Clinical Investigation Plan

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Study title	Automatic Control of Total Intravenous Anesthesia: Closed-loop Delivery of Propofol and Remifentanil Using Bispectral Index as Feedback Variable. Acronym: ACTIVA 2.
Identifier code of the clinical investigation	NP-2861
Version number of the clinical investigation	Version 4
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Sponsor	Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia
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Index

List of abbreviations

ACTIVA = automatic control of total intravenous anesthesia;
ASA = american society of anesthesiologists
BIS = bispectral index scale;
EEG = electroencephalogram;
GUI = graphical user interface;
HR = heart rate;
MBP = mean blood pressure;
MD = medical device;
PC = personal computer;
PID = proportional-integral-derivative;
PONV = postoperative nausea and vomiting;
SQI = signal quality index;
TCI = target controlled infusion;
TIVA = total intravenous anesthesia.

Summary

Study title	Automatic Control of Total Intravenous Anesthesia: Closed-loop Delivery of Propofol and Remifentanil Using Bispectral Index as Feedback Variable.
Acronym	ACTIVA 2
Identifier code of the clinical investigation	NP-2861
Version number of the clinical investigation	Version 4
Data della versione	07/03/2019
NCT number	NCT04432974
Study rationale	This study concerns the clinical evaluation of a closed loop control system for the automatic administration of anesthetic drugs in total intravenous anesthesia.
Purpose of the experimentation	Evaluating the control system reliability, safety, applicability and capability of inducing and maintaining an optimal anesthetic level.
Primary outcome	Depth of hypnosis adequacy.
Secondary outcome	System dysfunctions, level of satisfaction of the experimenter, effect of drugs delivery on heart rate, effect of drugs delivery on mean blood pressure, postoperative heart rate stability, postoperative mean blood pressure stability, postoperative sedation, postoperative nausea and vomiting, postoperative analgesia.
Inclusion criteria	Adults patients undergoing total intravenous general anesthesia for elective surgery.
Exclusion criteria	Patients under the age of 18. Patients incapable of giving consent.
Study design	Pragmatic, interventional, nonrandomized, single-arm, single-center.
Statistical analysis	Descriptive data analysis.
Procedure for the patient	The patient will undergo an anesthesiological treatment conducted in a closed-loop manner according to the study protocol, under constant

	supervision of the investigator. The anesthetic drugs used are those recommended for total intravenous general anesthesia: propofol and remifentanil.
Risk/Benefit assessment	The major risk of the study is the malfunction of the control program, which would require a switch to manual control (the traditional approach to general anesthesia). There is constant supervision by the investigator, and the control software and infusion pumps have adequate alarm systems in case of malfunction. The ACTIVA software has been developed and subjected to simulations to ensure the minimization of risks related to the infusion system. The benefits for enrolled patients are related to the increased stability of anesthesia during induction and maintenance phases. Constant closed-loop control of infusions and the level of hypnosis could lead to a superior quality of the postoperative recovery. The closed-loop system could also reduce the hemodynamic impact that general anesthesia has on the patient, particularly by reducing hypotension.
Study duration	One year, considering an average enrollment of three patients per week.
Follow up	Each patient is reassessed at 6 hours and at 24 hours after awakening from total intravenous anesthesia.

Study rationale and literature review

Study rationale

In current clinical practice, total intravenous anesthesia (TIVA) can be performed in two ways: manually or through a computerized system called Target Controlled Infusion (TCI).
In the first case, the anesthesiologist manually manages the administration of anesthetic drugs, determining the initial doses to be administered during the induction phase and the infusion rates during the maintenance phase. Manual management of TIVA requires a thorough knowledge of the pharmacokinetics of the drugs used by the anesthesiologist. It is not possible to establish fixed initial dosages and infusion rates because they would not automatically result in a similarly stable concentration of the drug in the brain or plasma. Instead, it depends on each patient's subjective response to the drug administration, as well as the duration and speed of the infusion, thus carrying the risk of overdosing or underdosing. Therefore, for effective manual TIVA, it is necessary to combine knowledge of pharmacokinetic models that indicate the most appropriate drug doses with a “clinical calibration” based on the patient's response observed by the anesthesiologist.
Conversely, the TCI methodology involves the use of infusion pumps equipped with microprocessors programmed with pharmacokinetic models for various drugs. In this mode, the anesthesiologist interacts with the computerized system by selecting the drug, the pharmacokinetic model, the desired plasma or brain concentration, and the model covariates (often represented by the patient's anthropometric measurements). Based on all these data, the pump can calculate the initial dosage for the induction phase and the infusion rates for the maintenance phase. The use of TCI reduces the cognitive workload required of the anesthesiologist because the application of pharmacokinetic models for calculating infusion rates is performed by the machine and does not have to be done manually by the physician, as in the case of manual management. However, it is important to note that a pharmacokinetic model is applicable and provides reproducible results only when applied to patients with characteristics similar to those used to construct the model itself. In most cases, these models are based on young, healthy, and normal-weight volunteers. Therefore, caution is required when applying these models to patients who do not possess these characteristics, and even in cases where they do, there are still inevitable modeling errors and significant variability in the subjective response to drug administration. It is therefore evident that actual plasma and brain concentrations are unlikely to be identical to those predicted by these models and indicated by TCI systems. Thus, even in this mode, the anesthesiologist will need to make manual adjustments, conducting a 'clinical calibration' of the model by appropriately adjusting the desired drug concentration values based on the clinical response observed in the patient.
In light of these considerations, we can assert that TCI represents a so-called “open-loop” control system because it receives input data and calculates the infusion rates of drugs, but it does not receive any information regarding the measurement of the clinical effect that these rates have on the patient. When TCI is employed in clinical practice, the “closure of the loop” is carried out by the anesthesiologist, who observes the patient's clinical response and adjusts the TCI's target concentrations accordingly. Therefore, TCI fundamentally remains a manual control methodology and, although supported by a machine, it does not eliminate the workload of the anesthesiologist regarding the adjustment of the dosages of anesthetic drugs.

The anesthesiologist has a role that includes controlling and regulating various parameters and vital functions of the patient through the administration of drugs, fluids, and the adjustment of hypnosis, analgesia, neuromuscular blockade, temperature, metabolic state, ventilation, and hemodynamics. The complexity of these tasks is further compounded by the intra- and inter-individual variability of patients and anesthesiologists themselves. These factors lead to a range of effects: they make human control suboptimal, influence the outcome of the anesthetic procedure, and significantly limit the ability to establish strict standards of care.

