OFFICIAL STUDY TITLE: HIGH FLOW OXYGEN THERAPY VERSUS CONVENTIONAL OXYGEN THERAPY IN CARDIAC SURGERY PATIENTS-OPTICAR STUDY

PROTOCOL SUBMITTED FOR IRB APPROVAL: Evaggelismos General Hospital, Athens, Greece, Date: March 3, 2017 [Protocol ID: NKU ATHENS; OPTICAR 47/03/03/2017]

ClinicalTrials.gov Identifier: NCT03282552

High Flow Oxygen therapy versus Conventional Oxygen Therapy in Cardiac Surgery Patients-OPTICAR study

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Brief summary

High flow oxygen therapy has been applied after extubation in cardiac surgery patients with uncertain efficacy. The current authors plan to conduct a prospective, randomized, controlled study of nasal high flow therapy (NHF) application with higher (60 L/min) or lower flow (40 L/min) oxygen mixture administration versus standard oxygen treatment (Venturi mask) after extubation of patients undergoing elective or non-elective cardiac surgery.

Detailed description

Over the past decade, nasal high flow (NHF) has been introduced for oxygen therapy in adults. Its indications have been expanded, especially in cases of acute hypoxemic respiratory failure.

The device consists of an air/oxygen blender connected via an active heated humidifier to a nasal cannula, through a single limb, heated inspiratory circuit. It delivers a fraction of inspired oxygen (FiO_2) from 21% to 100% with a flow rate up to 60 L/min. FiO_2 adjustments are independent of the set flow rate so that the patient is given heated, humidified high-flow oxygen, with a flow that can be adjusted above the patient's maximum inspiratory flow rate, thereby increasing confidence about the actual FiO_2 being delivered to the patient.[1] These device characteristics make it more promising in comparison with conventional low- and high-flow oxygen devices (e.g., nasal cannula, non-rebreathing masks, Venturi masks), especially in patients with high inspiratory flow rates, such as patients with acute respiratory failure (ARF).[1,2]

The benefits arising from application of oxygen with high flow rates via NHF are 1) reduction in the entrainment of room air and thus ensuring higher and more stable FiO_2 values,[3,4] 2) generation of positive airway pressures during expiration as a result of the expiratory resistance imposed to the patient's exhalation against the continuous high flow of incoming oxygen gas,[5-8] 3) improving mucociliary function and clearance of secretion by continuous heating and humidifying of the administered gas,[9,10] 4) reducing dead space ventilation[11,12] and 5) reducing work of breathing[13].

All the aforementioned NHF mechanisms of actions exert various effects on the respiratory system, including improved gas exchange, lower respiratory rate and effort and improved lung mechanics which are correlated with more comfort and less subjective dyspnea.[13-15]

Respiratory complications after cardiac surgery can affect morbidity and mortality, and increase the healthcare cost.[16,17] Advanced age, duration of extracorporeal circulation, history of significant underlying cardiac or pulmonary disease and phrenic nerve injury are the main

prognostic factors for post cardiac surgery respiratory complications.[18,19] Traditionally, low- and high-flow oxygen systems are used to reverse postsurgical respiratory complications with or without addition of continuous (CPAP) or bi-level (NIV) positive airway pressure.[20-22] NHF might be superior for the prevention or treatment of those respiratory complications, since it can provide high-flow of heated and hydrated oxygen while the positive airway pressure created by the high gas flow can recruit alveoli and increase the end-expiratory lung volume.[23,24]

Studies applying NHF immediately after extubation in cardiac surgery patients revealed better oxygenation and less need for advanced methods of respiratory support compared to conventional oxygen devices[25,26] , and similar results compared to noninvasive ventilation[27]. However, Zochios et al,[28] summarized all the available up to date data of NHF compared to conventional oxygen devices and non-invasive ventilation in patients undergoing cardiothoracic surgery and they did not find any further benefit by NHF use. The aforementioned discordant results could be explained by the differences in the studied populations and NHF flow settings. The proposed initial flow rate differs among the studies, with some authors[2,4] suggesting initial lower flows (35-40 L/min) that will be better tolerated by the patients and others suggesting initial maximal flows (60 L/min) to rapidly relieve dyspnea and prevent muscle fatigue. [29,30]

Aim

The primary goal of the study is to evaluate the efficacy of NHF versus conventional oxygen systems as regards treatment failure (as defined below) and respiratory parameters [respiratory rate, PaO_2 / (fraction of inspired oxygen) FiO_2, peripheral oxygen saturation (SpO_2), use of accessory muscles, and dyspnea and comfort as regards the technique of respiratory support by using a visual analogue scale (VAS) after the extubation of cardiac surgery patients. An additional major goal of the study is to compare two different initial NHF flows of 60 L/min and 40 L/min, intensive care unit (ICU) Length of Stay, Hospital Length of Stay, rates of ICU re-admission and re-intubation and any other respiratory / non-respiratory complications and adverse events. The rate of failure of the initial treatment will be determined as the primary study outcome.

Methods

This is a prospective, non-blinded, randomized study in post-extubated cardiac surgery patients. The study population will consist of three patient groups: The first group (Study Group 1) will include patients on NHF with initial settings of FiO_2=0.6 and gas flow=60L/min. The second group (Study Group 2) will include patients on NHF with initial settings of FiO_2=0.6 and gas flow=40L/min. In the third group (control group) all patients will receive oxygen therapy according to the standard practice of our cardiac ICU department, i.e., Venturi mask with FiO_2=0.6 and flow of 15 L/min.

Treatment failure will be defined as any crossover from one treatment to another due to patient's respiratory distress and discomfort. To be more specific, switch of gas flow from 40L/min to 60L/min, crossover from either NHF group to standard practice (Venturi mask) or need for more advanced respiratory support such as non-invasive ventilation or invasive mechanical ventilation. inability to reverse FiO_2 and/or gas flow escalation above initial settings within 48 hours of its initiation. Escalation reversal will be defined as return to initial (or lower) FiO_2 and/or gas flow for $\geq$4 hours.

Inclusion criteria will be: Cardiac ICU adult patients > 18 years after elective or urgent cardiac surgery having passed a successful Spontaneous Breathing Trial (SBT) with T-piece and FiO_2=0.6. A successful SBT will have to fulfil the following criteria[31, 32, 33] respiratory rate: 12-29 breaths/min, SpO_2> 92%, $PaCO_2$ <45mmHg, heart rate <120/min, and systolic arterial pressure of 90-160 mmHg while receiving norepinephrine at a rate of 0.00 μg/kg/min to 0.15 μg/kg/min. The most important inclusion criterion is residual respiratory impairment at the end of SBT defined as PaO_2/FiO_2 <200 mmHg while receiving FiO_2=0.6. The decision to extubate under these specific conditions will be made by the attending physicians.

The exclusion criteria will comprise: 1) Obstructive Sleep Apnea Syndrome supported by a continuous positive airways pressure device, 2) preoperative diagnosis of Chronic Obstructive Pulmonary disease, 3) patients already tracheostomized, 4) do not resuscitate status, 5) Glasgow Coma Scale score <13, 6) Insufficient knowledge of Greek Language , and 7) any visual or hearing impairment.

In the preoperative period, the investigators will have to provide detailed information about the nature of the study to cardiac surgery patients and their next-of-kin. A study information sheet will be provided and the study will also be verbally explained during a preoperative investigator visit. Postoperatively, written, informed next of kin consent will be requested. Patient consent for continued study participation will also be requested as soon as allowed by their clinical condition. Pertinent criteria will include absence of any acute physiological derangement (e.g. hypoxemia or hemodynamic instability) necessitating therapeutic intervention; patients will have to be alert and oriented, and without any concurrent symptoms such as shortness of breath or moderate-to-severe postoperative pain.

