drug law was adopted.

1981 Establishment of Ethics Committees

During the conference of the German Medical Faculties in Mainz, Germany, the establishment of Ethics Committees was claimed. The Ethics Committee at the Medical Faculty of the RWTH Aachen was founded.

1994 Establishment of BfArM

Founding of an independent Ministry for Medicinal Products and Medical Devices (BfArM).

2004 Uniform European regulation for authorisation of clinical trials

The Clincial Trials Directive 2001/20EG is the basis for the first uniform European regulation for authorisation of clinical trials. Transposition into national law (German drug law) was in August 2004.

2.2 Declaration of Helsinki

The Declaration of Helsinki is an internationally recognized ethical quality standard established by the World Medical Association. The two main quality objectives of the Declaration is to ensure safety and well-being of the study subjects and to collect valid, objective and reliable data. The collection of low quality data is considered as unethical course of action.

The development of quality standards, guidelines, norms and of legally binding regulations of the World Medical Association as well as other institutions have been strongly inspired and guided by the Declaration of Helsinki (Fig 1).

Figure 1: Ethical quality standards of the World medical Association.

2.3 Further Directives, Regulations, and Guidelines

Controlled clinical trials are prospective research projects on human subjects to gain new or further information about specific interventions and/or to generate data about safety and efficacy. The conduction of clinical trials is only accepted by Ethics and Authorities after providing all information to demonstrate that the project is in line with the applicable regulations and legislation that are relevant in the country where approval of the clinical trial is sought.

In Figure 2, important rules and regulations for the conduction of trials with non-approved medical devices are listed. The legal obligation decreases from bottom to top and European directives are at the highest level and are translated into national law. The national legislations and regulations refer to norms of the ISO that are based on established ethical guidelines and principles. Guidelines and principles are no legal instruments but strongly linked to the national law.

Figure 2: Regulations, ethical guidelines, and standards applying to the RASimAs trials.

The internal regulations and standards are explained in detail in the essential documents (Chapter 8, ICH-GCP) which are newly and specific generated for each trial. The Clinical Trial Center Aachen CTC-A additionally provides an ISO 9001 certified quality management system for preparation, conduction and completion of high end quality research projects on human subjects.

3 Regulatory Aspects in RASimAs Trials

From the administrative point of view, both trials which are planned in RASimAs are fundamentally different. In contrast to the simulator, the assistant system is a non-approved medical device that will be evaluated within a clinical trial. This means that the clinical trial with the assistant is regulated by law and the efforts for preparation, submission for approval and conduction are far greater compared to the trial with the simulator that is not under the Medical Device Act since the simulator is no medical device (Tab. 1).

The RA simulator does not match the definitions for a medical device as stated in the relevant Medical Device Directive 93/42/EEC. Therefore its evaluation within a trial recruiting anaesthesia trainees is not regulated by the national Medical Device Act. The national Medical Professional Code of Conduct regarding research on humans is applicable. The favorable opinion of all responsible Ethics Committees has to be obtained to perform the simulator trial.

Table 1: Main regulatory aspects of both RASimAs trials

	Simulator Trial	Assistant Trial
Ethical Requirements	ICH-GCP	ICH-GCP ISO 14155 (“ISO-GCP”)
Legal Requirements	Medical Professional Code of Conduct Data Protection Act	Medical Device Act Data Protection Act
Study Design	International, randomised controlled, multicenter training trial	International, randomized controlled clinical multicenter trial

	Simulator Trial	Assistant Trial
Study Population	Healthy volunteers (anaesthesiologists)	Patients eligible for RA
Central Documents	Study Protocol Informed Consent Form Case Report Form	Clinical Trial Protocol Informed Consent Form Case Report Form Investigator`s Brochure
Favorable opinion of each relevant Ethics Committee	Yes	Yes
Authorization by the relevant Competent Authority	No	Yes

The assistant system is a medical device by definition and the clinical evaluation will be regulated by the applicable national Medical Device Act and beside the favorable opinion of the Ethics Committees the authorization of the responsible Competent Authorities is required to be obtained.

3.1 Authorities

Trials are prepared and conducted by a multi-professional project team. The rights and obligations of the different roles of the stakeholders conducting a trial are clearly defined by legal regulations as well as by the established guidelines such as ICH-GCP as internationally recognized quality standard for good clinical practice in human research.