A step forward in this direction can be provided by so-called “closed-loop” control systems. These are automatic control systems that operate on the principle of feedback, and their key elements consist of a measuring device (sensor), a control device (controller), and an actuating device (effector). The sensor measures the controlled variable, which is representative of the desired behavior of the system (system output). This measurement is compared with the desired value (set-point), and the difference between these two values (error) is used by the controller to calculate the value of the control variable (system input).

In the case of TIVA, the system under control is identified as the patient, the effector is represented by the means through which drugs are administered (for example, infusion pumps), the manipulated variable is represented by the infusion rate of drugs, the controlled variable can be a parameter that quantifies the desired effect directly or indirectly, and the sensor is the respective monitoring system. For example, the controlled variable can be represented by the depth of hypnosis measured with a brain activity monitoring system based on the measurement and processing of the patient's electroencephalogram (EEG).

Closed-loop control systems, compared to open-loop control systems, have reduced sensitivity to external stimuli that can act as disturbances, their performance does not depend on predetermined pharmacokinetic models, and they can handle interindividual variability. Furthermore, compared to an anesthesiologist, they can operate at higher frequencies, more accurately, and without distractions. Their use offers several advantages, such as increased patient safety, reduced variability in the quality of anesthetic care, and a decrease in the workload of the anesthesiologist, allowing them to focus on other less repetitive and less suitable tasks for automation than the control of anesthetic drug administration. This last point becomes particularly relevant in the event of emergencies during surgery. Despite these benefits, closed-loop control systems are not yet used in routine clinical practice. This is primarily due to the lack of a complete, simple, and flexible control system that can be easily understood and used by anesthesiologists in the operating room.

This clinical investigation falls within the scope of developing closed-loop control systems for the automatic administration of anesthetic drugs during total intravenous anesthesia, which can be effectively used in routine clinical practice. Its focus is on the evaluation of a control software called ACTIVA and its associated infusion system. The objective of the experimentation is to evaluate the reliability, safety and applicability of the infusion system for anesthetic drugs controlled by the ACTIVA software and to carry out the clinical evaluation of the automatic control system during the induction and maintenance of general intravenous anesthesia. The benefits for enrolled patients could be linked to greater stability of anesthesia in the induction and maintenance phases. Constant closed-loop control of infusions and the level of hypnosis could also reduce the hemodynamic impact that general anesthesia has on the patient, by reducing the onset of hypotension episodes.

Literature review

Closed-loop control systems for the administration of anesthetic drugs (closed-loop anesthesia) were first proposed in the 1950s and were followed by intensive research in the 1980s and 1990s. This research initially focused on closed-loop control of end-tidal concentrations of anesthetic gasses, neuromuscular blockade, and mean arterial pressure. Further impetus for research in this field came in the 1990s with the introduction of cerebral monitoring into clinical practice, thanks to its ability to indicate the depth of hypnosis (West N, 2013) (Dumont GA, 2013).

Several studies have investigated the advantages of closed-loop systems for anesthesia management compared to manual control or TCI, both in the pediatric and adult populations, with both limitations and encouraging results, as discussed below.

The first work on closed-loop anesthesia dates back to the late 1980s, conducted on 11 healthy volunteers using EEG (Schwilden H, 1989).

From the mid-1990s, there was a spread of the BIS, and in the early 2000s, BIS was used with proportional-integral-derivative (PID) control in TCI during the maintenance phase of intravenous general anesthesia (Absalom AR, 2002) (Absalom AR, 2003). These early studies only involved the infusion of propofol while remifentanil was left under open-loop control.

The first multicenter randomized clinical trial on closed-loop anesthesia was conducted in France by Liu with good results, successfully maintaining the ideal BIS range better than manual control with equal hemodynamic stability. This study also used propofol as the sole agent (Liu N, 2006).

In the mid-2000s, the CLADS system by the Indian group led by Puri was developed, and in 2010, the first studies on the McSleepy system by the Canadian group led by Hemmerling were conducted. Both systems had propofol as the only agent (Puri GD, 2007) (Hemmerling TM, 2010).

In addition to the adult population, interest in closed-loop anesthesia began to involve pediatric patients as well. Dumont's group in Canada conducted the first studies, still using propofol as the only agent and maintaining remifentanil at a constant dose during the procedure (Dumont GA, 2011) (Van Heusden K, 2012).

In 2011, Liu conducted the first clinical trial using two agents (propofol and remifentanil) in a closed-loop system, but only during the maintenance phase, while induction used TCI pumps (Liu N, 2011).

More recent studies have shown encouraging results when closed-loop systems involve both propofol and remifentanil.

Orliaguet, comparing two groups of pediatric patients undergoing scheduled surgeries lasting at least one hour, demonstrated that administering Propofol and Remifentanil through a closed-loop system controlled by BIS values is correlated with a higher percentage of time in which BIS remains within the predefined range (40-60). This results in a lower percentage of time when BIS falls below 40 compared to manual control (Orliaguet GA, 2015). Similar results were obtained by Liu in a multicenter randomized controlled study (Liu Y, 2015).

In a pilot study conducted on patients undergoing aortocoronary bypass surgery, in which a system for controlling all three components of anesthesia was used, it was possible to effectively complete the anesthesia procedure without any intervention by the anesthesiologist in 80% of cases (Zaouter C, 2016). The McSleepy system was also employed in a randomized controlled trial involving 186 patients undergoing surgeries lasting at least one hour. The results demonstrate that both hypnosis and analgesia are better controlled by the automatic system compared to the manual control group. Additionally, the