Study protocol

Postoperative cardiac surgery patients will be assessed for SBT trial after having been weaned off sedation. According to routine practice criteria of the cardiothoracic ICU, before SBT initiation, patients will have to be deemed as clinically stable by their attending physicians as regards their underlying cardiovascular disease and afebrile (body temperature <38 °C); their a hemoglobin concentration should normally exceed 8 g/dL. The SBT will be conducted using a T-piece with 0.6 FiO_2 for a period of 60 min. Before extubation, an arterial blood gas sample will be obtained to determine whether PaO_2/FiO_2 is <200 mmHg. Patients will be included in the study as long as they fulfill all the inclusion criteria and none of the exclusion criteria. They will then be randomized to any of the three study groups and oxygen therapy will commence immediately after extubation.

The 3 study groups will be the following;
Study group 1) NHF with FiO_2=0.6, T=37°C, gas flow 60L/min,
Study group 2) NHF with FiO_2=0.6, T=37 FiO_2=0.4C, gas flow 40L/min,
Control group 3) Venturi mask with FiO_2=0.6, oxygen flow 15 L/min.

Randomization procedure

Following extubation, patients will be randomly assigned to Study group 1 or 2, or to Control group at 1:1:1 ratio. Blocks of 3 numbers will be consecutively drawn from a sequence of 99 unique random numbers (range, 1-99). Random numbers will be generated by using Research Randomizer version 4.0 (www.randomizer.org). Upon patient enrollment, attending investigators will receive text message on their mobile phone devices. The text message will display the patient's code number and group.

Patient monitoring and data collection

Continuous patient monitoring will include electrocardiographic lead II, intra-arterial pressure, SpO_2, and respiratory rate.

Data on patient characteristics, including the European System for Cardiac Operative Risk Evaluation (EUROSCORE) II will be collected at baseline. Data collection time points for SpO_2, respiratory rate, PaO_2/FiO_2, comfort with respect to dyspnea and respiratory support modality (VAS score[34,35,36]), accessory muscles' use, arterial pressure and heart rate, vasopressor support, and core body temperature will be as follows: within 30 min of extubation (baseline) and at 1, 2, and 4 hours, and every 4 hours onwards until 48 hours postextubation. Fluid balance of the first 24 and 48 hours postextubation will be recorded as well.

Adverse events/clinical course complications (e.g. hypoxemia and/or need for re-intubation, arrhythmias such as atrial fibrillation, occurrence of delirium,[37,38,39,40,41] epileptic seizures, surgical re-exploration due to bleeding, ICU readmission, chest wound infection), and any patient discomfort/intolerance related to HFNC will also be recorded.

Management of respiratory support

Patients will be assessed for gradual reduction in the intensity of respiratory support or need for support escalation every 4 hours postextubation. Gradual weaning from NHF will be accomplished by FiO_2 decrease to 0.5, followed by gas flow decrease to 30 L/min NHF weaning target will include an FiO_2 of 0.4 and a gas flow of 20 L/min.[8,42] If at an NHF FiO_2 of 0.4 and a flow rate of 20 L/min, SpO_2 can be maintained at >92% and respiratory rate remains within 12-20 breaths/min for ≥2 hours, patients will be switched to a Venturi mask providing an FiO_2 of 0.4). In the Control group, a reduction of FiO_2 to 0.4 (via a Venturi mask) will be sought. Patients of all groups fulfilling the aforementioned SpO_2/respiratory rate criteria for at least 4 hours while receiving an FiO_2 of 0.4 via a Venturi mask will be considered for ICU discharge. As part of standard practice, patients will be scheduled for twice-daily physiotherapy.

Regarding treatment escalation in Study groups, if SpO_2 drops to ≤92% for at least 5 min at a gas flow of less than 60 L/min, gas flow will first be increased by 5-10 L/min.[4] Next, if SpO_2 remains at or below 92%, FiO_2 will be increased[43] to achieve an SpO_2 of >92%. In the Control group, an SpO_2 of 92% or less for at least 5 min will be initially treated with FiO_2 increase. In all groups, persistent and/or worsening hypoxemia will be ultimately treated with non-invasive mechanical ventilation and/or reintubation and initiation of invasive mechanical ventilation.

Treatment decisions and premature discontinuation of physiological data collection

Changes in the intensity and/or modality of respiratory support will ultimately be decided by the primary attending physicians of the patients. Initiation of mechanical ventilation or ICU discharge within 48 hours of extubation will result in discontinuation of the pre-specified 4-hourly patient data collection.

Outcome measures

Primary: Occurrence of treatment failure; regarding the NHF groups, this will be further specified as inability of weaning from NHF (i.e. inability of achieving successful weaning from NHF) according to study protocol.

Secondary: 1] Successful maintenance of an SpO_2 of >92% and a respiratory rate of 12-29 breaths/min at the specified time points of follow-up; the term ″successful″ corresponds to the absence of any escalation of respiratory support above its initially specified level for each one of the Study groups and the Control group; 2] PaO_2/FiO_2 at the specified time points of follow-up; 3] Any use of accessory respiratory muscles at the specified time points of follow-up; and 4] Patient comfort as regards dyspnea, and patient tolerance of NHF support according to a VAS score.

Additional: 1] Length of cardiothoracic ICU stay; 2] Length of hospital stay; 3] ICU and in-hospital mortality; and 4] Adverse events (e.g. hypoxemia and/or need for re-intubation, arrhythmias such as atrial fibrillation, occurrence of delirium, epileptic seizures, surgical re-exploration due to bleeding, ICU readmission, chest wound infection), and any patient discomfort/intolerance related to NHF.

Sample Size and Power Analysis

The proposed sample size is based on a formal power calculation, i.e. an apriori power analysis, which is an efficient method of controlling statistical power before a study is actually conducted; for power analysis, G*Power 3 software was used.[44] We predict a treatment failure rate of 15% in the 2 Study groups (10% in Study group 1 and 20% in Study group 2) and a failure rate of 51% in the Control group. The predicted NHF-to-control treatment failure ratio of 0.29 corresponds to the lower limit of the 95% confidence interval (CI) of a previously determined ″NHF vs. Control″ odds ratio for support escalation.[25] For alpha=0.05 and power=0.80, 63 patients (n=21 per group) will be required. However, we cannot exclude a potential risk for dropouts and/or missing data. To compensate for such a risk, we propose the ultimate enrolment of 99 patients (i.e. n=33 per group), in order to achieve an alpha value of 0.05, a power of 0.96, and a ″safety margin″ of 57% as regards possible dropouts and/or missing data. The predicted study enrollment rate is 40-50 patients per year.

Interim Analysis and Data Monitoring

At 1 year following study start, an interim analysis will be conducted by Drs. Sotirios Malachias (Senior Consultant in Intensive Care Medicine, First Department of Intensive Care Medicine, University National and Kapodistrian University of Athens Medical School, Evaggelismos General Hospital, Athens, Greece) and Michail Argyriou (Senior Consultant, Department of Cardiac Surgery, Evaggelismos General Hospital, Athens, Greece). The analysis will be focused at evaluating and confirming 1) the safety of the study protocol (including any reported adverse events); 2) the applicability of the study protocol (including an assessment of the achieved level of adherence to the specified investigational interventions); 3) the completion of the attached study forms as mandated by the study protocol; and 4) the safety of the electronically stored patient data. Actions related to the

aforementioned points 1-4 may be undertaken at the discretion of the aforementioned study-independent Colleagues at any time point throughout the conduct of the current study. Data quality and completeness will also be evaluated by the aforementioned study-independent Colleagues after the completion of the study.

