Universität Zürich[UZH]

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Clinical Investigation Plan (CIP)

Preoperative microbial reduction of the nasal cavity with antimicrobial Photodynamic Therapy (aPDT).

A randomized, controlled, double blinded national single-center study to evaluate the Steriwave™ antimicrobial photodynamic therapy system for preoperative nasal cavity decolonization in adult patients.

Nasal aPDT 01

"Antimikrobielle photodynamische Therapie zur preoperativen endonasalen Dekontamination"

Type of investigation	clinical investigation concerning medical devices (MD)
Categorization	category A1
Registration	international: ClinicalTrials.gov national: SNCTP
Identifier	Nasal aPDT 01
Sponsor-Investigator	Prof. Dr. med. Dr. med. dent. Harald Essig Head of department ad interim Department of Oral and Maxillofacial Surgery University Hospital Zurich (USZ) CH-8091 Zurich Switzerland Tel: +41 44 255 50 31 Mail: harald.essig@usz.ch
Medical Device	Steriwave™ Nasal Photodisinfection System SW4000 Light Source SW3200 Nasal Light Illuminator SW3100 Formulation Applicator photosensitizer: methylene blue
CIP version and date	Version 01.5, 11/06/2024

Signature Page

ID number of the investigation:	Nasal aPDT 01
Title:	Preoperative microbial reduction of the nasal cavity with antimicrobial Photodynamic Therapy (aPDT).

The sponsor-investigator and the scientific advisor have approved the CIP version 1.5 (dated 11.06.2024) and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Sponsor-Investigator: Prof. Dr. med. Dr. med. dent. Harald Essig
University Hospital Zurich, Department of Oral and Maxillofacial Surgery
Head of department ad interim

Zürich, 11.06.2024
Place/Date

Signature

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SYNOPSIS

Sponsor-Investigator	Prof. Dr. med. Dr. med. dent. Harald Essig Head of department ad interim Department of Oral and Maxillofacial Surgery University Hospital Zurich CH-8091 Zurich Switzerland Tel: +41 44 255 50 31 Mail: harald.essig@usz.ch
Title	Preoperative microbial reduction of the nasal cavity with antimicrobial Photodynamic Therapy (aPDT).
Short title	Nasal aPDT 01
Clinical Investigation Plan version and date	Version 01.5, 11/06/2024
Registration	international: ClinicalTrials.gov national: SNCTP
Category and its rationale	Category A1: minimal risk The medical device used for this study carries conformity marking (CE label). The medical device will be used in accordance with the instructions for use. Participants are not subjected to any additional invasive or stressful procedures, and the benefit-risk analysis is positive.
Name of the MD, name of the manufacturer **Unique Device Identification (UDI)**	Steriwave™ Nasal Photodisinfection System SW4000 Light Source SW3200 Nasal Light Illuminator SW3100 Formulation Applicator photosensitizer: methylene blue Manufacturer Ondine Biomedical Inc. 888-1100 Melville Street Vancouver, BC V6E 4A6 Canada Carolyn Cross — Chairman and Chief Executive Officer Nicolas G. Loebel PhD — President and Chief Technology Officer UDI 081000287SW4000RF
Stage of development	post-market stage
Background and rationale	Antimicrobial Photo-Dynamic Therapy (aPDT) is known to reduce microbial load with minimal risks, a very high degree of efficacy, and no known development of resistance. Its antimicrobial activity against various infectious agents has been proven. Surgical site infection is one of the most common healthcare associated infections. Today preoperative decontamination protocols involving different disinfecting solutions such as chlorhexidine, povidone-iodine, Octenidindihydrochlorid or alcohol-based antiseptic or no disinfection at all are used. Application of the disinfectant solution in the nasal cavity is difficult to control due to the anatomical conditions. The application of methylene blue followed by antibacterial photodynamic therapy is a method that is easy to standardize.

Objectives	This study aims to investigate the following objectives in a population of adult patients undergoing surgery under general anesthesia in the department of oral and maxillofacial surgery of University Hospital Zurich: Primary objective: - to determine the additional efficacy of nasal cavity photodisinfection in reducing local microbial colonization in a preoperative setting compared to 0.2% chlorhexidine gluconate and non-light activated methylene blue. Secondary objectives: - determine the additional efficacy of nasal cavity photodisinfection in reducing local microbial colonization after 14 (+/-1) days follow-up compared to 0.2% chlorhexidine gluconate and non-light activated methylene blue. - additional short-term comparison after 2 days follow-up of patients treated for midface fractures by open reduction and internal fixation (trauma surgery subgroup). - Longitudinal comparison of microbial colonization at baseline, 5 min after aPDT and 14 (+/-1) days after aPDT. - develop an aPDT disinfection protocol for preoperative nasal cavity disinfection at University Hospital Zürich Safety objective: - the safety of nasal cavity photo disinfection by aPDT
Outcomes	The following outcomes shall be analyzed in patients undergoing surgery under general anesthesia in the department of oral and maxillofacial surgery of University Hospital Zurich: Primary outcome: - Bacterial colonization 5 minutes after aPDT across the nine analyzed microbe groups, expressed as a score (range 0-27). Secondary outcomes: - Bacterial colonization 14 (+/-1) days after aPDT across the nine analyzed microbe groups and expressed as score (range 0-27). - additional analysis of bacterial colonization 2 days after aPDT for trauma surgery subgroup Safety outcome: - Adverse effects (inquired by standardized survey on first day post intervention and on day 14 (+/- 1d) during regular postoperative follow up.
Design	Randomized controlled prospective single-center double blinded study

Inclusion criteria **Exclusion criteria**	Inclusion criteria: • provision of a signed and dated informed consent form • stated willingness to comply with all study procedures and availability for the duration of the study • male or female ≥ 18 years of age • surgical intervention in general anesthesia with oral intubation at the department of oral and maxillofacial surgery of University Hospital Zurich Exclusion criteria: • inability to tolerate insertion of the light illuminator or the photosensitizer applicator due to anatomic variations (size, shape of oro-nasal region) or disease • inability to follow the procedure of the investigation, e.g., due to language problems or psychological disorders of the subject • known allergic reactions to components of the nasal decolonization treatment, including methylene blue or chlorhexidine gluconate • planed surgery in the nasal cavity • necessary nasal intubation for surgical intervention • vulnerable persons (subjects incapable of judgment or subjects under tutelage) • pregnant or breastfeeding women
Measurements and procedures	Measurements: • microbiological analysis of nasal swabs 3 minutes before and 5 minutes after aPDT • standardized survey and nasal swab test during regular postoperative follow up after 14 days (+/- 1 day) • additional nasal swab after 2 days before discharge of hospital for midfacial trauma group The nasal swab test will be analyzed at the Institute of Medical Microbiology of the University of Zurich according to the standard procedure with classification of bacterial colonization in "not detectable"; "sporadic" (<10^4 CFU); "moderate" (10^4 – 10^5 CFU) and "plentiful" (>10^5 CFU). aPDT treatment will take place prior to surgery in the operating facilities (Nord2 C OP or AOU USZ Circle) at University Hospital Zurich.
Study intervention	The intervention consists of the following steps: 1. Swabbing the formulation applicator (soft swab pre-saturated with the photosensitizer formulation) inside the patient's nostrils. 2. Connection of the nasal light illuminator to the light source and insertion of the nasal light illuminator into the patient's right and left nostrils. 3. **A: Experimental group**: **Activation of the light source** and illumination of the nose and nasopharynx for 2 minutes. 4. Repetition of steps 1.-3. to complete photo disinfection of all nasal regions. Duration of study intervention: 14 minutes Intervention is performed during preparations prior to surgery and followed by regular disinfection of oral cavity (not nasal cavity) according to hospital standards after nasal swab test

Control intervention	The intervention consists of the following steps: 1. Swabbing the formulation applicator (soft swab pre-saturated with the photosensitizer formulation) inside the patient's nostrils. 2. Connection of the nasal light illuminator to the light source and insertion of the nasal light illuminator into the patient's right and left nostrils. **3. B: Control group: no activation of light source** 4. Repetition of steps 1.-3. to complete control intervention. Duration of treatment: 14 minutes Intervention is performed during preparations prior to surgery and followed by regular disinfection of oral cavity (not nasal cavity) according to hospital standards after nasal swab test
Number of subjects with rationale	208 patients (experimental group n=104; control group n=104) The inclusion of 208 patients allows for the collection of sufficient data for statistical analysis of the primary outcome and can be accomplished within a reasonable period. Including approximately 100 patients in subgroup "midfacial fracture" (experimental group n=50; control group n=50)
Duration of the investigation	1 year from start of screening of first subject to last subject processed
Investigation schedule	Month/year of first subject in (planned): 08/2024 Month/year of last subject out (planned): 12/2025
Investigators	Sponsor-Investigator / principal investigator Prof. Dr. med. Dr. med. dent. Harald Essig Head of department ad interim Department of Oral and Maxillofacial Surgery University Hospital Zurich CH-8091 Zurich Switzerland Tel: +41 44 255 50 31 Mail: harald.essig@usz.ch Scientific advisor Prof. Dr. rer. nat. em. Heinrich Walt Investigator Dr. med. Dr. med. dent. Raphael Ferrari
Investigational Site	Single-center study: University Hospital Zurich Department of Oral and Maxillofacial Surgery Frauenklinikstrasse 24 8091 Zurich Switzerland