duration of episodes with poor or inadequate hypnosis control was significantly shorter in the first group (Hemmerling TM, 2013).
Even when using entropy as a method of brain monitoring, closed-loop systems have shown the ability to maintain the controlled variable within the desired range longer compared to TCI (Liu N, 2012).
A closed-loop system for administering Propofol and Remifentanil based on BIS values also yielded good results in obese patients. These patients are considered at high anesthetic risk and have different pharmacokinetic and pharmacodynamic profiles compared to the general population, which are not taken into account by common TCI algorithms (Liu N, 2015).
Ramos-Luengo and Asensio-Merino demonstrated that using a closed-loop system for Propofol administration based on BIS values reduces discharge times for patients undergoing vascular surgery (safenectomy) (Ramos-Luengo A, 2017).
In 2017, the first meta-analysis of randomized clinical trials on closed-loop anesthesia versus manual administration or TCI was published. The study, published in Anesthesia & Analgesia, concluded that during induction, the closed-loop system reduces the need for propofol, better maintains the desired depth of anesthesia during the maintenance phase, and reduces wake-up times (Pasin L, 2017).
On the other hand, these tools can pose some risks. In particular, if the system controller is designed inaccurately, exerting either too tight or overly weak control, it can lead to instability in the system. Furthermore, the performance of such systems can be affected not only by system response delays but also by their potential variability over time.
To overcome these limitations, it is important for the feedback controller to be carefully designed to strike a balance between optimal performance and system robustness. One of the most commonly used controllers with these characteristics is the PID controller (Astrom KJ, 2006) (Ang KH, 2005).
The PID controller, by relating error and control signals with three constants, allows for the correct infusion of drugs based on the difference between the depth of hypnosis and the set point (proportional function). It also takes into account past values (integral function) and anticipates future differences (derivative function) (West N, 2013) (Dumont GA, 2013) (Nascu I, 2015).
According to the principles outlined in the editorial written by Kuck and Johnson (Kuck K, 2017), the use of closed-loop systems in anesthesia is governed by three key principles:

1. Patient Safety and Benefit. The use of these systems should not harm patients and should provide clear benefits to them. Even if the system encounters operational issues during its use, it should not negatively impact the patient's well-being. The primary focus should always be on ensuring the safety and well-being of the patient.

2. Transparency. The system must reliably, predictably, and achieve the predefined targets in a comprehensible manner. Anesthesiologists should be able to anticipate the system's future behavior based on its operating principles. It is important that the limits related to the controlled variable are well-defined, and it should be clear whether the system is maintaining the variable within these limits.

3. Reduction of Cognitive Workload. Closed-loop systems should allow anesthesiologists to concentrate on tasks that require their expertise and are less amenable to automation compared to drug infusion. To make this possible, the system should not demand excessive and prolonged attention from the medical practitioner and should operate correctly. It is essential to prioritize patient well-being

and the efficiency of the surgical team. However, it's important to note that these systems are not intended to completely replace the anesthesiologist's role; the anesthesiologist must always maintain adequate vigilance (Mandel JE, 2012).

In summary, these principles aim to ensure that closed-loop systems enhance patient safety and the efficiency of anesthesia delivery while allowing anesthesiologists to focus on critical aspects of patient care and decision-making. Closed-loop systems are seen as tools that aid medical professionals rather than as substitutes for their expertise and oversight.

Medical device information

The medical device under investigation is composed of the ACTIVA software, developed to automatically control the infusion of drugs during total intravenous general anesthesia. The ACTIVA software has been designed to optimize the infusion of anesthetic drugs using a closed-loop system, ensuring the maintenance of a constant and optimal level of anesthesia for the patient. The device under investigation is a software application installed on a personal computer (PC) running the Windows operating system and developed using Matlab. The software consists of an executable file named ACTIVA.exe, located on the desktop of the dedicated PC for the clinical investigation. The primary investigator can start the software by double-clicking the ACTIVA.exe file after powering on the PC. The file is write-protected and locked against deletion to prevent accidental modifications. The PC with the ACTIVA software installed has a label on its external surface indicating “For clinical investigations only.” The considered version of the ACTIVA software is version 1.0 from 2017. The depth of anesthesia is measured using the Bispectral Index Scale (BIS) from Aspect Medical Systems, Norwood, USA, which provides an index capable of quantifying the depth of anesthesia. The administration of anesthetic drugs is automatically regulated by the ACTIVA software based on BIS readings and is constantly supervised by the anesthesiologist through the graphical user interface (GUI) integrated into the software. The control algorithm is implemented as a part of a full control software, which has been developed with Matlab (MathWorks Inc., Natick, Massachusetts, USA) and runs on a Hewlett-Packard 15-da1000nl (HP Inc., Palo Alto, California, USA) personal computer. The control software executes the control algorithm, provides a user-friendly graphical user interface (GUI) and manages the communication with a Dräger Infinity Delta (Drägerwerk, Lübeck, DE) patient monitor, which is used to obtain the BIS and other parameters of interest, and two Alaris GH syringe pumps (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA), which are used as actuators to administer propofol (20 mg/ml) and remifentanil (50 µg/ml). The data are acquired from the patient monitor with a sampling period of 1 second. New values of propofol and remifentanil infusion rates are sent to the pumps every 5 seconds. The connections between the personal computer and the medical devices are made by means of three USB-RS232 converter cables. The full control system is shown in Figure 1. A screenshot of the control software’s GUI is shown in Figure 2.
The infusion system also includes commonly used medical equipment in the clinical setting for intravenous anesthesia administration, specifically:

- Sterile single-use 60 ml syringes without needles with a Luer Lock connection, latex-free.

- Single-use sterile PVC extension lines (1mm) with a length of 200 cm, male-to-female, with a ring.
- Single-use, sterile, latex-free infusion kits.
- Single-use, latex-free BIS Quatro sensors.

Purpose of use for the experimental device

The target population for the device consists of surgical patients undergoing elective procedures requiring general anesthesia, and for whom intravenous anesthesia is advantageous. The ACTIVA software is programmed to operate exclusively during intravenous anesthesia when propofol is administered as a hypnotic agent and remifentanil as an analgesic. The experimenters must be specialists in anesthesia and intensive care with adequate knowledge of the operation of the ACTIVA software and its GUI. In particular, familiarity with the user manual is required. The primary experimenter is responsible for training the experimenters in the use of the ACTIVA software before its clinical application and for providing guidance during the clinical investigation until the experimenters achieve complete autonomy in using the ACTIVA software.