Statistical Analysis Plan

Analyses will be performed according to intention-to-treat principle. Distribution normality will be determined by Kolmogorov Smirnov test. Continuous variables will be presented as mean±SD or median (IQR). Qualitative variables will be presented as number (percentage). Percentages will be compared by Fisher's exact test.

The effect of group on treatment failure will be assessed using multivariable Cox regression. Hazard ratios and respective 95% confidence intervals will be determined for group, EUROSCORE II (which includes age and gender as risk factors), body mass index, cardiopulmonary bypass time, and duration of postoperative sedation and pre-extubation assisted and spontaneous breathing.

SpO_2 >92%, and respiratory rate within 12- 20 breaths/min will be assessed as binary outcomes (i.e. maintenance vs. no maintenance of SpO_2/respiratory rate above/within the aforementioned limits without escalation of support above initial level) Logistic regression models will be fitted using group, time, and group*time interaction as explanatory variables. Changes in oxygenation, VAS comfort scale score, and non-outcome follow-up variables (i.e. $PaCO_2$, arterial blood lactate, hemoglobin concentration, hemodynamic variables, temperature, and vasopressor support) will be analysed by using linear mixed models analyses with group, time, and group*time, as fixed factors, and ″patients″ as random factor. Dependent variables with skewed distributions will be log-transformed. The Bonferroni correction will be applied on the P values of pairwise comparisons.

Two-tailed P values will be reported. Statistical significance will be accepted at 0.05. Analyses will be conducted using SPSS version 21 or any subsequent version (IBM corporation, Armonk NY).

Importance of the study

The early use of NHF in post-extubated cardiac surgery patients may potentially assist them in achieving a faster recovery by providing higher and more stable levels of humidified and warmed oxygen while supporting the respiratory effort through positive airway pressures. This could also be associated with a reduction in the risk for postoperative pulmonary complications. This study may also help in determining the best level of initial NHF support in cardiac surgery patients with postoperative hypoxemia.

Study Funding Statement

The AIRVO^{TM} 2 (Fisher & Paykel Healthcare, Auckland New Zealand) device (with built in flow generator) is already available at our institution. Regarding disposables, we estimate a total cost of 90 Euro per patient (heated humidifier, 60 Euro; Nasal prongs, 15 Euro; compatible opti flow circuit, 15 Euro. The maximum cost of disposables is estimated at 5940

Euro (+24% value added tax). This cost will be covered by the Special Account for Research Funds, University of Athens Medical School, Athens, Greece. The current study will not cause any financial burden to Evaggelismos Hospital.

Doctoral Thesis

This study corresponds to the Doctoral Thesis of Mr. Stavros Theologou.

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STUDY INFORMATION SHEET [ClinicalTrials.gov ID: NCT03282552]

PATIENT INITIALS (if applicable):

PATIENT CODE (if applicable):

Main Investigators: Stavros Theologou, Eleni Ischaki, Spyros G. Zakynthinos, Christos Charitos, Spyros D. Mentzelopoulos

STUDY TITLE: High Flow Oxygen therapy versus Conventional Oxygen Therapy in Cardiac Surgery Patients-OPTICAR study

Introduction

We request your consent for your family member's participation in this scientific study. The study has been approved by our Institutional Review Board (IRB – Scientific & Ethics Committee). To decide whether you agree (or disagree) with your relative's participation in this study you should fully understand the pertinent risks and benefits. You are asked to read this text and discuss anything you do not understand with the study investigators, or other clinicians of the Department of Cardiac Surgery, or any other competent healthcare professional who enjoys your confidence. If you understand the study, you may be asked to sign and date the consent form in the postoperative period. If you choose your relative's participation in the study, you will be given a copy of the signed consent form. **Please note that as soon as your relative regains decision making capacity, they will be asked whether they agree to their continued study participation, and may validate your signed consent form by signing on it next to their name.**

CONSENTING FOR YOUR RELATIVE'S PARTICIPATION CONSTITUTES A FREE AND RESPONSIBLE CHOICE OF YOURS.

Your relative may participate or discontinue his/her participation in the study at any time, according to your decision, without in any way losing the advantages of scientifically sound medical care based international guidelines and available medical literature evidence.

If desired, the principal investigators of the study or your relative's attending physician will contact your relative's family physician to inform him/her about the study.

Study Scientific Background

Weaning (liberation) from mechanical ventilation and extubation after major surgery occur when certain criteria are met.[1-3] Post-extubation respiratory failure after cardiothoracic surgery is a common and significant complication predisposing to increased intensive care unit (ICU) and hospital length of stay, and ultimately, poor in-hospital outcome.[4,5] Its etiology is multifactorial and may include pleural effusions, impaired airway mucociliary function, ineffective cough due to pain, atelectasis, reduced lung/chest wall compliance, ventilator-associated and extracorporeal circulation-associated lung injury, dysfunction of the respiratory muscles and abnormal ventilatory responses to gas exchange disturbances.[5,6]

Standard oxygen delivery devices include the Venturi mask and the nasal catheter. The Venturi mask is most commonly used in clinical practice and can provide an inspired oxygen fraction (FiO_2) of 24%-60% with oxygen-in-air mixture outflows of 30-50 L/min.[8] At a delivered oxygen concentration of 60%, inspired gas outflow is approximately 27-30 L/min.[8] The Venturi mask delivers a dry oxygen-in-air mixture that may cause dehydration of secretions, and disturbance of the mucociliary function of the upper airways. This might increase the risk of postoperative atelectasis and infection.[4-6]

High flow nasal cannula oxygen therapy (Nasal High Flow, NHF) is an oxygen delivery technique that seems to be gaining ground in recent years. The device consists of an oxygen/air mixer connected through an efficient heated humidifier and a heated circuit to a nasal cannula. NHF delivers an FiO_2 of 21% to 100% with a gas flow rate of up to 60 L/min.[7,8] FiO_2 adjustments are independent of flow settings, and patients can receive heated, humidified and oxygen-rich gas mixtures at flow rates exceeding their own maximum inspiratory flow rates.[7-9] NHF physiological benefits include more predictable FiO_2 values

due to reduced dilution of oxygen,[10,11] flow-dependent positive airway pressure,[15,16] reduced anatomical dead-space ventilation,[14,15] improved mucociliary function and clearance of secretions[16,17] and reduced work of breathing.[18] Therefore, NHF may improve gas-exchange and lung mechanics, reduce respiratory rate and effort, and ameliorate dyspnea.[18-20]

Despite these overall, encouraging results, it is still uncertain whether NHF can confer a clinical outcome benefit compared to conventional oxygen devices in postoperative cardiac surgery patients.[21,22] Discordant results among relevant studies could be explained by differences in the studied populations and NHF flow settings.[21,22] The proposed initial flow rate differs among the studies, with some authors[7,8] suggesting initial lower flows (35-40 L/min) that will be better tolerated by the patients and others suggesting initial maximal flows (60 L/min) to rapidly relieve dyspnea and prevent muscle fatigue.[22,23]

Study Objective

We aim to evaluate to evaluate the efficacy of NHF (with initial flows of 60 L/min or 40 L/min) versus conventional oxygen therapy with respect to the adequacy of postoperative respiratory support (i.e. occurrence or no occurrence of treatment failure) and respiratory function (respiratory rate, oxygenation, use of accessory muscles, dyspnea, comfort, and immediately after the extubation of cardiac surgery patients with postoperative hypoxemia.