In the multi-professional research team, the roles, rights, and duties of each stakeholder are clearly defined and distinguished (Fig. 3). The sponsor plays a crucial role regarding the legal responsibility and the project coordination as well as the communication with or between team partners (manufacturer, supplier, investigator), Independent Ethics Committees (IEC) and the Competent Authorities (CA). The safety of the study population (healthy volunteers; patients) is always the ultimate goal of the sponsor. These administrative structures and distribution of tasks are installed to implement ethical research principles for the protection of study subjects and to ensure and maintain the ethical acceptability of the research project in general.

Figure 3: Authorities, Stakeholders and their Roles in Clinical Trials

3.1.1 Sponsor

The sponsor is responsible for the overall coordination of the partners and assumes the legal responsibility for clinical trials. As a natural or legal person, the sponsor takes over the complete trial management to ensure that the planning and conduction of the trials will comply properly with all the legal requirements that apply to the trial (chapter 5, ICH-GCP). The CTC-A will take over sponsorship for the clinical trial with the assistant system and the overall management of both research projects involving human subjects in RASimAs. As central project office, the CTC-A will lead the communication with the Independent Ethics Committees (IEC), the Competent Authorities (CA) and the project partners (manufacturer, supplier, investigators). The Sponsor will provide monitors and auditors for quality assurance and control, project manager who are responsible for the planning, preparation, conduction and completion of the trial in compliance with all ethical and legal requirements applying to the project. Data manager of the sponsor will be responsible for the creation and maintenance of the electronic data capture and the user management of the electronic case report form.

The sponsor is also responsible for the creation and update of all essential documents as study specific documents, for the procedure for submission for approval of Ethics and Authorities responsible for each study site, for the implementation of quality management, and for the communication and informing Ethics and Authorities of the progress of the trial.

Responsibilities and duties will be regulated by the sponsor and determined in agreements between the sponsor and the investigators of each participating study sites.

The authorization of relevant competent authority and approval of the ethics committee for any amendments, which will become necessary during the study, will be applied for by the sponsor.

3.1.2 Independent Ethics Committee (IEC)

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

In accordance with the Declaration of Helsinki, as well as the Good Clinical Practice (GCP)-guideline the trials will be presented to all responsible Independent Ethics Committee and their endorsement will be obtained prior to inclusion of any subject into the trials.

Any change in the trial protocol and/or informed consent form will be presented to the named Ethics Committee (Fig. 4). They have to be approved by the Ethics Committee before implementation (except for changes in logistics and administration or when necessary to eliminate immediate hazards).

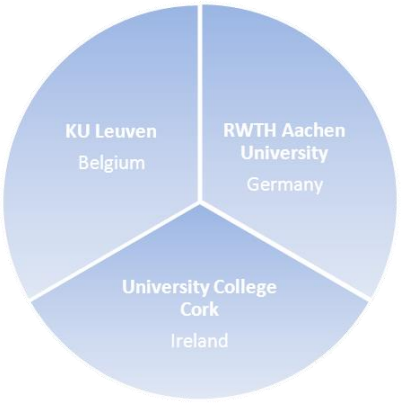

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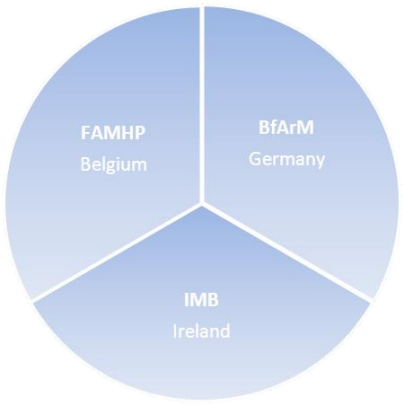
Figure 4: The trials that are planned in the RASimAs project will be performed at study sites in Belgium, Germany, and Ireland.

3.1.3 Competent Authorities

The Competent Authorities are governmental bodies with a statutory role to ensure compliance with the relevant current legislation (Fig. 5). After reviewing the submitted clinical research project they are responsible for granting approval. During and after the conduction of a clinical trial they are allowed to inspect the trial performance on site and to get direct access to all data that are relevant to check compliance with the applicable regulations.