Statistical considerations	The sample size was calculated to show the superiority of the intervention compared to the control regarding the primary outcome with a power of 90 % at a significance level of 5 %. We calculated the sample size for a Wilcoxon-Mann-Whitney test but did this via the sample size for a two-sample t-test and by increasing the sample size using the Asymptotic Relative Efficiency (ARE) of the Wilcoxon-Mann-Whitney test (compared to the t-test), which is never less than 0.864. To show a mean difference in the primary outcome of 3 with a standard deviation of 6, a total of 170 evaluable patients would be required for a two-sample t-test. For a Wicoxon-Mann-Whitney test we increased the sample size, dividing 170 by 0.864, which resulted in 198 patients (rounded up to an even number). Assuming a drop-out rate of 5 %, 208 patients need to be enrolled. The primary outcome, bacterial colonization 5 minutes after aPDT across the nine analyzed microbe groups, expressed as a score (range 0–27), will be compared between the randomized groups (intervention vs. control) by a Wilcoxon-Mann-Whitney test. In addition, we will apply a proportional odds logistic regression model, in order to adjust for the baseline measurement of bacterial colonization and the type of surgery used for stratifying the randomization. The colonization with individual types of bacteria (9 types) will be descriptively analyzed and summary statistics (frequency and percentage of each category) will be reported by treatment group.
Compliance statement	This investigation will be conducted in compliance with the CIP, the current version of the Declaration of Helsinki, ISO14155, ICH-GCP as far as applicable, as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
AOU	Ambulantes Operieren USZ (Outpatient Surgery University Hospital Zurich)
aPDT	antimicrobial photodynamic therapy
ASADE	Anticipated Serious Adverse Device Effect
ASR	Annual Safety Report
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO-MD	Ordinance on Clinical Trials with Medical Devices
CRF	Case Report Form (eCRF: electronic CRF)
CTC	Clinical Trials Center
DD	Device Deficiency
HRA	Federal Act on Research involving Human Beings
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonization – guidelines of Good Clinical Practice
IFU	Instruction For Use
ISO	International Organization for Standardization
MedDO	Medical Devices Ordinance
MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
MKG	Mund-, Kiefer- und Gesichtschirurgie
ORIF	Open Reduction and Internal Fixation
PCR	Polymerase Chain Reaction
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SARS-CoV-2	severe acute respiratory syndrome coronavirus type 2
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect
USZ	University Hospital Zurich

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INVESTIGATION SCHEDULE

Table 1: Contact with study participants and procedures accomplished at each study visit

	Visit Number	*0*	*1*	*2*	*3*	*4*	*5*	*x*
	Visit Name	Patient enrolment	nasal decolonization	nasal decolonization	postoperative survey	nasal swab trauma subgroup	survey regular follow up 14d (+/-1)	unscheduled visits d 1-14
	Time*	*min -1day*	*-3 minutes*	*+5 minutes*	*1 day*	*2 days*	*14 (+/-1) days*	*any*
	Repeated event?	*no*	*no*	*no*	*no*	*no*	*no*	*no*
Repeated	**Form name**							
no	Informed consent; Inclusion / exclusion criteria	x						
no	Visit	x	x		x	x	x	x
no	Randomization		x					
no	Demographics	x						
no	Medical history	x						
yes	Survey concomitant treatment	x			x		x	x
no	Nasal swab* and microbiom data (*contains info on Intervention only in event +5 min)		x	x		x	x	
no	Survey expected side effects **				x		x	x
yes	SAE and device deficiency (templates from CTC, not part of PL)		x		x	x	x	x
no	Device deficiencies		x					
no	Study End						x	

**Study or control-Intervention = Timepoint 0*

*** For outpatients "Survey expected side effects" is carried out by telephone*

1. INVESTIGATION ADMINISTRATIVE STRUCTURE

1.1 Sponsor-Investigator and principal investigator

This is an investigator-initiated study.
Sponsor-Investigator and principal investigator:

Prof. Dr. med. Dr. med. dent. Harald Essig
Head of department ad interim
Department of Oral and Maxillofacial Surgery
University Hospital Zurich
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Tel: +41 44 255 50 31
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1.2 Statistician

Statistical advice was provided by Dr. sc. Stefanie von Felten:

Dr. sc. Stefanie von Felten
Epidemiology, Biostatistics and Prevention Institute
University of Zurich

Hirschengraben 84, 8001 Zurich
Tel: 044 634 46 44
Mail: stefanie.vonfelten@uzh.ch

1.3 Microbiological Analyses

The Institute of Medical Microbiology of the University of Zurich will be involved in this study. All samples will be handled according to clinical standards, safety demands, and daily routine.

Institute for Medical Microbiology
University of Zurich
Prof. Dr. med. Dr. phil. Adrian Egli
head of department
Gloriastrasse 28/30
CH-8006 Zurich
Switzerland

1.4 Monitoring institution

This study will be monitored by the Clinical Trials Center of the University Hospital Zurich.

Clinical Trials Center University Hospital Zurich
Monitoring
Rämistrasse 100
CH-8091 Zurich
Switzerland

1.5 Other study personnel

For investigators, clinical study nurse and other study personnel: compare staff list

2. ETHICAL AND REGULATORY ASPECTS

The ethical requirements in clinical research according to E. Emanuel are met(1).
Antimicrobial Photodynamic Therapy (aPDT) is known to reduce the microbial burden with minimal risks, a very high degree of efficacy, and no known development of resistance. Its antimicrobial activity against various infectious agents has been proven(2,3).

Subjects will be selected based on previously established inclusion and exclusion criteria. Since all patients are in the same treatment group, risks and benefits are evenly distributed and similar for all participants. aPDT is carried out under general anesthesia during the surgical preparation work prior to intervention. Therefore, no relevant extended duration of general anesthesia nor risk of psychologically stressful / traumatizing intervention for the patient is given. Vulnerability or privilege do not play a role. The selection of subjects can therefore be considered fair. For a benefit-risk analysis, see section 3.7.

Before this study is conducted, the protocol, proposed participant information, and consent form, as well as other study-specific documents, will be submitted to a properly constituted Competent Ethics Committee (CEC) for formal approval in accordance with local legal requirements. Any amendment to the CIP must as well be approved (if legally required) by the CEC. The decision of the CEC concerning the conduct of the study will be made in writing to the principal Investigator before the commencement of this study. The clinical study cannot begin until approval from the CEC has been obtained.

2.1 Registration of the investigation

This investigation will be registered in international and national registries:
a) international: *ClinicalTrials.gov*
b) national: *SNCTP (via BASEC)*

The investigation will be registered after positive decision of the responsible Ethics Committee; therefore, a registration number cannot be given yet.

2.2 Categorization of the investigation

This investigation is a clinical trial with a medical device. It falls under risk category A1: minimal risk. The health-related study intervention entails only minimal risks and burdens. The rationale for this classification is as follows:

- The medical device to be investigated in this study bears a mark of conformity (CE marking) in accordance with Article 13 MedDO (Medical Devices Ordinance).
- The medical device is used in accordance with the instructions for use.
- In Switzerland, it is not prohibited to make the medical device available on the market, to put it into service, or to use it.
- Participants will not undergo any additional invasive or stressful procedures as part of this study or need additional consultations.
- UDI 081000287SW4000RF

2.3 Competent Ethics Committee (CEC): Reporting duties

Approval from the appropriate constituted Competent Ethics Committee (CEC) is sought for the clinical trial in question. The reporting duties and allowed time frame are adhered too. No substantial amendments are made to the protocol without prior CEC approval, except where necessary to eliminate apparent immediate hazards to study participants. Premature study end or interruption of the study will be reported within 15 days (within 24 hours if it is due to security reasons). The reasons for a premature end or an interruption will be explained. The regular end of the study is reported to the CEC within 90 days, and the final study report will be submitted within one year of the end of the study and within 3 months after a premature end of the investigation. Amendments are reported according to chapter 2.9. This is in accordance with Art. 15 ClinO-MD, Art. 36 ClinO-MD, and Art. 37 ClinO-MD.

2.4 Ethical conduct of the investigation

The investigation will be carried out in accordance with the CIP and with principles enunciated in the current version of the Declaration of Helsinki(4), the European regulation on medical devices 2017/745 (MDR)(5), the Norms ISO14155 and ISO14971(6,7), the Swiss Human Research Act (HRA)(8) and its Ordinances and Swiss regulatory authority's requirements . The CEC will receive the Annual Safety Report (ASR) and interim reports and be notified about investigation stop/end in agreement with local requirements.

2.5 Declaration of interests

There are no conflicts of interest to declare.

The consumables in this study are provided free of charge by Ondine Biomedical Inc. The study design was based in part on a previous nasal decolonization study conducted by Ondine Biomedical Inc. The final study design was not influenced by any demands or requirements of the company. Data collection, data management, data analysis, and data interpretation are not influenced by Ondine Biomedical Inc. Ondine Biomedical Inc. does not have access to the original study data and is not involved in the preparation of the report. Intellectual and copyright independence is guaranteed.

2.6 Patient information and informed consent

The principal investigator or his designated trained physicians (co-investigators; residents at the department of oral and maxillofacial surgery with individual training in the subject matter of this study) will explain to each subject the nature of the investigation, its purpose, the procedures involved, the anticipated duration, the potential risks and benefits, and any discomfort it may entail. Each subject will be informed that participation in the investigation is voluntary and that they may withdraw from the investigation at any time and that withdrawal of consent will not affect subsequent medical care and treatment. Subjects will be informed that they may ask any question, and consult with family members, friends, their treating physicians, or other experts before deciding whether to participate in the investigation. Subjects will be given adequate time. Participants may withdraw at any time, even after enrolling in this investigation. No vulnerable subjects (minors, subjects lacking capacity of judgment, or subjects under tutelage) will be included in this study. Subjects will be informed that authorized individuals other than their treating physician may review their medical records. All subjects will be provided with an information sheet and informed consent form describing the investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation. Formal informed consent will be obtained from the subject using the approved consent form before the subject is submitted to any investigational procedure. The subject should read, understand, and voluntarily consent before signing and dating the informed consent form, and will be given a copy of the signed document. The consent form is signed and dated by the subject and the principal investigator or his designee. The original signed consent form will be retained as part of the investigation records.