Additional study outcomes will include ICU length of stay, hospital length of stay, rates of ICU re-admission and re-intubation and any other respiratory/non-respiratory complications and adverse events.

Study protocol

This is a prospective, non-blinded, randomized study in postoperative cardiac surgery patients. The study population will consist of three patient groups:

The first group (Study Group 1) will include patients on NHF with initial settings of FiO_2=60% and gas flow=60L/min.

The second group (Study Group 2) will include patients on NHF with initial settings of FiO_2=60% and gas flow=40L/min

In the third group (Control group), all patients will receive oxygen therapy according to the standard practice of our cardiac ICU department, i.e., Venturi mask delivering an FiO_2 of 60% and a flow of 15 L/min.

Baseline measurements will be undertaken within 30 min after extubation. Subsequently, all patients will be assessed for downward titration of respiratory support at 1, 2 hours, and then, every 4 hours after extubation. Respiratory physiological follow-up will extend up to 48 hours after extubation. At the aforementioned follow-up time points, data collection will include SpO_2, respiratory rate, PaO_2/FiO_2, comfort as regards dyspnea and respiratory support modality [visual analogue scale (VAS) score[24]], accessory muscles' use, arterial pressure and heart rate, vasopressor support, and core body temperature Fluid balance of the first 24 and 48 hours postextubation will also be recorded.

Gradual weaning from NHF support will include FiO_2 downward titration to 50%, followed by downward titration of gas flow to 30 L/min, aiming at a final wean-off goal of FiO_2=0.4 and gas flow=20 L/min (unless the attending physician decides to turn the patient to a Venturi mask from a gas flow of 25 to 30 L/min).[12] If at NHF FiO_2=0.4 and flow rate=20 L/min, pulse oximeter-measured, peripheral oxygen saturation (SpO_2) and respiratory rate can be respectively maintained above 92% and within 12 to 20 breaths/min for at least 2 hours, patients will be switched to conventional oxygen therapy with a Venturi mask (FiO_2=0.4). In the control group, downward titration of support will be aimed at Venturi mask FiO_2=0.4. Patients of all groups fulfilling the aforementioned SpO_2/respiratory rate criteria for at least 4 hours while receiving an FiO_2 of 0.4 via a Venturi mask will be considered for cardiothoracic ICU discharge.

During the postoperative/postextubation period, respiratory support may be escalated to maintain an SpO_2 of >92% and a respiratory rate of 12-29 breaths/min. Changes in respiratory support level and/or modality will ultimately made and/or approved by the patients' primary attending physicians.

Study Eligibility Criteria

• Adult Cardiac ICU patients.

• Age of more than 18 years.

• After elective or urgent cardiac surgery.

• Successful spontaneous breathing trial with T-piece and an FiO_2 of 60% (eligibility criterion for extubation).

• PaO_2/FiO_2 of less than 200 mmHg (moderate hypoxemia – normal value ~500 mmHg)

• Hemodynamically stable, defined as systolic arterial pressure within 90 to 160 mmHg with or without low-to-moderate vasopressor support.

Exclusion Criteria:

• Obstructive sleep apnea syndrome supported by continuous positive airways pressure.

• Diagnosis of exacerbation of chronic obstructive pulmonary disease.

• Patients with tracheostomy.

• Do-not-attempt resuscitation status.

• Glasgow Coma Scale score below 13 (inability of satisfactory communication).

• Insufficient knowledge of Greek language.

• Visual or hearing impairment.

Possible intervention-related risks:

We do not expect any NHF-associated increase in the risk of any clinically important adverse event. We cannot however exclude the possibility of subjective poor tolerance to the NHF device. This may occasionally be related to mucus dryness, or an episode of nasal bleeding.[25]

Possible intervention-related benefits

For the participating patient: Improvement of postoperative respiratory function and subjective breathing comfort και της υποκειμενικής άνεσης, and possible reduction in the risk of postoperative pulmonary complications and length of cardiothoracic ICU/hospital

stay.

For medical science: Improvement in the clinical management of cardiac surgery patients with moderate postextubation hypoxemia.

Discontinuation of study participation

The attending or principal investigator and the attending physician have the right (and obligation) to terminate your relative's participation in this study without your consent, in case of any unexpected and potentially harmful (to your relative) event. The participation of your relative in this study is completely voluntary and you may discontinue it at any time. You will be timely informed about the time of study termination. You will be timely informed about the clinical course of your relative throughout the study's follow-up period.

Compensation in case of injury related to the investigational interventions

In case of a study protocol-related complication, the responsible researchers will inform you about the complication, the potential for complication reversal, and about your relative's compensation.

Use of medical information privacy and authorization

All data collected will be safe-guarded for the protection of medical confidentiality. Your relative will be referred to only by initials and a code number. The study information may be used in study reports or scientific presentations.

Additional scientific information of the study (eg, values of variables resulting from measurements of the protocol) will not be recorded in the patient's file. This information will be entered electronically by researchers and will be protected by a password and antiviral computer programs. If desired, the researchers will provide you with a pertinent study information note.

By signing the consent form you permit the aforementioned persons to take the above actions. There will be no publication or communication of the data that reveal your relative's identity. The withdrawal of your relative from the study does not automatically cancel the

use of his-her personal information. If you wish to cancel the use of your relative's data you should provide a written request to the responsible investigators, who will then be obliged to respond (to your request).

YOU UNDERSTAND THAT YOU HAVE THE RIGHT OF ACCESS TO THE MEDICAL RESEARCH RECORDS OF YOUR RELATIVE IN ACCORDANCE WITH THE LAW.

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Patient Initials:_____
Patient Number:_____