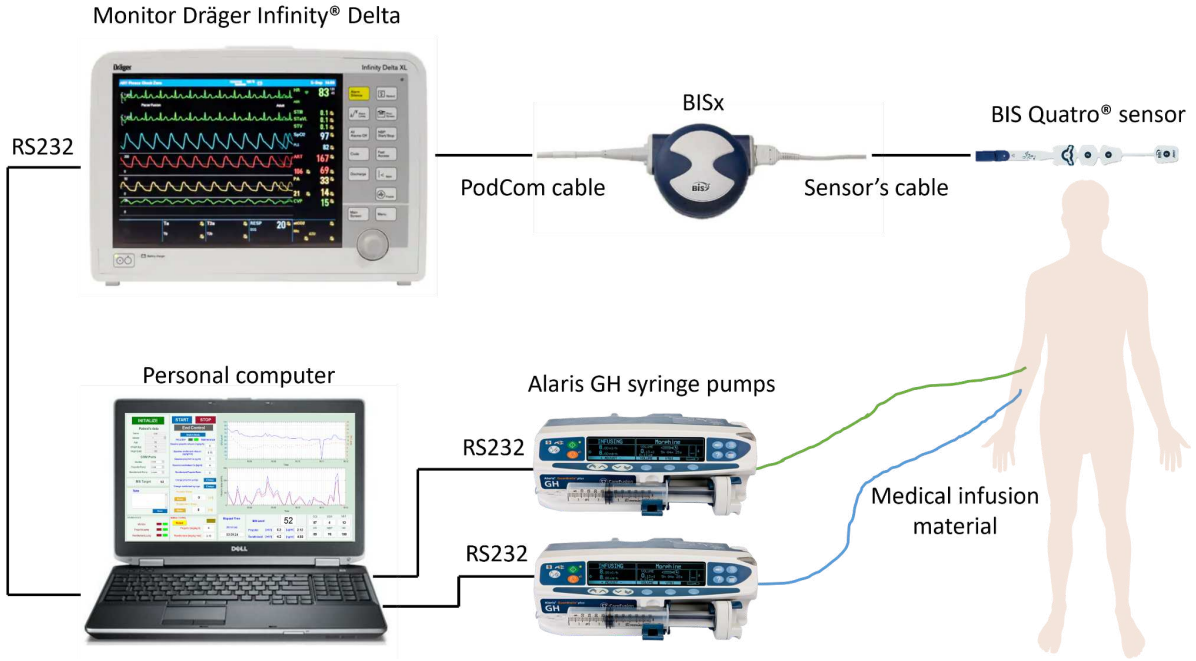

Figure 1: Schematic representation of the infusion system for anesthetic drugs based on the ACTIVA software.

Figure 2: Graphical User Interface (GUI) of the ACTIVA software.

Number of experimental medical devices expected to be used

It is expected to use a single experimental medical device.

Risks and benefits of the medical device

The sponsor is responsible for evaluating the safety of the medical device under investigation in the clinical trial, reviewing recorded adverse events, conducting investigations into unforeseen serious adverse events, and notifying the regulatory authorities as per applicable regulations. The sponsor is also responsible for training investigators prior to the commencement of the study, including reporting of serious adverse events. The sponsor will oversee the procedures for adverse events related to the clinical investigation and may assist investigators in the medical review of reported adverse events.
The principal investigator is responsible for ensuring the safety and health of enrolled subjects and must report adverse events to the manufacturer, the relevant ethics committee, and the investigational site. The investigator must provide all necessary information for the completion of the adverse event form at the investigational site. The principal investigator is responsible for reporting a serious adverse event to the Ethics Committee and the relevant regulatory authority according to local regulations. The investigator must assist the sponsor and the manufacturer in the clinical review of the adverse event, providing all available documentation. The sponsor and the principal investigator are obligated to inform other investigators, regulatory authorities, and the ethics committee of the serious adverse event in accordance with local regulations.

Expected clinical benefits

The medical device ACTIVA, the subject of the clinical investigation, has been developed to be reliable, safe for the patient, and clinically effective. Specifically, the device is designed to be user-friendly through its user-friendly (GUI).

In a clinical setting, the medical device should be effective in maintaining the enrolled subject within the desired hypnosis range (BIS between 40 and 60), minimizing periods during which the enrolled subject exhibits anesthesia levels that are either too shallow or too deep.

Predicted clinical risks associated with the device and residual risks

The clinical risk associated with the use of the ACTIVA software should not exceed the clinical risk associated with manual control (standard of care). In cases where the results obtained during simulations are not replicated in a clinical setting, it is possible that the software may fail to ensure adequate levels of anesthesia. The principal investigator will decide to interrupt the system and switch to manual mode (current standard of care).
The clinical investigation of the ACTIVA software is the first of its kind for the system, where anticipated adverse events related to the device and risk analysis are the primary focus of this clinical study. During the software development, the primary objective was to eliminate/minimize these risks.
To minimize device-related risks, the ACTIVA software cannot be initiated if the connected devices are not functioning correctly (refer to the user manual). The proper functioning of the control software and its components is indicated on the graphical user interface with a green light, allowing the principal investigator to promptly assess the system's correct operation.
Although the device has undergone extensive testing and simulations during its development, it is possible for it to stop functioning during use. Therefore, the ACTIVA software must be under constant supervision by the investigator, who can detect malfunctions or anomalies through the graphical user interface and take prompt action.
In particular, simulation tests have been conducted to verify that the ACTIVA control system can be interrupted and switched to manual mode (standard of care) in less than 20 seconds. This time period is shorter or overlapping with the time it takes for an anesthesiologist to manage a normal infusion pump that needs to be turned off and restarted and much shorter than the time required to replace a malfunctioning infusion pump.
In the event of a malfunction during drug infusion, the ACTIVA software is capable of promptly alerting the investigator by emitting appropriate auditory and visual signals (red light) on the graphical interface and auditory signals directly from the infusion pumps. Additionally, the investigator can easily and quickly switch to manual control mode for the pumps (see user manual). Examples of malfunctions may include:

- Software freeze/crash.
- Data transmission malfunctions.
- Infusion pump malfunctions.

The ACTIVA software always generates a report file, even in the case of malfunctions, containing all the data from patient monitoring, infusion pumps, and the software itself, along with notes entered by the principal investigator. Through data analysis, it is possible to identify the source of the technical issue.
In the event of ACTIVA software malfunction, the patient monitoring systems, particularly the Bispectral Index (BIS), are never altered or damaged (the data flow is only outbound to the computer where the ACTIVA software is installed), while the infusion pumps continue to operate in manual mode (standard/classic mode controlled by the anesthesiologist).
Switching to manual control is always possible at the discretion of the principal investigator, even in the absence of system malfunctions.

Risks associated with participation in the clinical investigation

The investigator monitors the system to prevent any consequences for the enrolled subject in the clinical investigation in case the reliability and safety of the system are compromised. From a clinical perspective, it is possible for the software to provide stable and adequate anesthesia. The investigator may choose to switch to manual control if this is not the case.
The drugs Propofol and Remifentanil have received marketing authorization and are standard of care for intravenous general anesthesia. The ACTIVA software does not increase the known risks associated with the infusion of these drugs.
The pumps and the monitor are not altered in their original functions by the software; therefore, the risks associated with these devices are not increased.