2.7 Subject privacy and confidentiality

The sponsor-investigator assures that he will uphold the principle of the subjects' right to privacy and will comply with the applicable privacy and data protection laws. In particular, the anonymity of the subjects will be guaranteed when the data are presented at scientific meetings or published in scientific journals. Data generation, transmission, archiving, and analysis of personal data in the context of this study will be carried out in strict compliance with the current applicable Swiss legal requirements for data protection. A prerequisite is the voluntary approval of the participant given by signing the informed consent prior to the start of participation in the clinical trial. The individual medical information of the participants obtained during this study is considered confidential and must not be disclosed to third parties. Participant confidentiality will be further ensured by utilizing participant identification code numbers that correspond to treatment data in the computer files. For data verification purposes, authorized representatives of the CEC, or the entity responsible for monitoring and audits may request direct access to parts of the medical records relevant to the investigation, including subjects' medical histories.

2.8 Early termination of the investigation

The sponsor-investigator, as well as the CEC, may terminate the investigation prematurely in certain circumstances, such as in the event of:

- ethical concerns,
- insufficient subject recruitment,
- changes in accepted clinical practice that makes it unwise to continue the trial,
- early evidence of benefit or harm from the experimental intervention; or
- if the safety of the subjects is in doubt or at risk.

2.9 Clinical investigation plan amendments

Substantial amendments are implemented only after approval by the CEC (Art. 15 ClinO-MD).
In emergency cases, deviations from the CIP may be made to protect the rights, safety, and well-being of subjects without prior approval by the CEC. Such deviations will be documented and reported to the CEC within 2 days (Art. 34 ClinO-MD). All non-substantial amendments will be reported to the CEC together with the Annual Safety Report (ASR) (Art. 15 ClinO-MD). The ASR includes any deviations from the CIP that may have affected the rights, safety, or well-being of the subject or the scientific integrity of the investigation (ISO14155).

Significant changes to be approved by the CEC include the following:

- changes that affect the safety and health of participants, or their rights and responsibilities,
- changes to the protocol, particularly changes based on new scientific evidence affecting study design, study methodology, endpoints, or the form of statistical analysis,
- a change of trial site, or the conduct of the clinical trial at an additional investigational site; or
- a change in sponsor-investigator (principal investigator).

2.10 Deviation from the Clinical Investigation Plan (CIP)

The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR). The investigators will not deviate from the CIP except in the cases specified in 2.9. (emergencies). Instruction of all investigators concerning the contents of the CIP is mandatory and helps to avoid deviations from the CIP. Any investigator who deviates from the CIP without urgent reasons will be excluded from further cooperation in this project.

3. BACKGROUND AND RATIONALE

3.1 Background and rationale for the clinical investigation

The human nasal cavity is colonized by a large variety of microorganisms as bacteria, viruses and fungi. Many of these belong to normal colonization and are harmless. However, due to its function as a respiratory organ, the nose is also an entry point for pathogens. Especially its anterior part (nares, nostrils), and the nasopharynx are considered the primary respiratory reservoir of pathological microorganisms.
Elimination of the pathogens from this reservoir could play a critical role in preventing surgical site infections after open surgical intervention around the nasal or oral cavity.

Surgical site infection is one of the most common health care associated infections(9,10). Today preoperative decontamination protocols involving different disinfecting solutions such as chlorhexidine, povidone-iodine, Octenidindihydrochlorid or alcohol-based antiseptic are used. Application of the disinfectant solution in the nasal cavity is difficult to control due to the anatomical conditions. In contrast, the application of methylene blue followed by antibacterial photodynamic therapy is a method that is easy to standardize.

Antimicrobial photodynamic therapy (aPDT) has been shown to effectively reduce microbial load with minimal risks. It is quick, easy, and inexpensive to use. Unlike conventional antibiotic therapies, there is no evidence of resistance formation to aPDT in any of the targeted pathogens (11–14). aPDT may therefore represent an approach to temporarily reduce the pathogens in the nasal cavity to a minimum before surgical interventions. aPDT is already routinely used in several hospitals in Canada, and the method is considered standard by Health Canada(2).

Upper and lower respiratory tract infections are common diseases, especially in the colder seasons. aPDT could provide an additional therapeutic option that is low-risk, non-toxic, and effective. Moreover, it could help prevent secondary fungal or bacterial infections after an initial damage to the respiratory epithelium by pathogens: The nose is colonized with various bacteria, including facultative pathogens such as C. auris or multidrug-resistant bacteria such as methicillin-resistant staphylococcus aureus (MRSA, 15,16). aPDT aimed at eliminating pathogens of respiratory infections and could simultaneously reduce the overall microbial burden. aPDT has been shown to be lethal to bacteria and fungi, including drug-resistant strains. Decolonization of the respiratory tract from any bacterial or fungal elements therefore appears to be an additional means of protecting patients and reduce nosocomial infections(3).

In conclusion, aPDT could be a relevant component of reducing surgical site infections within the nasal cavity as an effective and inexpensive method for pathogenic microbial decolonization and prevention of infections. The aim of this study is to collect data on the safety and efficacy of aPDT to the nasal cavity in reducing colonization of pathogenic microorganisms. Analysis of the change in microbial spectrum in the nose will provide additional information on overall antimicrobial efficacy and future indication for aPDT.

3.2 Identification and description of the investigational medical device

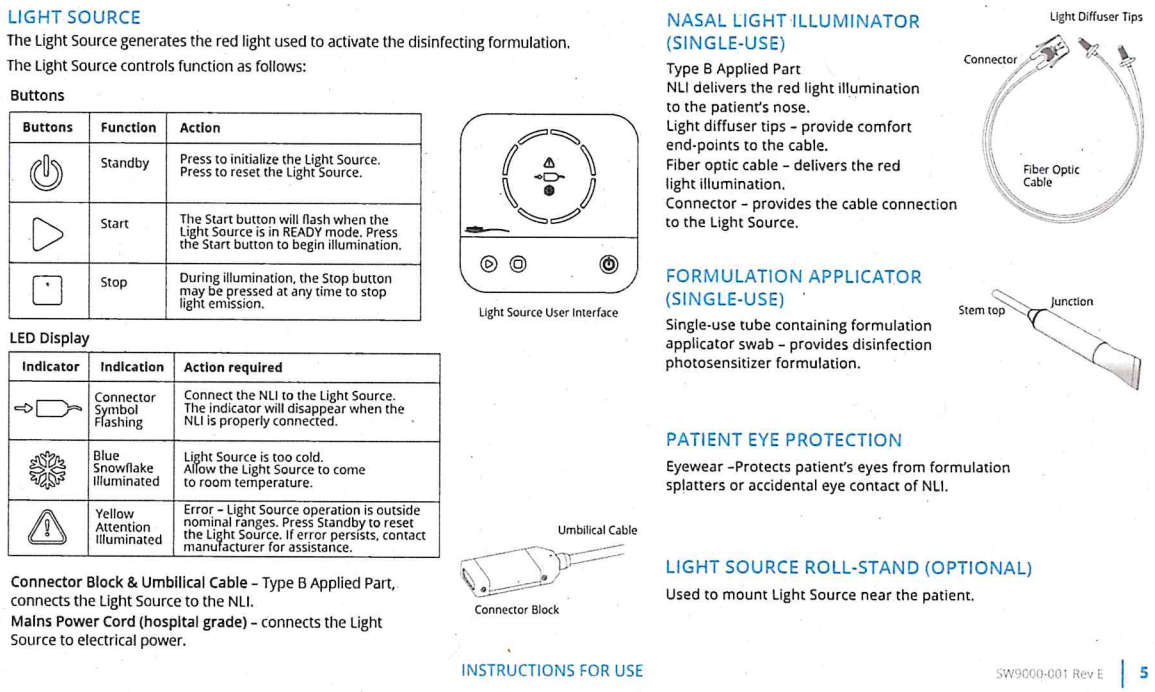
In this study, the following medical device will be tested:

Steriwave™ Nasal Photodisinfection System
Ondine Biomedical Inc., Vancouver, Canada.

It consists of three parts with the corresponding model numbers (shown in **Figure 1**):
SW4000 Light Source
SW3200 Nasal Light Illuminator (single-use)
SW3100 Formulation Applicator (single-use)
photosensitizer: methylene blue

Upper Airway Decolonization

Figure 1 (Steriwave™ instructions for use, page 5; Ondine Biomedical Inc.)



COMPONENT FUNCTIONS

LIGHT SOURCE

The Light Source generates the red light used to activate the disinfecting formulation.

The Light Source controls function as follows:

Buttons

Buttons	Function	Action
	Standby	Press to initialize the Light Source. Press to reset the Light Source.
	Start	The Start button will flash when the Light Source is in READY mode. Press the Start button to begin illumination.
	Stop	During illumination, the Stop button may be pressed at any time to stop light emission.

LED Display

Indicator	Indication	Action required
	Connector Symbol Flashing	Connect the NLI to the Light Source. The indicator will disappear when the NLI is properly connected.
	Blue Snowflake Illuminated	Light Source is too cold. Allow the Light Source to come to room temperature.
	Yellow Attention Illuminated	Error – Light Source operation is outside nominal ranges. Press Standby to reset the Light Source. If error persists, contact manufacturer for assistance.

Connector Block & Umbilical Cable – Type B Applied Part, connects the Light Source to the NLI.

Mains Power Cord (hospital grade) – connects the Light Source to electrical power.

Light Source User Interface

Umbilical Cable

Connector Block

NASAL LIGHT ILLUMINATOR (SINGLE-USE)

Type B Applied Part

NLI delivers the red light illumination to the patient's nose.

Light diffuser tips – provide comfort end-points to the cable.

Fiber optic cable – delivers the red light illumination.

Connector – provides the cable connection to the Light Source.

Light Diffuser Tips

Connector

Fiber Optic Cable

FORMULATION APPLICATOR (SINGLE-USE)

Single-use tube containing formulation applicator swab – provides disinfection photosensitizer formulation.