Belgium	Germany	Ireland
Federal Agency for Medicines and Health Products	Bundesministerium für Arzneimittel und Medizinprodukte	Irish Medicine Board
FAMHP	**BfArM**	**IMB**

Figure 5: Competent Authorities in Belgium, Germany, and Ireland.

3.2 Other Stakeholders

3.2.1 Manufacturer

In RASimAs two project partners are in the role of a manufacturer. SenseGraphics will be responsible for the assembly of the simulator since SINTEF will assemble the assistant system. Both manufacturers will take care of their legally defined duties that apply to each device under the supervision of the CTC-A as sponsor and overall trial management body within RASimAs.

3.2.2 Study Population

Beside study specific inclusion and exclusion criteria that will be defined in the trial protocol some criteria for the enrolment of study subjects are defined in general (Tab. 2).

Table 2: General inclusion and exclusion criteria

Criteria	Simulator trial	Assistant trial
Inclusion	• Male or female equally aged > 18 years • Written informed consent prior to study participation	• Male or female equally aged > 18 years • Written informed consent prior to study participation
Exclusion	• The subject is mentally or legally incapacitated • Subject has been committed to an institution by legal or regulatory order	• Pregnant and lactating females • The subject is mentally or legally incapacitated • Subject has been committed to an institution by legal or regulatory order

3.2.3 Investigators and Study Sites

Both trials in RASimAs are planned as international multicenter trials. The investigators will perform the trial on site. Beside the performance of the medical activities as scheduled in the trial protocol, the information of study subjects and the obtaining of written consent prior to inclusion is an exclusive medical activity. The investigators will ensure, that all assisting study personnel will be adequately qualified and informed about the study protocol, any amendments, the medical devices, and their study related responsibilities and functions.

Physicians have to prove their professional qualification and experience prior to the performance of a clinical trial to be accepted as an investigator by the Ethics Committee. Regarding the extent of leadership within in the study team one overall coordinating investigator, one principal investigator per site and participating sub-investigators can be distinguished (Tab. 3).

Table 3: Types and roles of investigators

Type of Role	Description
Coordinating Investigator	One investigator of the coordinating study site in Aachen, Germany, will be responsible for the coordination of the investigators at all different study sites.
Principal Investigator	One principal investigator at each study site will be the team leader at this site.
Sub-Investigator	All persons who have proven their eligibility to perform the trial due to their professional qualification and experience without leadership will be sub-investigators.

For the evaluation of the RASimAs assistant system within a clinical trial the study sites will be assessed by the responsible Ethics Committee to its suitability to perform the trial according to all principles of Good Clinical Practice. In particular, details of infrastructure and resources of each site that may influence the performance of the trial will be checked especially. Examples include the area of the availability of qualified personnel and of the number of potential study subjects in the indication of interest as well as the physical conditions on site. Table 4 gives a general overview on the issues that are relevant to assess the suitability of a study site.

Table 4: A set of indicators will be used to assess the suitability of a study site.

Indicator	Index
Numbers of performed trials in total	|___|___|___|
how many during the last year	|___|___|
numbers of trials planned at the same time	|___|___|
Numbers of notified SAE during the last year	0 ☐ , 1-5 ☐ , > 5 ☐
Numbers of physicians available as investigators	|___|___|
Study experience, physician 1	< 1Y ☐, 1-2 Y ☐, > 2 Y ☐
Study experience, physician 2	< 1Y ☐, 1-2 Y ☐, > 2 Y ☐
Study experience, physician 3	< 1Y ☐, 1-2 Y ☐, > 2 Y ☐

Indicator	Index
Average time off of the physicians for performing the trial	Not applicable ☐ ≤ ½ day/week ☐ > ½ day/week ☐
Numbers of study nurses Study experience, study nurse 1 Study experience, study nurse 2 Study experience, study nurse 3	|___|___| < 1Y ☐, 1-2 Y ☐, > 2 Y ☐ < 1Y ☐, 1-2 Y ☐, > 2 Y ☐ < 1Y ☐, 1-2 Y ☐, > 2 Y ☐
Numbers of potential study subjects in this indication during the last year	|___|___|___|
Are there competing parallel studies?	Yes ☐ No ☐

4 Conduction of Trials Involving Human Subjects

Performance and course of the study specific procedures and visits will be defined by the trial protocol and the applicable essential documents that are in line with the relevant ethical principles and legal regulations and approved by the relevant bodies.