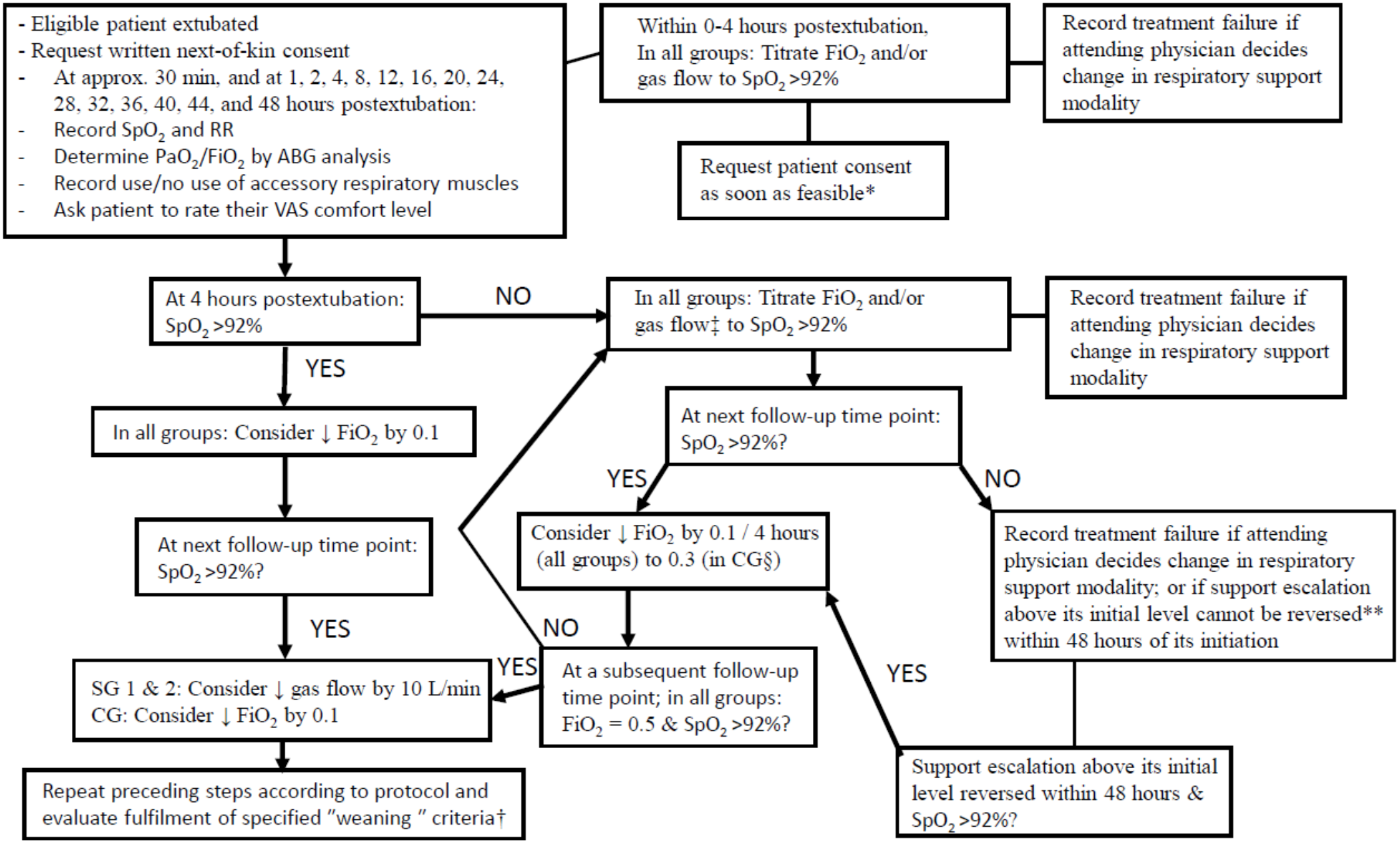
CONSENT DECLARATION OF THE PATIENT'S LEGAL REPRESENTATIVE

"High Flow Oxygen therapy versus Conventional Oxygen Therapy in Cardiac Surgery Patients-OPTICAR study" ClinicalTrials.gov Identifier: NCT03282552

Note in the following blank the name of the clinician who informed you about the research and cycle the following answers.

1. I have read the study information leaflet.	YES / NO
2. I was given the opportunity to ask questions and discuss the issues related to the study with the researcher: ----------	YES / NO
3. I was given satisfactory answers and information to all my questions.	YES / NO
4. I am aware of the fact that I reserve the right to withdraw my consent to the participation of my relative in the study at any time and without any obligation to explain the underlying reasons.	YES / NO
5. I understand that by my signature, I authorize access to and release of my relative's personal and medical data to competent persons authorized by the study investigator, to the competent authorities, and to the Independent Ethics Committee as necessary. I understand that I can withdraw my authorization at any time for the use or disclosure of my relative's personal and medical data. I agree to give my permission to these individuals to access my relative's files.	YES / NO
6. Have you had adequate time to make your decision?	YES / NO
7. Do you accept your relative's participation in this clinical trial?	YES / NO

PATIENT NAME [CAPITAL LETTERS]:	**[SIGNATURE & DATE]**
NAME OF THE PATIENT'S LEGAL REPRESENTATIVE [CAPITAL LETTERS]:	
ADDRESS:	**SIGNATURE & DATE**
PHONE:	
INVESTIGATOR NAME (CAPITAL LETTERS):	
ADDRESS:	**SIGNATURE & DATE**
PHONE:	


- Eligible patient extubated
- Request written next-of-kin consent
- At approx. 30 min, and at 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours postextubation:
- Record SpO_2 and RR
- Determine PaO_2/FiO_2 by ABG analysis
- Record use/no use of accessory respiratory muscles
- Ask patient to rate their VAS comfort level
Within 0-4 hours postextubation, In all groups: Titrate FiO_2 and/or gas flow to SpO_2 >92%
Record treatment failure if attending physician decides change in respiratory support modality
Request patient consent as soon as feasible*
At 4 hours postextubation: SpO_2 >92%
NO
In all groups: Titrate FiO_2 and/or gas flow‡ to SpO_2 >92%
Record treatment failure if attending physician decides change in respiratory support modality
YES
In all groups: Consider ↓ FiO_2 by 0.1
At next follow-up time point: SpO_2 >92%?
YES
NO
At next follow-up time point: SpO_2 >92%?
Consider ↓ FiO_2 by 0.1 / 4 hours (all groups) to 0.3 (in CG§)
Record treatment failure if attending physician decides change in respiratory support modality; or if support escalation above its initial level cannot be reversed** within 48 hours of its initiation
YES
NO
SG 1 & 2: Consider ↓ gas flow by 10 L/min
CG: Consider ↓ FiO_2 by 0.1
YES
At a subsequent follow-up time point; in all groups: FiO_2 = 0.5 & SpO_2 >92%?
YES
Repeat preceding steps according to protocol and evaluate fulfilment of specified "weaning " criteria†
Support escalation above its initial level reversed within 48 hours & SpO_2 >92%?

DIAGRAMMATIC STANDARD OPERATING PROCEDURE (SOP) FOR THE ALGORITHMIC PERFORMANCE OF INVESTIGATIONAL INTERVENTIONS

SpO_2: peripheral oxygen saturation; ABG: arterial blood gas; VAS, visual analogue scale; PaO_2: arterial oxygen tension; FiO_2: inspired oxygen fraction; SG: study group; CG: control group.

*, Patient consent for continued study participation may be obtained verbally provided that: 1) Informed, written consent has already been obtained from the patient's next-of-kin; 2) The patient is deemed competent for decision making by the primary attending physician; and 3) A study-independent healthcare professional is present as a witness to the consent procedure. Written patient consent for continued study participation may also be obtained by the patient's signing on (and thereby **"ratifying"**) the existent next-of-kin consent form; the patient may sign next to his/her name. **If the patient refuses to continue his/her participation in the study, the protocol must stop and the attending physician must be accordingly notified; high-standard patient management must be smoothly continued.**

†, Weaning criteria **(including SpO_2 exceeding 92% AND respiratory rate within 12-20 breaths/min)** are detailed in the current protocol's Methods section; **IMPORTANT NOTE:** preceding steps restart from the step that includes consideration to further reduce FiO_2 by 0.1 if SpO2 exceeds 92%.

‡, In SG 2, support escalation should be initially accomplished by gas flow increase of 5-10 L/min; this can be followed by FiO_2 titration to an SpO_2 of more than 92%.

§, Regarding CG patients on nonrebreathing mask due to respiratory support escalation, an FiO_2 reduction from 0.9 to 0.6 via a Venturi mask should be performed for escalation reversal.

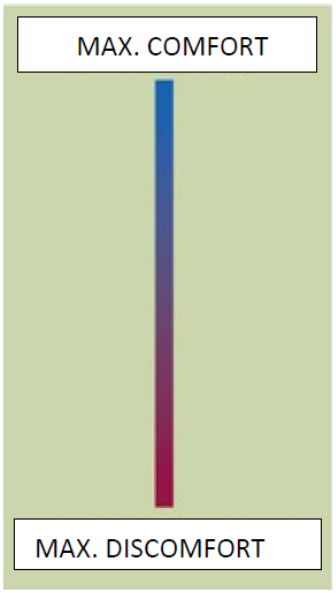
**, Reversal of respiratory support escalation is defined as return to initial (or lower) FiO_2 and/or gas flow for at least 4 hours.