Stem top

Junction

PATIENT EYE PROTECTION

Eyewear –Protects patient's eyes from formulation splatters or accidental eye contact of NLI.

LIGHT SOURCE ROLL-STAND (OPTIONAL)

Used to mount Light Source near the patient.

INSTRUCTIONS FOR USE

SW9000-001 Rev E | 5

The medical device bears a conformity marking (CE label) and is thus approved for medical use. Its intended use is aPDT of the nose and nasopharynx after topical application of a photosensitizer (methylene blue). No deviations from the original CE-marked instructions for use will be made in this study. No changes will be made to the design of the device.

The nasal light illuminator and the formulation applicator preloaded with the photosensitizer, which both are single-use disposable products, are the two parts of the device that get in contact with human tissue and body fluid (nasal secretion).

The manufacturer has provided training on the use of the medical device. All investigators and study personnel involved in the use of the medical device have been sufficiently trained and are experienced in the use of the device. All investigators and all members of the clinical study personnel have been provided with a copy of the instructions for use.

3.3 Preclinical evidence

Since the medical device carries a conformity marking (CE label) and there is no off-label use, preclinical evidence can be omitted in the CIP. Data from the manufacturer (Ondine Biomedical Inc.) can be obtained upon request.

3.4 Clinical evidence to date

Adverse device effects

No serious adverse events were reported in >150,000 treatments in Canada, where the medical device is considered standard by Health Canada. Minor adverse events included a runny nose, sneezing, irritation, etcetera, and were self-limited.

Toxicology: A review of literature toxicity data for methylene blue suggests that the toxicity of the compound, if any, comes from doses or concentrations of 5,000 µg/mL or more along with light irradiation of >500 J/cm^2. By comparison, the nasal photodisinfection treatment will be applied at a maximum concentration of 100 µg/mL and approximately 160 joules total of light energy or 360J/cm^2. This miniscule dose of maximum 100 µg/mL is also safe during pregnancy with no reported adverse event in pregnant woman for oral or nasal methylene blue formulation over the past 15 years of use.

Light disturbance: The light emitted by the medical device is not harmful to the eyes.

History of modification or recall

The photosensitizer formulation, swabs, and the patient-contacting nasal illuminator device remained unchanged throughout the entire marketing history in Canada. While the laser light source has evolved over three models, the laser diode wavelength, light dosimetry, and light path have remained unchanged throughout.

Post-marketing data

Post-marketing studies focused on various infectious agents residing in the nose, particularly multi-drug resistant bacteria. Studies found high efficacy against multidrug-resistant Staphylococcus aureus (MRSA) (Bryce et al, 2014; Street C, 2009 and 2010).

3.5 Justification for the design of the clinical investigation

Today there is no standardized protocol for nasal cavity decolonization. With our study design analyzing the microbial decontamination and test the applicability in the preoperative setting under general anesthesia allows gaining valuable information to establish a standardized disinfection protocol for the nasal cavity.

Combining the study intervention with a surgical intervention in the head and neck area allows for minimal stress on the patient. After the second swab test the study intervention is followed by regular disinfection protocol as performed according to today's hygiene standards at University Hospital Zürich.

aPDT must be performed within established limits for light power, light time, and photosensitizer concentration and dosage. All settings in this study are be based on the manufacturer's instructions for use and correspond to the standard of care in Canada, where the medical device is routinely used, as well as to the CE-labeled instructions of use.

Light power: The power is set at 150 mW/cm^2. This value has been shown to have an antimicrobial effect in various nostril sizes without thermal effects on the nasal tissues. The wavelength of the device is set at 663 nm which is the optimal excitation wavelength for activation of methylene blue.

Light time: A double two-minute treatment cycle (total 4min illumination) is selected to ensure appropriate therapeutic effect regardless of nasal cavity size, biofilm thickness, anatomical variances, or increased mucus layers.

Photosensitizer concentration: 0.01% methylene blue is used for this study, which corresponds to 100µg/ml. This concentration reflects a balance between sufficient photosensitizing effect and increasing light blockade. Methylene blue shows peak light absorption at 660 nm wavelength (red light). As a cationic molecule, it is attracted to negatively charged surface structures and preferentially binds to them. This keeps the aPDT reaction tightly confined to the targets, as microbial surfaces are usually negatively charged, compared to human tissue cells. When exposed to red light, the methylene blue can transfer light energy to surrounding molecular oxygen in the tissue, which in turn generates short-lived reactive oxygen species. They are lethal to microbial cell membranes while they have only little effect on eukaryotes (Cieplik, 2018).

Photosensitizer dosage: One formulation applicator (soft swab pre-saturated with photosensitizer) will be applied to each nostril (one right, one left) prior to the first two-minute light treatment. This sequence is repeated with repositioned light delivery tips to achieve maximum coverage of the nose. The maximum dose of the photosensitizer formulation per treatment is calculated as follows:

- 2 saturated swabs of 1.5 ml each = 3.0 ml of formulation
  repeated once = 6.0 ml of formulation
- 0.01% methylene blue solution = 600µg total dose, assuming complete absorption
  for a 70 kg adult, this represents 0.014 mg/kg/day

- an average patient treated for methemoglobinemia would receive about 1-2 mg/kg methylene blue; the topical nasal decolonization dosage is hence less than 1/200th of the i.v. dose for methemoglobinemia treatment.

3.6 Explanation for choice of comparator

In our study, there will be a comparison of every patient pre- and post-intervention (nasal swab test for microbial analysis). Therefore, the individual microbial decontamination will be analyzed. To reduce bias of concomitant treatment / medication and the disinfection effect of chlorhexidine gluconate, patient randomization either to experimental or control group is mandatory.

3.7 Risk evaluation (benefit-to-risk rationale)

Anticipated adverse device effects

The photosensitizer used for aPDT in this study (methylene blue with chlorhexidine gluconate) has been approved as a complete System by the appropriate agencies and both ingredients have been shown to be effective against microbial colonization. The photosensitizer formulation has been used on patients for many years with a minimum of reported adverse events. It is used by Orcos-Dental in Switzerland, and it is even approved for i.v.-use. Chlorhexidine is listed in Annex V in the List of preservatives as approved. The concentration of the active ingredient (0.01% methylene blue) is many times lower than when the same products are used separately, for example for classical surgical site disinfection (chlorhexidine) or treatment of methemoglobinemia (methylene blue). The used system is certified in the European Union and in Canada.

In Canada in thousands of patients, there is considerable real-world data on the adverse event profile. Data from 49'313 nasal aPDT treatments in an industrial setting (meat industry) showed that 49'009 treatments were not associated with any adverse events. 304 (0.6%) minor adverse events were reported during treatment and 2'214 (4.5%) in the 24 hours after treatment as shown in **Table 2**. No serious adverse events occurred.

Reported minor adverse events included a runny nose (1.9%), sneezing (1.3%), nasal irritation (0.5%), and throat irritation (0.3%) and were all self-limited. Less commonly reported adverse events included local itchiness, nasal congestion, altered smell and/or taste, feeling of warmth, cough, headache, or nosebleed.

Table 2: Reported adverse events from a nasal aPDT study in Canada (Ondine Biomedical Inc.)

	During Treatment		Within 24 Hrs		Total	
Total # of Survey responses	**49,313**	**100.0%**	**48,841**	**100.0%**		
No Side Effects	**49,009**	99.4%	46,627	95.5%		
Had Side Effects	**304**	0.6%	2,214	4.5%		
Total # of Side Effects	**313**	**0.6%**	**2,702**	**5.8%**	**3,015**	**6.1%**
Expected	**246**	**0.5%**	**2,087**	**4.5%**	**2,333**	**4.7%**
Runny nose	32	0.1%	909	1.9%	941	1.9%
Sneeze	57	0.1%	603	1.3%	660	1.3%
Nose irritation	71	0.1%	188	0.4%	259	0.5%
Throat irritation	24	0.0%	130	0.3%	154	0.3%
Itchy nose	35	0.1%	110	0.2%	145	0.3%
Nasal congestion	1	0.0%	96	0.2%	97	0.2%
Itchy throat	11	0.0%	31	0.1%	42	0.1%
Odd smell/taste	2	0.0%	12	0.0%	14	0.0%
Warm feeling	8	0.0%	2	0.0%	10	0.0%
Watery eyes	3	0.0%	3	0.0%	6	0.0%
Cough	1	0.0%	1	0.0%	2	0.0%
Noticeable blue stain around nostrils	1	0.0%	1	0.0%	2	0.0%
Clear nasal passage			1	0.0%	1	0.0%
Unexpected	**67**	**0.1%**	**615**	**1.3%**	**682**	**1.4%**
Headache	3	0.0%	270	0.6%	273	0.6%
Dry nose	24	0.0%	152	0.3%	176	0.4%
Dry throat	11	0.0%	83	0.2%	94	0.2%
Nose bleed	23	0.0%	48	0.1%	71	0.1%
Dizzy	2	0.0%	21	0.0%	23	0.0%
Red / blood-tinged mucus	2	0.0%	14	0.0%	16	0.0%
Drowsy	1	0.0%	4	0.0%	5	0.0%
Furunculosis (pimple in nose)			4	0.0%	4	0.0%
Itchy			3	0.0%	3	0.0%
Uncomfortable	1	0.0%	2	0.0%	3	0.0%
Increased acne			2	0.0%	2	0.0%
Sense of smell is diminishing			3	0.0%	3	0.0%
Vomit			1	0.0%	1	0.0%
Fever/flu			1	0.0%	1	0.0%
Swelling in the eye			1	0.0%	1	0.0%
Heart rate increase			1	0.0%	1	0.0%
Anxiety			1	0.0%	1	0.0%
Hard to breathe / Shortness of breath			2	0.0%	2	0.0%
Stomach ache			1	0.0%	1	0.0%
Triggered sinusitis			1	0.0%	1	0.0%
Other - unspecified	25	0.1%	46	0.1%	71	0.1%

Results of phase 2 nasal photodisinfection trial. Full title: Bacterial Eradication of the Nasal Epithelium From Infectious Toxins With PDT (BENEFIT-PDT); Ondine Biomedical Inc., Vancouver, Canada (https://clinicaltrials.gov/ct2/show/NCT05090657)

Risks due to interaction with concomitant treatments

Methylene blue is administered intravenously for the treatment of methemoglobinemia. From this use, data is known on interactions with pharmacologic agents that act on serotonin metabolism. These include selective serotonin reuptake inhibitors (SSRIs) and other types of antidepressants. The risk of serotonin syndrome exists in patients taking serotonergic drugs when methylene blue is used at doses exceeding 5 mg/kg. In this study the estimated dosage of methylene blue is under 0.1 micrograms per kg, and it is being administered topically in the nasal cavity. Regarding the applied topical dose an exclusion of patients with SSRI medication is not necessary.