4.1 Information & Informed Consent

The subjects have to confirm voluntarily their willingness to participate in the trial, after having been informed by an investigator (physician) in writing and verbally of all aspects of the trial that are relevant to the subject's decision to participate. They will be informed about requirements concerning data protection and have to agree to the direct access to their individual data. The subjects will sign an informed consent form for study participation as well as disclosure of individual data. The informed consent form has to be signed and personally dated by the subject and one of the sub-investigators.

Before informed consent is obtained, the investigator has to provide the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial have to be answered to the satisfaction of the subject.

Copies of the informed consent forms will be given to the volunteers. The subject information and informed consent form will be prepared and informed consent will be obtained from the subject according to sponsors SOPs.

The subject will be informed by a physician in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be documented. The subject will receive a copy of any amendments to the written information and a copy of the signed and dated consent form updates. Subjects will be informed that they are free to withdraw from the study at any time at their own discretion without necessarily giving reasons.

The subject’s informed consent, which bears subject’s printed name and signature will accordingly filed separately in the investigators file.

Monitors, auditors or the Competent Authorities will have access to personal data, but under no circumstances may copy the subject identification list or an informed consent.

Where required, personal data, and health data in particular, may be:

- hold for inspection by the Competent Authorities or for monitoring the orderly performance of the study,
- passed on to the investigators or an authorized party for analysis in an pseudonymized manner.

4.2 Adverse Event Management

Adverse events (AE) are identified by the investigator using non suggestive questions at every study visit or are documented during spontaneous statement of the participant. According to the MEDDEV guideline 2.7/3 Dec 2010 an adverse event is defined as:

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

- This includes events related to the investigational device or the comparator.
- This includes events related to the procedures involved (any procedure in the clinical investigation plan).
- For users or other persons this is restricted to events related to the investigational medical device.

Each AE will be documented and assessed for seriousness and relationship to the investigational medical device (adverse device effect) or any other study specific treatment.

4.2.1 Serious Adverse Events (SAE)

A serious adverse event (SAE) is defined as an adverse event that

- results in death (fatal);
- is immediately life-threatening;
- results in persistent or significant disability/incapacity;
- requires or prolongs patient hospitalization;
- is a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the afore listed outcomes from occurring (e.g. intensive treatment in an emergency room without hospitalization).

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event.

4.2.2 Reporting Procedures of SAE

All serious adverse events (SAEs) will be reported by the principle investigators to the sponsor (CTC-A) within 24 hours of discovery or notification of the event. The sponsor will cooperate closely with the manufacturers to decide whether further notification processes has to be initiated to inform the relevant Competent Authority. According to annex 7 of Directive 90/385/EEC and to annex X of Directive 93/42/EEC:

All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.

4.3 Termination of the Study

The study will be prematurely terminated for an individual subject, if one of the following criteria is fulfilled:

- Occurrence of a serious adverse event, which does not allow further participation in the study.
- Occurrence of an adverse event, which would in case of further study participation, put the subject at any risk in the opinion of the investigators.
- Non-compliance.
- Subject withdraws informed consent.
- Administrative problems.

Reason, time point, and specific reason for premature study termination of each subject will be documented. The investigator should determine a primary reason for premature study termination of each subject. All relevant safety data until subject's study termination will be collected and reported.

The study will entirely be terminated in case the risk-benefit-ratio changes in such way, that premature study termination is indicated in order to protect subject's health.

4.4 Data Protection

Patients will be informed about data protection and that data will be pseudonymized and handed to third party anonymized. Access to encoded data or source documents will only be given to authorized bodies or persons (sponsor, authorized staff, monitors, auditors, competent authorities or ethics commission) for validation of data. In case of publication, confidentiality of collected data will be warranted.

All subjects will be identified by a unique randomization number. Each investigator holds a subject identification list according to the sponsor`s standard operating procedures (SOP), which will allow the identification of the subjects by holding information about the subject's personal data and randomization number. This list will be safely filed by the investigator in the investigator's file database, which– according to the general guidelines of the German association for internet-based medical research (TMV e.V.) – is operated independently from the database for eectronc data capture and avoids any physical access limitations to room and/or lockers.