Applicable definition of hypoxemia: SpO_2 drop to 92% or less for at least 5 min.

SOP FOR THE RATING OF THE LEVEL OF BREATHING COMFORT

At the specified time points of patient follow-up: Investigators should use the below-displayed comfort/discomfort visual analogue scale to help patients rate the level of their breathing comfort. The following simple question should be asked: How would you rate the level of your breathing comfort starting from 0 (maximum discomfort – feeling unable to breathe) to 10 (maximum comfort – feeling capable of smooth and steady breathing, without having even the slightest difficulty).

Number	Verbal Description
10	Maximum Comfort
9	
8	Good Comfort
7	
6	Acceptable Situation
5	Bearable Situation
4	
3	
2	Severe Discomfort
1	
0	Maximum Discomfort



Contents

1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure to be used by the investigator for the recording, management and reporting of Adverse Events (AEs), Adverse Reactions (ARs), Serious Adverse Events (SAEs), Suspected Serious Adverse Reactions (SSARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur in subjects participating in the non-commercial, academic, investigator-initiated, prospective, parallel-group, randomized, unblinded OPTICAR study.

2. BACKGROUND

This SOP is written in accordance with Good Clinical Practice (GCP) requirements as previously outlined in Directives 2001/20/EC and 2005/28/EC, and currently supported by the CLINICAL TRIALS REGULATION (EU) No 536/2014.

2.1. DEFINITIONS

The following definitions have been adapted:

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered an intervention (INT) and which does not necessarily have a causal relationship with this treatment.

Therefore, an AE can be any unfavorable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a subject to whom an INT has been administered, including occurrences which are not necessarily caused by or related to the INT.

Adverse Reaction

All untoward and unintended responses to the use of an INT related.

This definition also covers errors and uses outside what is foreseen in the protocol, including misuse and abuse of the INT device.

The definition implies a reasonable possibility of a causal relationship between the event and the INT. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Serious Adverse Event and Serious Adverse Reaction

Any adverse event or reaction in a trial subject that:

(a) results in death; or

(b) is life threatening; places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have caused death); or

(c) requires hospitalization or prolongation of existing hospitalization;

(d) results in persistent or significant disability or incapacity

Important Safety Issues

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention (medical or surgical) to prevent one of the other outcomes listed in the definition above should also be considered serious. Such events might include:

1. An alarming adverse experience
2. Specific Adverse events and/or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and requiring reporting.

Suspected Serious Adverse Reaction

An adverse reaction that is classed in nature as serious and which is consistent with the information about the INT device listed in the relevant reference documentation in the case of a licensed device being used within its licensed indication or in the Investigator's Brochure (IB) in the case of a licensed device being used outside its licensed indication.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction

An adverse reaction that is classified in nature as both serious and unexpected.

2.2 OTHER SAFETY ISSUES CONSIDERED TO BE SERIOUS IN THE CLINICAL TRIAL.

Events which may materially alter the current benefit-risk assessment of an investigational INT or which could be sufficient to consider changes in INT administration or in the overall conduct of the trial may fall into the category of 'Other Safety Issues' and be considered as serious events which will require reporting to the sponsor in a letter headed Safety Report:

a. An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important,

b. Post-study Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur after the patient has completed a clinical trial and are reported by the investigator to SEC,

c. New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:

1) A Serious Adverse Event (SAE) which could be associated with the trial procedures and which could modify the conduct of the trial,

2) A significant hazard to the subject population such as lack of efficacy of an IMT used for the treatment of a life-threatening disease,

Recommendations of the Data Monitoring Committee (DMC), if any, where relevant to the safety of the subjects.

An "Other Safety Issue" can also fall into the category of Urgent Safety Measures. Please refer to the Standard Operating Procedure for the Recording and Reporting of Deviations, Violations, Potential Serious Breaches, Serious Breaches and Urgent Safety Measures.

2.3 SEVERE ADVERSE EVENT OR REACTION

The term “severe” is often used to describe the intensity of an event or reaction (e.g. mild, moderate or severe) and should not be confused or interchanged with the term “serious”.

2.4 KEY RESPONSIBILITIES FOR THE INVESTIGATOR

This section describes the key responsibilities of the investigator, further delegation of these responsibilities to other team members must be documented on the trial delegation log.

1. The principal investigator (PI) must further ensure that the team are all familiar with the appropriate use of the INT, as described in the protocol.
2. Adverse Event (AE) Recording: All AEs must be recorded in the medical records (if source data) and/or the patient case report form (CRF), Serious Adverse Event (SAE) forms and AE logs as described in the protocol.
3. AE Assessment: The PI / investigator(s) must assess each event for **seriousness, expectedness and causality** using the appropriate documentation (protocol and safety reference document).
4. Trend/signal analysis: The PI must ensure the AE log is reviewed regularly. This can be performed by the PI alone or reviewed collectively at trial meetings. These reviews need to be documented.
5. SAE Reports: The PI must ensure that initial and follow-up SAE reports are sent to the Scientific and Ethics Committee (SEC), according to the protocol.
6. Confidentiality: The PI must always maintain subject confidentiality.
7. Urgent Safety Measure: The PI / investigator(s) may take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety. This may be taken immediately. However, following the measure the PI / investigator must follow the SOP on “Deviations, serious breaches and urgent safety measures” .

3. SCOPE OF THIS SOP

This SOP covers the procedures for the recording, management and reporting of all AEs, ARs, SAEs, SSARs and SUSARs that occur in subjects participating in the OPTICAR Study. This document further details, safety alerts, safety reference document updates, and highlights the key responsibilities of the PI (if applicable). **All pertinent documentation must always be readily accessible by the DMC.**

4. RESPONSIBLE PERSONNEL

The PI and the individual investigators within a trial team are responsible for keeping records of all adverse events that occur in trial subjects as per protocol.

5. PROCEDURE

Please ensure that you are using the most recent SOP version.

5.1 Duration of AE Recording

The protocol must clearly define the duration of AE recording.

5.2 Which AE to record and which Forms to use?

The table below provides guidelines for where to record AE information: The PI may further designate who within the trial team is qualified to perform the delegated task. This must be authorized in the delegation log.

Type of Adverse Events	Format of Recording Information
All Adverse events	Medical Records
All AEs and SAEs (as per protocol)	AE section of CRF
All SAEs (as per protocol)	AE log
All SAEs (as per protocol)	SAE report form

5.3 Which AE to report to the SEC?

All AEs/ARs that fulfill the criteria for the definition of serious, whether expected or not, need to be reported to the SEC.

5.4 Evaluation of AEs/ARs during the trial

The following documents need to be referred to when assessing any AE in the trial:

- Protocol
- Trial specific Procedure for unblinding (if applicable)

Each AE must be evaluated for **seriousness, causality, severity and expectedness.** The PI must assess the AE as serious as per the definition of an SAE in section 2.

5.5. Evaluation of causality

The PI's / investigator's causality assessment is vital information since the PI / investigator(s) is / are best placed to review how the subject has changed since baseline (before treatment is administered). Every effort must be made by the PI to obtain all the required information to determine whether the AE is related to the trial intervention.

The PI is asked to consider the following before reaching a decision:

- Medical History
- Lack of efficacy/worsening of existing condition
- Study treatment(s)
- Other treatments-concomitant or previous

- Withdrawal of study treatment-especially following study discontinuation/end of study
- If applicable, erroneous treatment with study INT
- Protocol related process
- The PI's / investigator's evaluation ofseverity

5.6. Evaluation of expectedness

The PI must evaluate whether the event is expected or unexpected against the protocol and the safety reference documents for the trial. An event can be considered as "unexpected" if it adds significant information on the specificity or severity of an expected event.