Risks due to microbiological testing

Swabbing of the anterior nose can in rare cases lead to a nosebleed due to superficial injury of the sensitive nasal mucosa.

Measures to control or mitigate the risks

Patients with known allergies to any of the photosensitizer's ingredients (methylene blue, chlorhexidine) are excluded from this study.

History of modification or recall in relation to safety and clinical performance

The photosensitizer formulation, swabs, and the patient-contacting nasal illuminator device remained unchanged throughout the entire marketing history in Canada. While the laser light source has evolved over three models, the laser diode wavelength, light dosimetry, and light path have remained unchanged throughout.

Anticipated clinical benefit

Nasal decolonization is known to reduce the risk of healthcare-associated infections and is routine care in many Canadian hospitals. A standardized protocol to disinfect the nasal cavity could reduce surgical site infections. In addition, it could be useful in eliminating multi resistant pathogens in the nasal cavity such as MRSA.

Benefit-risk rationale

Both individual patients (reduced likelihood of surgical site infection; unknown colonization with multi resistant pathogens) and future subjects (standardized protocol for preoperative nasal cavity disinfection) may benefit from participation in this study.

Risks to patients are minor treatment-related adverse effects that are self-limiting. The addition of nasal cavity aPDT in the preoperative disinfection protocol has a good benefit-risk ratio. The choice of light intensity and light duration as well as the testing of light power output before every treatment ensure sufficient efficacy of the medical device.

3.8 Justification of the choice of the investigation population

Microbial colonization of the nasal cavity poses a risk for surgical site infection during interventions in the oral cavity. Therefore, additional disinfection of nasal cavity and upper respiratory tract could be beneficial.
Inclusion of all patients undergoing surgery in general anesthesia in the Oral and Maxillofacial Surgery Department who meet the inclusion/exclusion criteria without further selection for age, gender, or co-morbidities will ensure adequate community representation in this study.

No vulnerable subjects (minors, subjects incapable of judgment or subjects under tutelage) will be included in this study. Patients will be informed about this study during regular consultation prior to surgery. Consent to the study can be withdrawn at any time.

Pregnant and breastfeeding women will be excluded from the study. Pregnancy induces significant physiological alterations, such as increased blood volume and nasal tissue engorgement (hyperemia) which could influence the clearance of the nasal mucosa and therefore influence the study results. Regarding the risks of topical application of methylene blue during pregnancy the miniscule dose of maximum 100 µg/mL is substantially lower than doses administered intravenously for conditions like methemoglobinemia (1-2 mg/kg). Based on the concentration applied topically and no reported adverse event in pregnant woman for oral or nasal methylene blue formulation over the past 15 years of use, it can be stated safe during pregnancy. We therefore believe that a pregnancy test before inclusion in the study is unjustified for all women of childbearing age. If pregnancy is reported in the survey, the patient will be excluded.

4. CLINICAL INVESTIGATION OBJECTIVES

4.1 Overall objective

Currently, the standard preoperative disinfection protocols for the nasal cavity varies from no disinfection at all to inconsistent application methods and disinfection solutions such as chlorhexidine, povidone-iodine, Octenidindihydrochlorid or alcohol-based antiseptics. In the department for Oral and Maxillofacial Surgery and the department for Otho-Rhino-Laryngology the standard of care is no disinfection for the nasal cavity even if open surgery within the nose is carried out. To standardize a relatively user-independent protocol aPDT with its advantageous lack of resistance formation will be tested for applicability.

4.2 Primary objective

The primary objective is to determine the additional efficacy of nasal cavity photodisinfection in reducing local microbial nasal colonization in a preoperative setting compared to 0.2% chlorhexidine gluconate and non-light activated methylene blue. Comparison of the 5 minutes after aPDT measure to the control group and to the baseline 3 minutes prior to intervention.

4.3 Secondary objectives

The secondary objectives are to:

- To determine the efficacy of nasal cavity photodisinfection as an add-on treatment to 0.2% chlorhexidine gluconate in reducing local microbial colonization after 14 (+/-1) days follow-up.
- To analyze short term effects in the critical time for wound healing after 2 days in the subgroup after fracture reduction of the midface
- Longitudinal comparison of microbial colonization at baseline, 5 minutes after aPDT and 14 (+/-1) days after aPDT.
- develop an aPDT disinfection protocol for preoperative nasal cavity disinfection at University Hospital Zürich

4.4 Safety objectives

The safety of nasal aPDT will be measured. Patients will be monitored for any untoward effects related to the nasal decolonization using aPDT.

5. CLINICAL INVESTIGATION OUTCOMES

5.1 Primary outcome

To objectively determine the efficacy of nasal cavity decolonization with aPDT in eliminating or significantly decreasing pathogens, relative abundance of CFU (colony forming unit) over nine analyzed microbe groups at timepoint 5 minutes after intervention, are grouped as score ranging from 0-27. The results will be adjusted to the baseline measure 3 minutes pre-intervention.
Comparing bacterial colonization scores of interventions to control group allows to measure additional disinfection effect of aPDT over chlorhexidine gluconate.

Score bacterial colonization:

Name	CFU's	Score
"not detectable"	*below detection limit*	*0*
"sporadic"	*<10^4*	*1*
"moderate"	*10^4 – 10^5*	*2*
"plentful"	*>10^5*	*3*

Nine microbial subgroups for analysis:

1. ß-hemolytic (group A and group B) *Streptococcus*
2. *Staphylococcus aureus* (with discrimination in MSSA and MRSA)
3. Coagulase negative Staphylococcus species (incl. *Staphylococcus epidermidis*)
4. α-hemolytic Streptococcus species (oral or viridans-group Streptococci)
5. Corynebacterium species
6. Candida species
7. Enterobacterales
8. Actinomyces species and miscellaneous aerotolerant bacteria
9. Anaerobic bacteria with focus on *Propionibacterium*

5.2 Secondary outcomes

Bacterial colonization 14 (+/-1) days after aPDT across the nine analyzed microbe groups and expressed as score (range 0-27).
Bacterial colonization 2 days after aPDT in the midface trauma subgroup across the nine analyzed microbe groups and expressed as score (range 0-27).

5.3 Safety outcomes

Standardized survey for adverse effects noted after treatment and on day 1 and day 14 (+/-1) during regular follow-up consultation after surgery. For outpatient procedures, side effects are surveyed after treatment on the first day as a telephone conversation.

6. CLINICAL INVESTIGATION DESIGN

6.1 General clinical investigation design and justification of design

Design and rationale

This is a randomized controlled prospective study. Randomization of participants to either experimental or control group is necessary to reduce bias caused by concomitant treatment / medication and to investigate the additional effect of aPDT (activated photosensitizer) over the disinfection effect of chlorhexidine gluconate or unactuated methylene blue.

Intended procedures

Preoperative consultation:
After patient information and obtaining of informed consent, the inclusion and exclusion criteria are checked, and patient demographic data and medical history are obtained. Data will be taken from their medical records in the clinical information system (KIS).

Surgery day:
Random assignment of patients to experimental or control group.

Consent to participate will be updated after admission to the hospital on the day of surgery.

After Intubation and during positioning and final preparations for surgery, participants will then be administered the medical device as described under 8.1.1 Experimental Intervention (medical device) depending on assignment to experimental or control group (no light activation in control group).

Participants will be asked about their subjective evaluation of the treatment on the first postoperative day (Visit 2). For outpatient procedures, the survey is carried out by telephone.

Additional nasal swab for the subgroup after open reduction and internal fixation of midfacial fracture on day 2 (Visit 3; day of hospital discharge)

Visit day 14 (+/- 1)
Participants will be revisited 14 days (+/-1 d) after intervention (Visit 4) as part of the regular follow up consultation. The appointment will be made before discharge from the hospital. All participants will be interviewed about possible adverse effects and a third nasal swab test for microbiological analysis will be performed.

Limitations of the design

The main limitation of this design is the risk of misattributing immediate adverse effects when study intervention is combined with surgical intervention under general anesthesia. Therefore, initial survey is caried out on the first postoperative day ("Visit 2") to reduce misinterpretation of surgery related symptoms. Exclusion of nasal intubation or surgery in the nose further reduce surgery or anesthesiology related effects. With an additional more homogenic subgroup of patients after open reduction and internal fixation of midface fractures, we can reduce these influences and gain additional information in the early phase after aPDT on day 2 (day of hospital discharge).
On the other hand, combining intervention and study keeps the number of lost patients to follow-up limited and therefore allows also conclusive analysis of later adverse events (till 14 days post intervention).

Population

Patients undergoing surgery in general anesthesia at Maxillofacial Surgery Department of University Hospital Zurich will be included in this study. There will be 208 patients enrolled in this study (experimental group n=104, control group n=104). The target sample size is expected to reflect the demographic characteristics of the local community in terms of age, gender, and comorbidities.

6.2 Methods for minimizing bias

The design as randomized controlled trial allows minimizing bias by disinfecting effects of chlorhexidine gluconate or unactuated methylene blue photosensitizer. In addition, a control group reduces influence due to concomitant therapies such as nasal rinse or antibiotic treatments as part of the standard postoperative protocol.