Interaction with concurrent medical treatments

The ACTIVA control system does not interfere in any way with the surgical procedure, and therefore, there are no surgical risks attributable to the control system.
During intravenous general anesthesia, medications that interact with the anesthetic drugs Propofol and Remifentanil may be administered for clinical reasons. This also occurs during the operation of the ACTIVA software. There are no additional risks compared to normal clinical practice regarding these interactions.

Procedures for risk control or reduction

For patient safety, approval must be obtained from the competent ethics committee for the investigational site, as well as authorization from the investigational site.
Investigators will be trained by the principal investigator and the manufacturer to ensure a clear understanding of the protocol, user manual, and all relevant study processes.
Each investigator will be registered on a list of investigators, which will be signed, expressing their commitment to conducting the study according to the protocol, recording the required data, and maintaining continuous supervision over the device.
A dedicated advisory board has been established to continuously assess subject safety and the suitability of the ACTIVA software to continue the clinical investigation. The group's responsibility also includes suggesting to the sponsor whether to continue or terminate the clinical investigation.
Risks are minimized by adhering to the protocol, using the device according to the user manual, following the hospital procedures of the sponsor's site, adhering to subject selection criteria, and maintaining constant supervision of the subject and ACTIVA software through the graphical user interface.

Risks/benefits ratio

The ACTIVA software should prove to be safe, reliable, and feasible. Furthermore, considering that the sample size of the study is calculated based on the clinical evaluation of the infusion system, it is possible that it will demonstrate the ability to maintain an optimal level of anesthesia compared to what is described in the literature for other similar systems and better than the standard of care.

Information related to the clinical investigation

Clinical study objectives

The primary objective of the clinical investigation is to investigate the clinical performances obtainable by the control system under study in terms of depth of hypnosis adequacy.
The secondary objective is to evaluate the reliability, safety and applicability of the control system under study and to carry out the clinical evaluation of the automatic control system during the induction, maintenance and recovery of general intravenous anesthesia.

Clinical study description

The clinical study ACTIVA 2 is a pragmatic, interventional, nonrandomized, single-arm, single-center.
The investigation is for research purposes (for publication in scientific journals), non-commercial, and for clinical development of the ACTIVA control software.

The primary outcome measure is the depth of hypnosis adequacy. It is assessed by means of the percentage of the anesthesia maintenance duration in which the BIS is kept inside the recommended range from 40 to 60. The percentage of the anesthesia maintenance duration in which the BIS is kept below 40 is also specified. Maintenance duration is the period of time that goes from the end of anesthesia induction to the point at which the automatic control is turned off at the conclusion of surgery. The end of anesthesia induction is defined as the time instant when the BIS drops below 40 for the first time and remains there for the subsequent 30 seconds.

The secondary outcomes measures are:

- Number and types of dysfunctions of the ACTIVA automatic infusion system.
- Level of satisfaction of the experimenter. It is expressed on a scale from 0 to 10 regarding the ease of use of the ACTIVA software and its infusion system, the induction phase of anesthesia and the maintenance phase of anesthesia.
- Effect of drugs delivery on heart rate. It is assessed by means of the percentage of the anesthesia maintenance duration in which the heart rate (HR) is kept inside the range from 50 to 100 beats per minute. The percentage of the anesthesia maintenance duration in which the HR is kept below 50 is also specified.
- Effect of drugs delivery on mean blood pressure. It is assessed by means of the percentage of the anesthesia maintenance duration in which the non-invasively measured mean blood pressure (MBP) is kept inside the range from 65 to 110 mmHg. The percentage of the anesthesia maintenance duration in which the MBP is kept below 65 is also specified.
- Postoperative heart rate stability. It is assessed by measuring the HR in bpm.
- Postoperative Mean Blood Pressure Stability. It is assessed by non-invasive measuring of the mean blood pressure in mmHg.

- Postoperative sedation. It is assessed by means of a Sedation Score scale. It is a 3 point scale from 0 (fully awake) to 3 (fully sedated).
- Postoperative nausea and vomiting (PONV). It is assessed by means of the Bellville PONV scale. It is a 3 point scale from 0 (no nausea and vomiting) to 3 (vomiting present).

- Postoperative analgesia. It is assessed using a 10-point numeric rating scale (NRS). It is a 10 point scale from 0 (no pain) to 10 (maximum pain).

Measured variables

For each patient enrolled in the study, the following variables will be collected:

- Age.
- Gender.
- Weight
- Height
- Type of surgical procedure
- Anesthesiological risk assessment according to the American Society of Anesthesiologists (ASA) physical status classification system.
- PONV risk assessment according to the Apfel simplified risk score.

These data are collected by the principal investigator at patient arrival in the operating room, before surgery and they are noted on the patient's anesthesiology clinical record form.
The following variables are automatically collected by the ACTIVA software, they are recorded in real-time every second and stored on a ".csv" file:

- HR.
- Peripheral oxygen saturation.
- MBP.
- BIS.
- BIS signal quality index (SQI).
- Burst suppression ratio[1] .
- Infusion rates of propofol and remifentanil.

The following data are collected by the principal investigator after surgery and noted on the patient's anesthesiology clinical record form.

- System dysfunctions.
- Level of satisfaction of the experimenter.
- HR.
- MBP.
- Postoperative sedation.

[1] Burst suppression is defined as a period on the EEG trace characterized by attenuated or suppressed signal (<10 mV) alternating with brief periods of cortical activity, precisely termed 'bursts.' More than 50% of this period is dominated by attenuated/suppressed activity. This effect may sometimes be intentionally induced, for example, during neuroanesthesia, as a protective measure against cerebral ischemia, as it coincides with a reduction in cerebral metabolism. However, it is important to consider that it is also associated with a higher incidence of postoperative delirium.

- PONV.
- Postoperative analgesia.

Participation criteria

The population considered in the clinical study consists of adult patients scheduled for elective surgery for whom total intravenous general anesthesia is indicated, using the hypnotic drug propofol and the analgesic drug remifentanil, and who have provided appropriate informed consent. Patients under the age of 18 and patients incapable of understanding and consenting are excluded from the study.
The selection of patients is made regardless of age (provided they are over 18), gender, weight, height, as well as anesthetic risk and the type of surgical procedure. This reduces systematic errors associated with specific patient selection for enrollment in the study.