6. REFERENCES

1. DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities. 2002; L121/34-L121/43.
2. COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Text with EEA relevance). Official Journal of the European Union. 2005; L91/13-L91/19.
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4. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. World Medical Association. JAMA. 2013; 310:2191-2194.
5. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union 2014; L158/1-L158/76.

Adverse Events Recording and Reporting Log

All events should continue to be recorded in source data and CRF as per protocol. This log must 1) be kept on site; 2) be readily accessible by the DMC; and 3) be sent to SEC upon request
The PI CANNOT DOWNGRADE THE ASSESSMENT.

Patient trial no	**Adverse Event term**	**INT Name**	**Is Event Serious Y/N**	**Serious 'Type'[1]**	**Start date - stop date**	**Causal relationship[2]**	**Severity Grade***	**Expected (Y/N)**	**Outcome[3]**	**Date site aware of SAE**	**Date SAE 1st reported to the SEC**

KEY:

[1] **1**=resulted in Death, **2**=life Threatening, **3**=required inpatient or prolonged existing hospitalization, **4**=resulted in persistent or significant disability/incapacity, **5**=resulted in congenital anomaly/birth defect, **6**= Important

Medical Event.

[2] **a**= definitely, **b**=probably, **c**=possibly, **d**=unlikely, **e**= not related, **f**=not assessable

[*] as per approved protocol or as per trial CRF definition

[3] **1**= Resolved, **2** = Resolved with sequelae, **3** = Unresolved, **4**= Worsening, **5** = Fatal, **6**= not assessable

Serious Adverse Event Reporting Form

Protocol No: **Name of PI:** **Name of Site:**	Initial Report ☐ Follow-up Report ☐

FOR THE ATTENTION OF:
DMC / SEC / Pharmacovigilance Manager / Regulatory Advisor

Please complete
Name of Person sending report:

Job title of Person sending report:

Email of Person sending report:

Contact Phone number of Person sending report:

THIS IS AN URGENT REPORT THAT REQUIRES IMMEDIATE ATTENTION ☐

1. SAE Onset Date:_____(dd/mm/yyyy)
2. SAE Stop Date:_____(dd/mm/yyyy)
3. Location of serious adverse event: _____
4. Was this an unexpected adverse event? Yes ☐ No ☐
5. Brief description of participant(s) with no personal identifiers:
   Sex: F ☐ M ☐ Age: ____
6. Brief description of the nature of the serious adverse event (attach description if more space needed): _____

7. Category of the serious adverse event:

   ☐ death – date__/__/__(dd/mmm/yyyy)
   ☐ life-threatening
   ☐ hospitalization-initial or prolonged
   ☐ disability / incapacity
   ☐ congenital anomaly / birth defect
   ☐ required intervention to prevent permanent impairment
   ☐ other:_____

8. Intervention type:

   ☐ Medication or Nutritional Supplement: specify_____
   ☐ Device: Specify: _____
   ☐ Surgery: Specify: _____
   ☐ Behavioral: Specify: _____

9. <u>Relationship of event to intervention</u>:

   ☐ Unrelated (clearly not related to the intervention)
   ☐ Possible (may be related to intervention)
   ☐ Definite (clearly related to intervention)

10. Was study intervention discontinued due to event? Yes No

11. What medications or other steps were taken to treat the serious adverse event?

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12. List any relevant tests, laboratory data, history, including preexisting medical conditions

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13. Type of report:

Initial	☐
Follow-up	☐
Final	☐

14. Full list of medications the patients was receiving at the time of the SAE

Signature of PI / investigator:_____Date: _____

Standard Operating Procedure for the Recording and Reporting of Deviations, Violations, Potential Serious breaches, Serious breaches and Urgent Safety Measures

Template Reference: Version Number: Author: Implementation date of current version:		1.0
Approved by:	Name/Position: Signature: Date:	
	Name/Position: Signature: Date:	
This Template will normally be reviewed every year unless changes to the legislation require otherwise		

ACRONYMS:	
GCP	Good Clinical Practice
INT	Intervention in the context of a Clinical Trial
DMC	Data Monitoring Committee
SOP	Standard Operating Procedure
ISF	Investigator Site File
PI	Principal Investigator
CI	Chief Investigator (Study Chair)
CRF	Case Report Form
SEC	Scientific and Research Ethics Committee
USM	Urgent safety measures
TMF	Trial Master File

Standard Operating Procedure for the Recording and Reporting of (protocol and /or GCP) Deviations, Violations, Potential Serious breaches, Serious Breaches and Urgent Safety Measures

1. PURPOSE

This Standard Operating Procedure (SOP) specifies the overall process and procedure for investigators to follow for the OPTICAR study in the event of a protocol and/or Good Clinical Practice (GCP) deviation. Criteria to follow are outlined to assess the impact of the deviation in light of the definition of a potential serious breach and / or an urgent safety measure.

This SOP describes the procedure for the principal investigator (PI) / investigator to record the event and notify the Scientific and Research Ethics Committee (SEC).

2. RESEARCH POLICY

All OPTICAR SOPs will be reviewed and approved by the SEC of Evaggelismos Hospital, Athens, Greece; This SEC is directly linked to the National Research Ethics Committee.

3. BACKGROUND

In concordance with the currently applicable European Union Clinical Trials Regulation 536/2014, the Investigator/Institution should only conduct the trial in accordance with the **approved protocol** unless an urgent safety measure must be taken.

The PI / investigator, or a person designated by the PI (in the trial delegation log), should **document and explain any deviation** from the approved protocol.

Definitions used throughout this document

3.1 Protocol Deviation: A deviation is usually an **un-intended** departure from the expected conduct of the trial (protocol, SOPs), e.g. a protocol visits date deviation (a common deviation in clinical trials). These events will be identified by the trial team during trial conduct and must be continually monitored by the chief investigator (CI)/PI and site team.

It is recognized that minor deviations from approved clinical trial protocols and GCP occur commonly in Clinical Trials. Not every deviation from the protocol will result in a serious breach. Many of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. These cases should be **documented in the case report form (CRF)** and *appropriate corrective and preventative action taken to ensure they do not recur*. Please use the CRF and the PI's **Log of (Protocol and/or GCP) Deviations / Violations / Potential Serious breaches / Serious breaches / Urgent Safety Measures.**

3.2 Violations: A violation can occur when there is a consistent variation in practice from trial protocol, SOPs. A violation can be classified as major if there is a significant occurrence which affects participant safety or integrity of the research. You are required to report to the PI any violation that may impact on the subjects' safety or affects the integrity of the study data.

Examples of this include but are not limited to;

- Failure to obtain informed consent (i.e. no documentation in source data or an Informed Consent form).
- Enrolment of subjects that do not meet the inclusion/exclusion criteria.
- Undertaking a trial procedure not approved by the SEC (unless for immediate safety reasons).
- Failure to report a Serious Adverse Event/Reaction.
- Incorrect use of an Intervention Device.

Minor Violation - a violation that does not impact on subjects' safety or compromise the integrity of study data. Examples of this maybe;

Missing original signed consent form (but clearly legible photocopy present)

3.3 Serious Breaches of the protocol and/or GCP

Please consider whether the violation that has occurred on site meets the following definitions. These cases must be reported to the SEC as soon as the PI / investigator has become aware of the event.

(1) The PI of OPTICAR shall notify the SEC in writing of any serious breach of -
(a) the conditions and principles of GCP in connection with OPTICAR **; or**
(b) the protocol relating to OPTICAR, as amended from time to time.