4.5 Data Management

All data to be collected will be entered on a case report form (CRF) and are to be considered source data. Automatic print outs as well as patient records and electronic patients are considered source data.

Investigators will enter the information required by the protocol into an electronic data collection system via internet (eCRF). The eCRF will be developed by the data manager for the study. Detailed information on the eCRF completion will be provided during the site initiation visits. Each site will also be provided with an eCRF completion manual. In general, all persons who will enter data into the eCRF will be trained by an e-learning tool. After successful completion of the training, all participants will receive a training certificate. The access to the e-learning tool and to the eCRF is password controlled.

Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data collection system; answers to queries or changes of the data will directly be documented in the system. Plausibility checks will be performed to ensure correctness and completeness of these data. After all data is entered and all queries are solved, the database will be closed.

4.6 Insurance

The sponsor will procure and maintain the legally required patient's insurance according to German medical device act at an insurance company of his choice, accredited within the scope of relevant legislation and shall provide other parties as well as responsible Ethics Committee with written evidence of such insurance prior to the commencement of the study. Insurance terms and conditions will be available on the part of investigator and will be handed over to the patient in his respective mother language.

5 Quality Management

The sponsor is responsible to implement and establish a quality management that is fully in scope of the clinical research project involving human subjects and according to all ethical and legal requirements.

In order to ensure standardized terminology and processes as well as the collection of accurate, consistent, and reliable data, this study will be performed according to the valid standard operating procedures of the respective study center. The investigational sites will agree on standardized measurements and assessments in order to ensure standardization across the sites. Each site will be required to follow the procedures as detailed in the protocol in order to improve reproducibility and data.

The CTC-A will analyze regularly if the implemented processes are still appropriate for efficient and effective trial performance and will improve weak processes that do not prove themselves and that may lead to a low trial quality (Fig. 5).

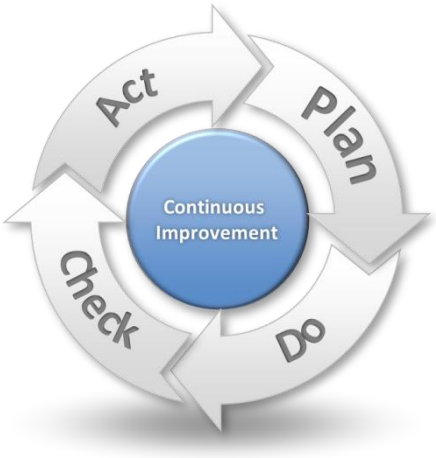


Figure 5: Quality management for continuous improvement.

5.1 Quality Assurance

Quality assurance procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, centralized evaluations, and validation

methods). The quality assurance plan developed specifically for RASimAs will be applied to the trials.

5.2 Monitoring

The studies in RASimAs will be monitored regularly by a qualified monitor from the CTC-A according to GCP guidelines and the respective SOPs. The monitors will be trained during a monitoring kick-off meeting. To prepare the investigators and to standardize performance, training will be held during an investigators' meeting before study start.

Monitoring procedures include one or more visits designed to clarify all prerequisites before the study commences. Interim monitoring visits will take place on a regular basis according to a mutually agreed schedule.

During these visits, the monitor will check for completion of the entries on the eCRF/CRF; for compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements; for the integrity of the source data with the eCRF/ CRF entries; and for subject eligibility. Monitoring will aim at detecting any misconduct or fraud. In addition, the monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits. In addition, the investigator is required to:

- Have all data properly recorded in the eCRF and subject files prior to each monitoring visit
- Have the source documentation available at the monitoring visits.

All subjects who give their informed consent, including those screened, but not entered into the study, will be listed on the subject screening/enrollment log. Further details of monitoring activities will be set forth in the monitoring manual.

6 Abbreviations & Keywords

Abbreviation	Keywords
ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
CTP	Clinical Trial Protocol
eCRF	electronic Case Report Form
ICH-GCP	International Conference on Harmonisation of Good Clinical Pratice
IEC	Independent Ethics Committee
MDD	Medical Device Directive
MEDDEV	Medical Device Guidance
RA	Regional Anaesthesia
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
USADE	Unanticipated Serious Adverse Device Effect