Enrollment procedure

The enrolled patients underwent an anesthesiological treatment conducted in a closed-loop system following the clinical protocol and under the constant supervision of the experimenter. The experimentation took place in a single operating room at the experimenter's center where plastic surgery procedures are performed. This allowed for maintaining a consistent surgical and environmental setting.
Patients are informed of the possibility to participate in the study during the preoperative anesthesia visit, which typically occurs two weeks before the surgical procedure. If the patient chooses to participate in the study, informed consent is obtained before the start of the medical procedure subject to the experimentation.
The patient enrolled in the study arrives in the operating room on the day of the procedure and undergoes the standard preoperative preparation, which is administered to all patients undergoing intravenous general anesthesia, regardless of their enrollment in the study. In particular:

- Venous access is established.
- Instrumental monitoring includes blood pressure, electrocardiogram, peripheral oxygen saturation, and BIS (Bispectral Index).
- Infusion pumps are connected to the venous access.

The ACTIVA control software is then initiated by the lead experimenter, who enters the necessary anthropometric data into the GUI, initializes the system, and starts the automatic control. During the surgical phase, the experimenter supervises the system and ensures its proper functioning. If necessary, annotations are added to the system according to the protocol. Once the surgical procedure is completed, the experimenter stops the drug infusions through the GUI but continues recording the BIS and other patient monitoring parameters. The patient awakens spontaneously. After awakening, the ACTIVA software is turned off by the experimenter.
The patient is then transferred to the recovery room where they undergo standard post-operative procedures. The study concludes 24 hours after the patient awakens from anesthesia with a postoperative anesthesia visit.

Number of patients enrolled

The sample size was determined based on the primary outcome measure concerning the depth of hypnosis adequacy provided by the ACTIVA control software. Specifically, it was calculated with the aim to assess the proportion of patients for whom the percentage of the anesthesia maintenance duration in which the BIS is kept inside the recommended range from 40 to 60 is greater than 43%. This latter value is the average percentage that was observed in a previous data acquisition campaign concerning manually controlled TIVA, which was performed in the same clinical setting considered for the present clinical trial (Study acronym: ACTIVA 1, Id code: NP-1843).
The proportion was estimated to be 90% of patients with a 95% confidence interval and a margin of error of 10%. The resulting sample size is 139 patients. This number of enrolled subjects also ensures that the ACTIVA control software is adequately tested for safety, reliability, feasibility, and applicability. Secondary outcome measures were not considered in the sample size calculation.

Subject Enrollment Count

All subjects enrolled in the clinical investigation (including patients withdrawn from the study before its initiation who have provided informed consent and patients lost to follow-up) must be counted and documented. If a subject withdraws from the study, the reasons should be documented and recorded. These patients will not be included in the sample size calculation for the study or in the primary or secondary objectives.
Patients who are withdrawn from the study before the initiation of the ACTIVA software due to device safety, reliability, or feasibility issues are considered enrolled in the study and will be followed throughout the study's duration.
Patients who discontinue the study during the operation of the ACTIVA software are considered fully enrolled, and all available data will be analyzed.

Study Duration

The expected duration of the study is 1 year, assuming a weekly enrollment of 3 patients. For each enrolled subject, their participation in the study concludes at the 24-hour post-awakening follow-up after intravenous general anesthesia.

Concomitant medications and medical treatments

The ACTIVA control system is used during intravenous general anesthesia for elective surgical procedures. During the operation of the ACTIVA software, the surgical procedure is ongoing. However, the ACTIVA control system does not interfere with the surgical procedure in any way.
For clinical needs, medications that interact with propofol and remifentanil may be administered. However, with the ACTIVA control system, there are no additional risks compared to the normal clinical practice of TIVA regarding these interactions. However, these medications could alter the interpretation of the outcome measures used to evaluate the secondary objective of the study. For this reason, the experimenter records the use of such medications in the notes section of the GUI so that this event is documented in the report file and can be considered during the analysis of the results.

Follow-up

Each enrolled patient was reassessed 6 hours and 24 hours after awakening from anesthesia during the postoperative anesthesia visits.

Statistical analysis

The statistical analysis consists in the descriptive statistics of the collected data.
Synthetic statistical data are calculated for all study variables.
For quantitative data mean and standard deviation, or median and interquartile range are calculated according to data distribution. Data normality is checked by using the Shapiro-Wilk test.
Categorical variables are synthesized by using patient count and percentage of patients belonging to each category.

Systematic errors prevention methods

Interaction between the ACTIVA software and the experimenter.
The user interface has been developed to make it easy for the experimenter to initiate the infusion system. Specifically, once the necessary connections between the monitor, PC, and infusion pumps have been set up, the experimenter can start the ACTIVA software and quickly check for any issues with the system. The software only starts when the experimenter has entered all the required data for startup, and the connections between the devices are correct and functioning. If the experimenter has not entered all the required data or if the devices are not functioning correctly or have not been turned on, the ACTIVA software cannot begin the infusion phase. This ensures both adequate safety and prevents incorrect or incomplete operation.

Selection bias during patient recruitment.
The clinical trial recruits patients to undergo intravenous general anesthesia for elective surgery. The experimentation takes place in a single operating room of the experimenter's center where plastic surgery procedures are performed, ensuring a constant surgical and environmental setting. Patient selection, excluding those under 18 years of age, is done regardless of age, gender, weight, height, anesthesiologic risk, or type of surgical procedure. This reduces systematic errors associated with specific patient selection.

Selection bias at the time of analysis.
The clinical trial requires that closed-loop anesthesia be practiced from the initiation of the ACTIVA software until the end of the surgical procedure. However, it may happen that:

- The primary experimenter decides to interrupt the software; in this case, it must be recorded in the report file.
- The software or its components (monitors, infusion pumps) may cease to function correctly; in this case, the system is halted and switches to manual mode or requires the experimenter's intervention. The experimenter must record the event in the report file. If the above occurs, it is the responsibility of the experimenter to assess the possibility of including in the data analysis what has been collected up to the moment of system interruption.

Measurement bias during data collection.
It is possible that during the operation of the ACTIVA software, there is a failure to read the BIS or a disturbance causing artifacts. The absence of a BIS signal or its distortion is not uncommon during normal clinical practice and is indirectly reported by the SQI and on the patient monitor. Such problems are usually caused by poor adherence of the BIS Quatro sensor to the skin. The experimenter can resolve the issue without consequences for the

infusion system. During the software development phase, these events have been anticipated, and appropriate filters and event checks have been incorporated, allowing for short-term toleration of BIS signal deficiencies (both qualitative - disturbances, and quantitative - signal absences). If the problem persists beyond 30 seconds or the experimenter deems it necessary, the system switches to manual mode. It should be emphasized that the BIS Monitor is an approved and certified instrument and undergoes regular maintenance by the clinical engineering service of the experimenter's center.
It is possible that during the operation of the ACTIVA software, there may be an issue with the infusion of one or both drugs due to malfunction or lack of control of the pumps (either one or both). The pumps are periodically checked and tested by the clinical engineering service of the experimenter's center, minimizing risks. In case of lack of control by the ACTIVA software, the pump emits an audible signal, and the user interface highlights the lack of connection on the corresponding pump with a red light. This allows the primary experimenter to rectify the problem or decide to halt the infusion system. During simulations, no issues with the infusion pumps were identified, and the infusion rates corresponded to what was commanded by the ACTIVA software and indicated on the GUI. This was made possible by developing a control system that respects the maximum infusion rates that the pump is capable of, in accordance with its mechanical components.