A "serious breach" is a breach which is likely to affect to a significant degree –
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial.

3.4 Urgent Safety Measures (Implementing a Protocol Deviation under an emergency)

The PI / investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects **without** prior approval from the SEC. This is defined as an Urgent Safety Measure:
The PI / investigator may take appropriate urgent safety measure(s) to protect clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. However, to meet the legal timelines, **the PI / investigator must inform the SEC in writing immediately and within 24 hours.**
See section 6.13 below for the REPORTING procedures.

4. SCOPE OF THIS SOP

This SOP details the process (for PI / investigators) to follow for the recording and reporting of OPTICAR protocol deviations and violations. It describes what consideration must be considered to assess whether the deviations and violations also meet the definition of a **potential serious breach** or **urgent safety measure and the reporting requirements.**

5. RESPONSIBLE PERSONNEL

The site PI has the responsibility to record and report any violations to the SEC within the agreed timeframes and in accordance with this SOP if these are deemed a potential serious breach/urgent safety measure. Deviations need only be documented on site, in the case report form (CRF) and on the PI's Log of (Protocol and/or GCP) Deviations/Violations/Potential Serious breaches/Serious breaches/Urgent Safety Measures and file noted where required. Any corrective and preventative action should also be documented and retained in the site file.

The SEC must consider the following actions:
Receipt and Assessment (i.e. assessment of deviations/violations, isolated/systematic incident, patient(s) harmed or put at risk/data credibility etc.)

- Investigation
- Corrective and Preventative Action (CAPA)
- Reporting to the National Research Ethics Committee
- Trial suspension or Trial termination
- Compliance with a 7-day reporting timescale

If the PI is unsure whether a deviation or violation is a potential serious breach, then please notify the Data Monitoring Committee (DMC) and the SEC as soon as possible and provide as much information as possible.

The DMC and SEC should assess the impact of the breach on the scientific value of the trial; this can be carried out in conjunction with the PI/ chief investigator (CI). If a potential serious breach is identified by a member of the DMC, the DMC should further discuss with the CI/PI in order to clarify the situation and recommend appropriate corrective and preventative action. Furthermore, The DMC must report the serious breach to the SEC.

The regulatory timeline will only commence once the DMC has been notified of an event and has assessed the event as being a serious breach.

6. PROCEDURE

6.1 Identification of deviations, violations and potential serious breaches

The judgment on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors e.g. the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc.

In addition, it is important that the PI notifies the SEC of what corrective and preventative action has been taken (CAPA) to devise a formal plan of corrective and preventative action.

6.1.1 Deviations

Recording: In the CRF and the deviations and violations log and file noted if necessary.

Reporting: Where a deviation is reoccurring and may result in identification of a serious breach, this should be notified to the PI / CI and the DMC.

Escalation: Corrective and preventative actions should be implemented for deviations. It is recommended that reoccurring deviations be discussed at trial meetings, trigger protocol amendments, and if required, detailed in the clinical study report.

6.1.2 Violations

Recording: In the CRF and the deviations and violations log and file noted if necessary.

Reporting: Violations of GCP, protocol and regulations must be notified to the PI / and the DMC within 2 calendar days of becoming aware of that violation.

Escalation: Corrective and preventative actions (including protocol amendments as appropriate) should be implemented for violations. If the violation is determined to be a potential serious breach, then this would be reported to the SEC within regulatory timelines.
It is recommended that reoccurring violations be discussed at trial meetings and detailed in the clinical study report. **Violations may result in trial suspension by Oversight Authorities.**

A violation may constitute the DMC / SEC to undertake a triggered monitoring visit. **All major violations must be resolved to conclusion.** Depending on the nature of the violation it may constitute a Serious Breach of GCP and further follow up and reporting may be required by the DMC in line with current regulations.

6.2 Procedure for notifying Oversight Authorities of a serious breach

6.2.1. Site team to complete the "Notification of Serious Breaches of GCP or Trial Protocol form (see Appendix 1) all available details pertaining to the breach should be documented on the form.

6.2.2. Completed Notification of Serious Breaches of GCP form to be sent to the DMC and the SEC.

6.2.3. Violation / serious breach to be noted on the Log of (Protocol and/ or GCP) Deviations/Violations/Potential Serious breaches/Serious breaches/Urgent Safety Measures

In addition, the PI must log the Potential serious breach in the PI's Log of (Protocol and/ or GCP) Deviations/Violations/Potential Serious breaches/Serious breaches/Urgent Safety Measures.

6.3 Assessment by the DMC / SEC

DMC / SEC to discuss potential serious breach internally through:

Discussion with appropriate team members (e.g. regulatory advisor)

Assess which relevant GCP, regulatory or protocol section the breach was identified in.

6.4 Corrective and Preventative Actions (CAPA):

The DMC, SEC, and the CI/PI must agree on the appropriate corrective and preventative action to be taken and this should be documented and detailed within the body of the notification report.

6.5 Follow up reports:

Follow up reports should be made in writing; the serious breaches form can also be used for this, provided that the "follow-up" nature of the report is clearly identified.

6.6 Escalation and dissemination process:

Internally:

The institutional manager(s) of the PI / investigator must be informed of what CAPA is in place. The manager(s) may have to inform their quality assurance and senior management if necessary.

6.7 Urgent Safety Measure and pertinent notification by a site

Where unexpected events require an urgent modification of a clinical trial, the PI may take urgent safety measures without awaiting prior authorization. If such measures justify a temporary halt of the trial, the PI should apply for a substantial modification before restarting the trial.

REFERENCES

1. DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities. 2002; L121/34-L121/43.
2. COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products (Text with EEA relevance). Official Journal of the European Union. 2005; L91/13-L91/19.
3. INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, AND AGENCIES. EUROPEAN COMMISSION. Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') Official Journal of the European Union 2011; C172/1–C172/13.
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5. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union 2014; L158/1-L158/76.

8. APPENDICES

Appendix 1 Notification of a Serious Breach form

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Appendix 1: Notification of a Serious Breach form

Notification of Serious Breach of Good Clinical Practice or Trial Protocol

Your Name:	**Your Organization:**
Your Contact Details:	**Date Breach Identified by PI:**
	Date Breach Notified to Scientifc and Research Ethics Committee:
Details of Individual committing breach:	**OPTICAR; ClinicalTrials.gov Identifier: NCT03282552**

Report: Tick appropriately	**Initial Report**	☐	**Follow-up Report**	☐

Please give details of the breach

Potential impact to patient safety and/or data credibility:

☐ Patient safety	☐ Scientific value / data credibility
☐ Patient confidentiality	☐ NA/None
☐ Approval Issues	☐ Other Non-compliances (specify)
☐ INT	

Background:

(continue on additional sheets if required)

Other relevant information:
(i.e. study status, site(s), SEC, PI details etc.)
(continue on additional sheets if required)

Please give details of the action taken:

This should include: Any investigations by your institution, the results and outcomes of the investigations (if known or details of when they will be available/submitted), how it will be reported in the final report/publication, the corrective & preventative action implemented to ensure the breach does not occur again.
(continue on additional sheets if required)

Actual impact to patient safety and/or data credibility:

☐ Patient safety	☐ Scientific value / data credibility
☐ Patient confidentiality	☐ NA/None
☐ Approval Issues	☐ Other Non-compliances (specify)
☐ INT	

SIGNATURE PAGE

Author and Job Title:	
Signature:	
Date:	
Authorized by: **Name and Job Title**	
Signature:	
Date:	