Exclusion of nasal intubation and nose surgery reduces misinterpretation of surgery or anesthesiology related side effects (nose bleeding, itchy nose, pain).

Third visit for midface trauma subgroup on day 2 (normally day of hospital discharge) helps to reduce intubation related changes and provide a low number of patients lost for follow-up.

Combining the fourth survey "Visit 4" with the regular 14 day follow up after surgery should cause a significant reduction of lost patients for follow-up.

There is no reasonable likelihood of introducing bias into the determination of colonization status. Clinical care and routine microbial analysis will be provided and conducted as usual with no change to the clinical pathway.

6.2.1 Randomization

Randomization will be performed in REDCap. Clinicians conducting the postoperative surveys will not have access to the eCRF form with the randomization result and therefore be blinded against the treatment group.
Stratified block randomization with variable block size for type of surgery (osteosynthesis removal; open reduction and internal fixation of midface fractures vs other).

Explanation for stratification:
Removal of osteosynthesis material rarely requires any of the under 8.6 mentioned concomitant treatments. In addition, the patients are generally younger and have less comorbidities. Therefore, a stratified randomization to intervention and control group is justified. The second stratification for patients undergoing open reduction and internal fixation of midface fractures is necessary to build the subgroup (target size n=50) with additional swab on day 2 (day of hospital discharge). Also, this patient collective is more consistent in duration of surgery and concomitant treatment.

6.2.2 Blinding procedures

Due to study intervention during general anesthesia blinding of study participants is fulfilled. The investigator conducting the postoperative survey (day 1 and 14 (+/- 1)) is not the same as conducting the study intervention during surgery. Therefore, the examiner is also blinded. Microbiological analysis is carried out via routine diagnostics without need for specific blinding.

7. CLINICAL INVESTIGATION POPULATION

7.1 Eligibility criteria

Subjects who meet all the following inclusion criteria are eligible for the investigation:

- Provision of a signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Male or female ≥ 18 years of age
- surgical intervention in general anesthesia at the department of oral and maxillofacial surgery of University Hospital Zurich

The presence of any of the following exclusion criteria will lead to the exclusion of the subject:

- inability to tolerate insertion of the light illuminator or the photosensitizer applicator due to anatomic variations (size, shape of oro-nasal region) or disease
- inability to follow the procedure of the investigation, e.g., due to language problems or psychological disorders of the subject
- known allergic reactions to components of the nasal decolonization treatment, including methylene blue or chlorhexidine gluconate
- planed surgery in the nasal cavity
- necessary nasal intubation for surgical intervention
- vulnerable persons (subjects incapable of judgment or subjects under tutelage)
- Pregnant or breastfeeding women

7.2 Recruitment and screening

Recruiting will take place during consultation at Department for Oral and Maxillofacial surgery at University Hospital Zürich. Patients will be asked and informed about the study in case of an indication for surgery in general anesthesia.
The study does not require long-term participation. Subjects do not receive payment or compensation.

7.3 Assignment to investigation groups

Of the total 208 participants 104 will be randomly assigned to the experimental group and 104 to the control group. Randomization process is executed as described under 6.2.1.

7.4 Criteria for withdrawal / discontinuation of subjects

Withdrawal of subjects
If a clinically significant finding is identified after enrollment in the study (including, but not limited to changes from baseline), the principal investigator or qualified designee will determine if any change in participant management is necessary. Any new clinically significant finding will be reported as an adverse event (AE).

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may exclude or withdraw a participant from the study for the following reasons:

- significant non-compliance with the study intervention due to intolerance of the nasal illumination
- if any clinical adverse event or other medical condition occurs such that continued participation in the study would not be in the best interest of the patient

The reason for the participant's discontinuation or withdrawal from the study will be recorded in the Case Report Form (CRF). Subjects who sign the informed consent form and are enrolled in the study, but do not receive the study intervention, may be replaced. Subjects who receive the study intervention and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Patients lost to follow-up
Participants are considered "lost to follow-up" if they fail to report for scheduled study visits and cannot be reached to complete all protocol-required study procedures.

The following actions will be taken if a participant fails to attend a required study visit:

- The investigator will attempt to contact the participant and reschedule the missed visit for 1 day. These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of "lost to follow-up".

8. CLINICAL INVESTIGATION INTERVENTION

8.1 Identity of the medical device under investigation

In this study, the following medical device will be investigated:

Steriwave™ Nasal Photodisinfection System
Ondine Biomedical Inc., Vancouver, Canada.

It consists of three parts with the corresponding model numbers:
SW4000 Light Source
SW3200 Nasal Light Illuminator
SW3100 Formulation Applicator
Photosensitizer: methylene blue

SW4000 Light Source
Class 1 Laser Device that generates red light consisting of 2 channels of 700 mW, 664 nm light (continuous wave) used to activate the disinfecting formulation.

SW3200 Nasal Light Illuminator
Light diffuser tips are attached to fiber optic cables that deliver red light through a plug-in connection to the Light Source. Diffuser cables are labeled with an "L" for the left nostril and "R" for the right nostril. Single-use item.

SW3100 Formulation Applicator
Sealed tubular package containing a formulation-saturated swab that extends from the detachable lid. The proprietary formulation includes methylene blue and chlorhexidine gluconate, along with several inactive ingredients. Single-use item.

8.1.1 Experimental intervention (medical device)

The intervention consists of the following steps:

1. Swabbing the formulation applicator (soft swab pre-saturated with the photosensitizer formulation) into patient's nostrils.

2. Connection of the nasal light illuminator to the light source and insertion of the nasal light illuminator into the patient's right and left nostrils.

3. Activation of the light source and illumination of the nose and nasopharynx for 2 minutes.

4. Repetition of steps 1.-3. to complete photodisinfection of all nasal regions.

Duration of treatment: 14 minutes

- pre-intervention nasal swab test (0.5 min)
- waiting time (3 min)
- nasal application of photosensitizer (0.5 min)
- 2min illumination
- Repetition of photosensitizer application (0.5 min)
- 2 min illumination
- Waiting time (5 min)
- Post-intervention nasal swab test (0.5 min)

All treatment steps follow the CE-labeled instructions for use of the medical device. There are no deviations from the commercial product. The corresponding part of the instructions for use provided by the manufacturer is shown in **Figure 2**.

The procedure will be performed by the investigators (physicians or clinical study nurses with special training provided by the manufacturer of the medical device).

All investigators and clinical study nurses have been trained by the manufacturer in the use of the medical device and its components. All consumables will be disposed of in accordance with hospital hygiene standards and treated as contaminated with infectious materials. The light source will be wiped down with the standard disinfectant solution provided by the hospital. Before starting the intervention, the optical power output will be checked with the manufacturer's approved power tester to ensure that the optical output power meets the technical specifications.

Figure 2: Steriwave™ instructions for use (pages 6 and 7; Ondine Biomedical Inc.)

PROCEDURE

Use the following instructions to perform the nasal photodisinfection procedure.

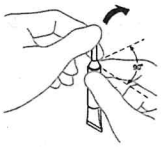
SETUP

1. Position the Light Source to ensure the light diffuser tips of the fiber optic cable can reach the patient's nose without tension. Ensure Light Source air vents are not obstructed.
2. Connect the Light Source power cord to mains power outlet. Ensure cord is not a tripping hazard.
3. Press the Standby button on the Light Source. The indicators will flash on the LED display. Any startup errors will display on the LED display and an audible tone will sound. If there are no errors, the Connector Indicator will flash, indicating system is ready to attach NLI.

   NOTE: In case of an emergency, disconnect the power cord from the Light Source.

PREPARING THE PATIENT

4. Position the patient in a seated, Semi-Fowler's, reverse-Trendelenburg, or supine position. Avoid Trendelenburg, if possible.
5. Have the patient blow their nose thoroughly and don a protective bib and protective eyewear.
6. Open the Formulation Applicator by:
   a. Squeeze the tube directly on the junction until tube "pops" open. Ensure the tube is held vertically and aimed away from the operator's face to avoid splashing formulation.
   b. Gently rock the stem back and forth to extract the swab.



7. Insert the single-use swab approximately 2–3 cm deep into one nostril. Swab the inside of the nasal passage to deposit formulation uniformly and generously in all areas below the turbinate, with special care taken to get good coverage in the most anterior nasal pocket area (the tip of the nose). Repeat with a second swab in the other nostril.

8. Dispose of the used swabs per standard hospital protocol for biohazardous waste.

APPLYING THE NASAL LIGHT ILLUMINATOR

9. Open the NLI packaging. DO NOT allow the NLI light diffuser tips to contact ANY surface before inserting into the patient's nose.

10. Connect the NLI to the Light Source by plugging into the connector block until it double-clicks. The Connector Indicator will stop flashing on the LED display and the Start button will flash, indicating the Light Source is in READY mode.

    NOTE: The NLI must be properly connected for the Light Source to be activated.

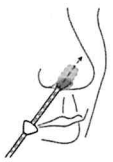
11. **Posterior Illumination:** Gently insert both light diffuser tips into the nasal passages, **orienting the light diffuser tips to point towards the forehead**. The light diffuser tips MUST be kept inserted during the entire treatment cycle.

    NOTE: Diffuser cables are identified with an "L" or "R" indicator, to designate the left or right patient nostril. Use the same cable for the same nostril throughout the complete treatment, to avoid potential cross-contamination of pathogens between nostrils.

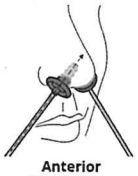
12. Press the flashing Start button to initiate light illumination. The circular indicator on the LED display turns off when the 2-minute illumination cycle is complete. An audible tone will sound, and illumination will automatically stop.