Instrument-phenomenon interaction.
The system relies on feedback control in which infusion rates are regulated by software after receiving BIS data to maintain the desired level of hypnosis. It is likely that the control system is better able to maintain the desired BIS level compared to manual control with or without TCI. If the primary experimenter observes an inability to maintain the BIS within the desired range despite apparent correct software operation, they may choose to suspend the software and switch to manual mode. This should be noted in the designated notes section and recorded in the report file.

Improper working conditions
The current version of the ACTIVA software is designed for exclusive use in the operating room with the equipment specified in the user manual. ACTIVA software should only be used with the propofol and remifentanil drugs for intravenous general anesthesia. The ACTIVA software must always be supervised by the primary experimenter and should not be used as a substitute for an anesthesiologist in any way.

Factors that may compromise the outcome and interpretation of the results

It is possible that the use of other sedative drugs in addition to propofol and remifentanil may affect the secondary objectives of the study, both in a negative and positive sense. The experimenter enters the use of such drugs in the notes of the ACTIVA software GUI, and this event remains recorded in the report file and will be considered during the analysis of the results.
It is possible that the experimenter may forget to enter events, drugs, or assessments relevant to the primary and secondary objectives in the notes of the ACTIVA software GUI. To minimize this risk, experimenters are trained according to the user manual and the current clinical protocol.
It is possible that the ACTIVA software, despite the pre-clinical development process and numerous simulations, does not meet reliability and safety criteria. In such a case, the study

will be interrupted, and the manufacturer will assess for a prompt solution. Only after producing a reliable version of the ACTIVA software can the clinical investigation resume.
It is possible that the monitor or one or both of the pumps may experience malfunctions during the clinical investigation. These malfunctions are not attributed to the ACTIVA software but will be recorded in the report file and evaluated during the results analysis. Repairing or replacing the faulty device resolves the issue.
It is possible that the primary experimenter may decide to discontinue the control system to switch to manual control or another anesthesiological technique, noting the choice, which will be recorded in the report file. Switching to manual control or another anesthesiological technique is possible at any time if the experimenter deems it appropriate, even in the absence of system malfunctions.

Clinical investigation monitoring plan

The clinical investigation monitoring plan is the responsibility of the principal investigator and the advisory board specifically established for this clinical investigation. Monitoring of the clinical investigation ensures constant adherence to the clinical protocol by investigators and the application of all recommendations in this protocol.
The principal investigator and the advisory board verify that data is collected and stored adequately and reported correctly without alterations, in compliance with timelines, adequacy, accuracy, and truthfulness.
The task of the advisory board is to ensure that the investigation has sufficient and adequate investigators and resources to be conducted safely and effectively.
Monitoring of the clinical investigation occurs on a monthly basis for the following:

- Adequate preparation of investigators.
- Regular enrollment (informed consent and informational sheets).
- Evaluation of the ACTIVA software (with reference to primary outcome measure).
- Regular data collection and storage.
- Regular follow-up of enrolled subjects.
- Analysis of emerging issues as directed by the investigator.
- Analysis of safety-related notes regarding the ACTIVA software.

The principal investigator is required to maintain the report files generated by the ACTIVA software in their integrity and make them available to the competent Ethics Committee, the manufacturer, and the investigational site.

Ethical considerations

Clinical experimentation was preceded by a careful phase of risk and benefit assessment resulting from the use of the control software under investigation. The main risk of the study

is constituted by the malfunction of the control software. This leads to a transition to manual control (current clinical standard) of general anesthesia without causing any clinical problems for the patient. Furthermore, the control software, infusion pumps, and monitor have adequate alarm systems in case of malfunction. The drugs propofol and remifentanil have received marketing authorization and are drugs used in the current clinical standard for intravenous general anesthesia. The ACTIVA control software does not increase the known risks associated with the infusion of these drugs. The infusion pumps and the monitor are not altered in their original functions by the control software. Therefore, the risks associated with the use of these devices are not increased by their connection to the control software. Thus, the clinical risk associated with the use of ACTIVA software is not considered higher than the clinical risk associated with manual control of intravenous general anesthesia. Risks are further reduced by adhering to the clinical protocol, using the device according to the user manual, following the hospital procedures of the sponsoring center, adhering to subject selection criteria, and maintaining constant supervision of the infusion system controlled by the ACTIVA software. In this regard, the investigators have been trained by the principal investigator and the manufacturer to ensure that the protocol, user manual, and all relevant study processes were well understood.
The expected benefits for patients are related to the increased stability of anesthesia during induction and maintenance phases achievable through constant closed-loop control of infusions, minimizing periods in which the patient presents anesthesia levels that are too shallow or too deep.
The experimentation has been approved by the competent ethics committee and has obtained the authorization of the co-investigator.
The patient is informed of the possibility to participate in the study during the preoperative anesthesiology visit, which usually takes place two weeks before the surgical procedure. On this occasion, the patient receives adequate information through an informative sheet and a discussion with the investigator. The informative sheet will then be retained by the patient. This document briefly describes the purpose of the study and its conduct, indicating the novelty of the clinical investigation compared to common clinical practice. If the patient intends to participate in the study, informed consent is signed before the start of the medical procedure subject to the experimentation.

Data management

The data management activities have been carried out in such a way as to ensure that data processing is complete, consistent, and logical, and that all data described in the clinical investigation are included in the study. The file recorded by the ACTIVA control software allows for the analysis of the control system's performance regarding malfunctions and/or critical issues identified by the experimenter, recorded in the form of notes. Furthermore, it contains recordings of time series data for drug infusion rates, BIS (Bispectral Index), and other standard monitoring data for general anesthesia. The report file allows for offline analysis of the control system's performance. The report file is generated automatically by the ACTIVA control software. Post-operative data, on the other hand, are manually recorded by the experimenter on the designated data collection sheet. Experimenters have filled out the data collection sheet and entered notes on the GUI during the operation of the ACTIVA software as prescribed. During the conduct of the clinical study, the data resulting from the study are stored by the lead experimenter in their original form on the PC dedicated to the

ACTIVA software and backed up on the experimenter center's PC. At the end of the study, all data have been migrated and are stored on a dedicated PC at the experimenter center. Access to the data is restricted to authorized individuals.