Posterior Illumination

13. Remove the light diffuser tips from the patient's nose. Take care to prevent the light diffuser tips from contacting other surfaces (e.g. place the connector block on the accessory hook on the side of the Light Source).
14. Use two new Formulation Applicators to reapply formulation to each of the anterior nasal passages, with special care taken to get good coverage in the most anterior nasal pocket area (the tip of the nose).



15. **Anterior Illumination:** Gently insert a light diffuser tip into each nostril and **orient the tips anteriorly and medially toward the tip of the nose.**



Anterior Illumination

16. Press the flashing Start button to initiate illumination.
17. Upon completion of the 2-minute illumination cycle, remove the light diffuser tips from the patient's nostrils.
18. Disconnect the NLI from the Light Source and dispose of all single-use items (NLI and FAs) per standard hospital protocol for biohazardous waste.

    NOTE: Temporary tissue staining beneath the nose may be removed with an alcohol wipe or soap and water.

19. Return the Connector Block to the accessory hook on the side of the Light Source.

STANDBY

20. Press the Standby Button to place the Light Source into SLEEP mode.

SHUT DOWN

21. Disconnect the power cord from mains power to move the Light Source.

    NOTE: In case of emergency, always disconnect the power cord from the Light Source.

8.1.2 Control intervention (standard/routine/comparator)

The control intervention consists of the following steps:

"Differences to experimental group in bold"

1. Swabbing the formulation applicator (soft swab pre-saturated with the photosensitizer formulation) into patient's nostrils.
2. Connection of the nasal light illuminator to the light source and insertion of the nasal light illuminator into the patient's right and left nostrils.
3. **No activation of the light source. Waiting for 2 minutes.**
4. Repetition of steps 1.-3. to complete control intervention

Duration of treatment: 14 minutes

- pre-intervention nasal swab test (0.5 min)
- waiting time (3 min)
- nasal application of photosensitizer (0.5 min)
- **2 min waiting "control intervention"**
- Repetition of photosensitizer application (0.5 min)
- **2 min waiting "control intervention"**
- Waiting time (5 min)
- Post-intervention nasal swab test (0.5 min)

8.1.3 Nasal swab testing

The nasal swab tests for microbial analysis are performed in both nostrils with the same nasal swab probe to allow for pooled microbial analysis of both nostrils' colonization status in one swab test.

The same swab testing procedure is used for the pre-intervention nasal swab (3 minutes before intervention), the post intervention swab (5 minutes after intervention), the 2 days swab for the midface trauma subgroup and the follow-up swab on day 14 (+/-1) after intervention.

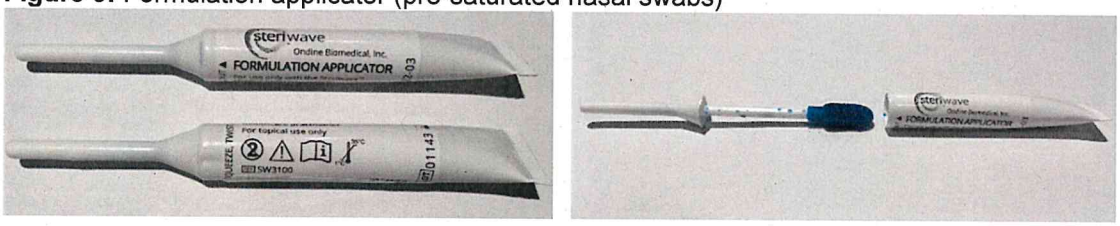
Storage and transfer of swabs is according to routine diagnostics of Institute for Medical Microbiology University of Zurich, Gloriastrasse 28/38, CH-8006 Zurich, head of department Prof. Dr. med. Dr. phil. Adrian Egli.

8.1.4 Labeling and supply

All consumables are pre-labeled by the manufacturer. Since the control group receive the same application of consumable (photosensitizer formulation), no additional labeling is needed. There are no deviations from the commercial products.

The manufacturer has provided two identical medical devices and the necessary consumables to perform 1'000 interventions. Replenishment during the study is not required as only 500 participants are to be included in this study. The light source has been validated for correct performance characteristics. The single-use formulation applicator (soft swab pre-saturated with photosensitizer) has been supplied by the manufacturer via approved carriers with itemized bills of lading. All consumables are stored in a controlled, secured location at room temperature. The formulation is non-sterile and is provided in the form of individually packaged, pre-saturated swabs. The formulation is labeled according to the manufacturer's standards (see **Figure 3**).

Figure 3: Formulation applicator (pre-saturated nasal swabs)



8.1.5 Storage conditions

The medical device and all required consumables are stored in a controlled, secured location at room temperature. The consumables are packed in a carton box for light protection. No reconstitution or mixing is required. The products are not sterile. Any consumables not used during the study will be returned to the manufacturer for further processing.

8.2 Discontinuation or modifications of the intervention

In case of an immediate adverse effect or upon the subject's request during the intervention, the device will be immediately removed from the patient. No modifications of the intervention are possible as the medical device only operates with the pre-defined settings.

8.3 Compliance with clinical investigation intervention

Subject compliance during the intervention will be monitored by the principal investigator or his designee as all patients will be observed during the light treatment.

8.4 Data collection and follow-up for withdrawn subjects

The reason for withdrawal will be noted in the CRF as described in chapter 7.4. In case of withdrawal, no further data will be collected. If the reason for the withdrawal is any problem related to the safety or performance of the medical device, the principal investigator will ask the subject for permission to follow their status and condition outside of the study. The data collected at the time of withdrawal will be used for statistical analysis in accordance with Art. 3 Abs. b ClinO-MD and subsequently anonymized. All biological material will be destroyed after evaluation.

8.5 Clinical investigation specific preventive measures

There are no specific preventive measures required for the subjects and no specific rescue medication. As the light is not harmful to the eyes, wearing protective goggles is not mandatory.

8.6 Concomitant interventions (treatments)

Any medically necessary treatment outside of the study is allowed. The only additional measure that could affect the study outcome is local antimicrobial therapy of the nose, for example, rinses with povidone iodine (Betadine), which could affect the nasal microbiome. For this reason, open surgery within the nasal cavity followed by antimicrobial therapy is an exclusion criterion. Further concomitant treatments such as nasal rinse therapy, antibiotic therapy, steroid therapy, and nasal decongestant therapy are recorded in the concomitant treatment survey on visits 0, 2 and 3. All patients undergo preoperative single-shot i.v antibiotic prophylaxis. Continuation of antibiotic prophylaxis or treatment depends on the surgical intervention.

8.7 Medical device accountability

The single-use formulation applicator (soft swab pre-saturated with photosensitizer) as well as the single-use nasal light illuminators; 1'000 each) have been supplied by the manufacturer via approved carriers with itemized bills of lading, as were the light sources. Both light sources have been tested and approved by the technical experts of the University Hospital Zurich. All serial numbers have been noted. Expiration dates have been checked to ensure that all consumables will expire only after the completion of this study. A list of consumables used will be kept.

8.8 Return, analysis, or destruction of the medical device

The medical device and any remaining consumables will be returned to the manufacturer for further processing at the end of the study. The medical devices will be shipped in their original packaging. Since it has not been in contact with biological material, no specific safety measures need to be taken for packaging or shipping.

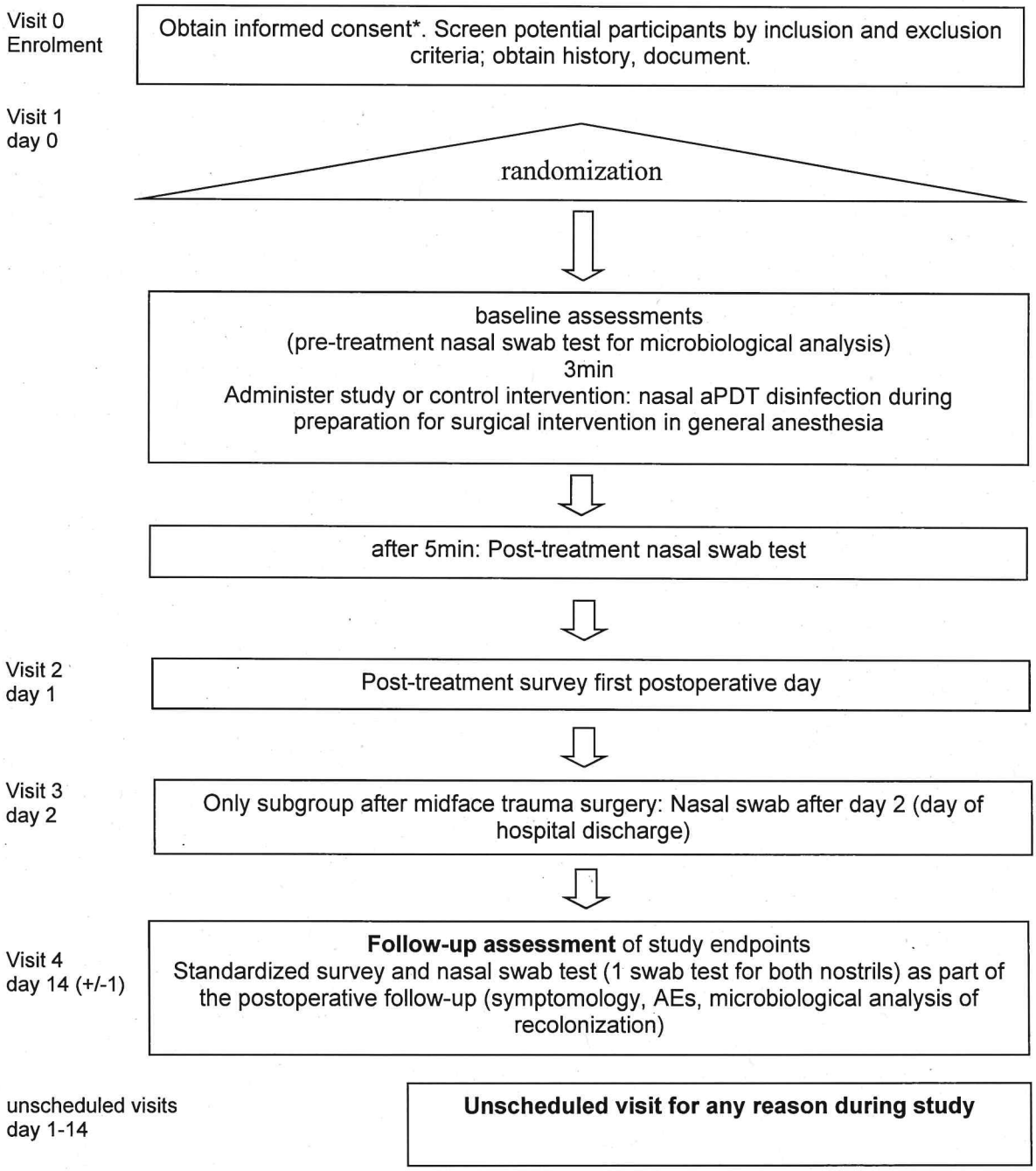
In the event of a medical device malfunctioning, the manufacturer's technical support service will be contacted. If the problem cannot be resolved on site, the device will be returned to the manufacturer for analysis. A replacement device will immediately be shipped to the study site to enable continuation of the study. The study will not be continued until all concerns for safety are eliminated.