Amendments to the clinical evaluation plan

Any amendment to the protocol will be submitted to the competent authorities for authorization or appropriate notification, depending on the nature of the change. Additionally, all administrative updates that do not require submission to the competent authorities or the ethics committee will still be documented. An administrative update is defined as a change that has no impact on patient safety, health, or the scientific validity of the study.

Deviations from the clinical evaluation plan

Except in cases of necessity, the principal investigator is not authorized to deviate from the clinical protocol. Deviations from the clinical evaluation plan that are decided upon by the investigator to protect the rights, safety, and health of the patient will be documented and communicated to the manufacturer and the sponsor as soon as possible.
The sponsor will define the level of deviations as major or minor and will present them to the relevant Ethics Committee for evaluation accordingly. Major deviations are defined as changes in the conduct of the clinical investigation compared to the current protocol that could compromise the subject's rights, safety, health, completeness, accuracy, or scientific integrity of the data.
Deviations should be reported to the principal investigator and recorded in the patient's chart. Cases where a regularly enrolled patient does not complete the study due to ACTIVA software issues or at the investigator's discretion are not considered deviations; the patient will not be considered for secondary outcome measures but will be evaluated for the primary outcome measure.

Device Responsibilities

Access to the investigational device will be restricted to the investigators, and the device must be used exclusively in accordance with this protocol.
The sponsor must keep track of the device's location, which may be returned to the manufacturer for inspections or updates following the assessments described in this clinical investigation plan. The device will then be returned to the sponsor/principal investigator for the continuation of the study once the necessary inspections or updates by the manufacturer have been completed.
In the event that device inspection by the manufacturer is deemed necessary at the request of the Principal Investigator or the advisory board, documents should be prepared, including:

1. Date of submission to the manufacturer.
2. Number of the last subject enrolled in the study.
3. Date of receipt from the manufacturer.

4. Report from the manufacturer regarding the device inspection and any modifications or updates to the ACTIVA software.

Once the device has been received, the trial may continue with communication to the relevant authorities.

Declaration of Compliance

The clinical investigation involving the ACTIVA software will be conducted under conditions similar to the normal conditions of device use, and the procedures used for conducting the clinical investigation are appropriate for the device under examination.
During the planning of the clinical investigation, all relevant characteristics, including those related to device safety, performance, and potential effects on the patient, have been examined, and these characteristics will be monitored throughout the duration of the investigation.
The clinical investigation will be conducted according to an appropriate clinical protocol that takes into account the current state of scientific and technical knowledge and is designed to confirm or refute the manufacturer's claims regarding the device. This investigation includes a sufficient number of observations to ensure the scientific validity of the conclusions.
The clinical investigation, with regard to the responsibility of the manufacturer/authorized representative, will be conducted in accordance with the provisions of Annexes VIII and X of Legislative Decree February 24, 1997, no. 46 and subsequent amendments, and Annexes 6 and 7 of Legislative Decree December 14, 1992, no. 507 and subsequent amendments, in compliance with the Declaration of Helsinki, as well as applicable sections of the ICH/GCP guidelines, UNI EN ISO 14155-2012, and subsequent updates or other internationally recognized equivalent standards. This will occur only after approval by the competent Ethics Committee of the experimental protocol, informed consent text, and documentation required by the aforementioned standards.
The medical device complies with the essential requirements as defined by current regulations, except for aspects that are the subject of the investigation. Necessary precautions have been taken to protect the health and safety of the patient.
Risk assessment has been performed in accordance with UNI EN ISO 14971:2012 and subsequent amendments, and all necessary measures have been taken to minimize these risks.
All serious adverse events will be fully recorded and immediately reported to the 6th Office of the DGDMF of the Ministry of Health and to all other competent authorities of the member states involved in the clinical investigation, in accordance with point 2.3.5 of Annex 7 of Legislative Decree December 14, 1992, no. 507 and subsequent amendments, and point 2.3.5 of Annex X of Legislative Decree February 24, 1997, no. 46 and subsequent amendments.
All financial burdens related to the clinical investigation are borne by the manufacturer and do not fall on the National Health Service or the patients.
The Clinical Trial Office of the Ministry of Health and the competent ethics committees will receive the final report prepared by the investigator at the end of the clinical investigation, including a critical evaluation of all data obtained during the study. This clinical investigation plan is prepared in accordance with UNI EN ISO 14155:2012 and subsequent updates.

Documents for obtaining informed consent have been prepared and have undergone evaluation by the competent Ethics Committee.
The manufacturer undertakes to make available to the Ministry of Health the dossier for the investigator and complete documentation related to risk analysis.
The manufacturer commits to provide the Ministry with all relevant information regarding the ACTIVA software, including the design, manufacturing methods, and descriptions and explanations necessary for understanding the aforementioned designs and schematics and the product's operation; the results of design calculations, controls, technical tests performed, and similar assessments conducted.

Vulnerable Population and Treatments in Emergency Circumstances

Not applicable.

Early Termination and Suspension of the Clinical Investigation

The clinical investigation may terminate prematurely in the event that:

1. Patient enrollment occurs at a faster rate than anticipated.

2. The ACTIVA software is found to be unreliable or unfeasible in a clinical setting with no possibility of correction.

3. Risks emerge that necessitate the immediate termination of the clinical investigation with no possibility of mitigating or eliminating these risks.

The clinical investigation may be suspended in the event that:

1. The ACTIVA software exhibits reliability, safety, or feasibility issues that warrant reevaluation by the manufacturer but are considered solvable.

2. Whenever the investigator deems it necessary to suspend the study, deferring the decision on resumption to the Principal Investigator. The Principal Investigator will analyze the reasons and determine a possible solution, possibly after consultation with the manufacturer and the advisory board."

Data Publication Policy

The results of the clinical investigation will be submitted for publication in scientific journals after the study is completed, and the data have been analyzed according to the statistical plan.
Publication may be sought in journals specializing in anesthesia and intensive care, anesthesia and analgesia, or national and international surgical journals.
Additionally, publication may be sought in other scientific journals deemed suitable by the manufacturer, even if the manufacturer has not previously published in those journals.

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