9. CLINICAL INVESTIGATION ASSESSMENTS

9.1 Clinical investigation flow chart and table of clinical investigation procedures and assessments

The following flow chart (**Figure 4**) and schedule of activities (**Table 1**) capture the procedures to accomplish at each study visit.

Figure 4: Study flow chart



9.2 Assessments of outcomes

To determine the efficacy of nasal cavity disinfection with aPDT in eliminating microbes all participants undergo baseline nasal swab test (one swab for both nostrils as pooled swab). Five minutes after treatment (nasal cavity disinfection-aPDT or control intervention), participants will undergo further nasal swab testing (again pooled in both nostrils with the same swab). This endpoint will determine with high accuracy the ability of nasal cavity disinfection. Comparing the bacterial colonization score (0-27) of all nine analyzed microbe-groups between experimental and control group avoids misinterpretation of disinfection effects of unactuated methylene blue photosensitizer or chlorhexidine gluconate.

9.2.1 Assessment of primary outcome

Nasal swab microbiological testing

Nasal swabs will be collected according to routine clinical practice. All investigators are trained and routinely perform diagnostic nasal swabs on patients. Nasal swabs for microbiological analysis of primary outcome are taken 5 minutes after the study or control intervention (as described in 8.1.3).

Immediately after collection, the swab will be placed in the designated sample tube with a transport medium. The sample tube will be tightly sealed and placed in a labeled plastic bag. The specimens will be stored at room temperature and sent to the laboratory by the transport service of the University Hospital Zurich according to routine transport algorithms. Microbiological analysis will all be processed at Institute for medical microbiology of University Zurich.

As primary outcome measures the microbial colonization 5 minutes after study or control intervention is expressed as score over the nine microbial subgroups (score from 0-3 according CFU count) resulting in a variable from 0-27.

Statistical analysis with comparing intervention and control group 5 minutes score is executed as described under 11.4.2.

Nine microbial subgroups for analysis:

1. ß-hemolytic (group A and group B) *Streptococcus*
2. *Staphylococcus aureus* (with discrimination in MSSA and MRSA)
3. Coagulase negative Staphylococcus species (incl. *Staphylococcus epidermidis*)
4. α-hemolytic Streptococcus species (oral or viridans-group Streptococci)
5. Corynebacterium species
6. Candida species
7. Enterobacterales
8. Actinomyces species and miscellaneous aerotolerant bacteria
9. Anaerobic bacteria with focus on *Propionibacterium*

Ranges of microbial colonization and bacterial colonization score:

Name	CFU's	Score
"not detectable"	*below detection limit*	*0*
"sporadic"	*<10^4*	*1*
"moderate"	*10^4 – 10^5*	*2*
"plentful"	*>10^5*	*3*

9.2.2 Assessment of secondary outcomes

Microbiological testing

The same score ranging from 0-27 is also used to express the colonization 3 minutes before intervention (baseline swab) and 14 (+/-1) days after study or control intervention (follow-up swab). Statistical analysis of baseline, post intervention and follow-up colonization scores allow for understanding the general effects of aPDT on nasal microbiota over a time period of 14 days. Analyzing the difference in microbial colonization scores of experimental and control groups between baseline, 5 minutes post intervention and 14 days after allows quantification of potential influence of concomitant treatment or disinfection effects of unactuated photosensitizer solution (methylene blue, chlorhexidine gluconate).
Only for the subgroup (open reduction and internal fixation of a midface fracture), an additional nasal swab test after 2 days is carried out. This additional testing allows for better understanding of the short-term effects with clinical importance in the initial wound healing. The reason for testing only the subgroup is mainly in the comparable postoperative management in terms of concomitant treatment (single shot antibiotic prophylaxis, CHX mouth rinse, decongestant nasal drops), duration of surgery and hospital stay.

To analyze for shifts within the microbiological colonization without change in total number of CFU, a descriptive subgroup analysis of the nine microbial groups is performed.

Obtaining personal data

Data on concomitant treatments will be taken from clinical information system KISIM.

Survey

The standardized survey for expected aPDT side effects will be conducted during clinical visit on the first postoperative day and regular 14 day (+/- 1d) postoperative follow-up.

9.2.3 Assessment of safety outcomes

9.2.3.1 Adverse events

Adverse events will be documented in the eCRF. The type of adverse event, its severity or intensity, time of onset and occurrence, duration, resolution, and association with the medical device will be recorded. It will be noted whether an adverse event is to be classified as expected/unexpected and serious. All immediate local treatment effects and all delayed local effects will be recorded to assess safety. At the second visit, participants will be asked about any adverse effects that occurred in the meantime (14; +/-1 days).

9.2.4 Assessments in subjects who prematurely stop the investigation

The reason for withdrawal will be noted in the eCRF as described in chapter 7.4. In case of withdrawal, no further data will be collected. If the reason for the withdrawal is problems related to the safety or performance of the medical device, the principal investigator will ask the subject for permission to follow their status and condition outside of the investigation. The data collected at the time of withdrawal will be used for statistical analysis in accordance with Art. 3 Abs. b ClinO-MD and subsequently anonymized. All biological material will be destroyed after evaluation.

9.2.5 Follow-up of the subjects after the regular termination of the investigation

If the performed surgical procedure requires further follow-up, this is carried out in the Department for Oral- and Maxillofacial Surgery at University Hospital Zurich. The study intervention needs no additional care after participation in this study. Patients are asked to contact their healthcare provider (primary care physician) and/or local public health authority in case of any medical problem after participation in this study.

9.2.6 Patients lost to follow up

Participants are considered "lost to follow-up" if they fail to report for scheduled study visits and cannot be reached to complete all protocol-required study procedures.

The following actions will be taken if a participant fails to attend a required study visit:

- The investigator will attempt to contact the participant and reschedule the missed visit for the next day and will counsel the participant on the importance of maintaining the assigned appointment and inquires as to whether the participant wishes to and/or should continue participating in the study.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of "lost to follow-up".

9.3 Procedures at each visit

9.3.1 Screening visit (Visit 0)

The screening visit takes place as part of the regular consultation hours for Oral- and Maxillofacial Surgery. Patients will be informed about the study. Informed consent will be obtained. Inclusion and exclusion criteria will be reviewed. Demographic information, patient's medical history and survey of concomitant treatments will be obtained.

9.3.2 Visit 1

The first visit will take place during preparation for surgical intervention. Patient is already under general anesthesia. Randomization takes place according to description 6.2.1.

Nasal swab + aPDT

Nasal swab test 3 minutes before the study intervention as described under 8.1.3. Administer study or control intervention as described under 8.1.1 and 8.1.2.

Nasal swab + follow up

After treatment, a second nasal swab test (5 minutes post intervention) for analysis of primary outcome will be taken.

In case of AE / SAE and/or device deficiencies the corresponding eCRF forms are recorded.

9.3.3 Visit 2

The second visit will take place on first postoperative day. The study investigator (not the same investigator who carried out the study intervention) will record the survey of concomitant treatment, survey of expected side effects and AE / SAE. In addition, scheduling of visit 3 on day 14 (+/- 1) post intervention is carried out. For outpatient procedures, visit 2 is carried out by telephone.

9.3.4 Visit 3 (only subgroup following ORIF of midface fracture)

The third study visit is on the day of discharge from hospital (day 2) and contains an additional nasal swab test (pooled for both nostrils as described under 8.1.3.

9.3.5 Visit 4

Study Visit 4 will be held combined with the regular follow-up after surgery (wound control, removing sutures etc.). Recording of survey of concomitant treatment, expected side effects, AE/SAE will be recorded. A third nasal swab test is performed for microbiological analysis to assess secondary objective. Last step during visit 4 is documentation of study end eCRF form.

10. SAFETY

10.1 Definition and assessment of (serious) adverse events and other safety related events

Adverse Event (AE) (Art. 2 Abs 57 MDR)
Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs in subjects, users, or others, whether related to the MD or not.

Serious Adverse Event (SAE) (Art. 2 Abs 58 MDR)
Any adverse event that led to any of the following:
(a) death,
(b) serious deterioration in the health of the subject that resulted in any of the following:
  (i) life-threatening illness or injury,
  (ii) permanent impairment of a body structure or a body function,
  (iii) hospitalization or prolongation of patient hospitalization,
  (iv) need for medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  (v) chronic disease,
(c) fetal distress, fetal death, or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for a pre-existing condition or a procedure required by the CIP that does not result in a serious deterioration of the subject's health is not considered an SAE.

Device deficiency (Art. 2 Abs 59 MDR)
Inadequacies of a medical device (investigational device) related to its identity, quality, durability, reliability, safety, or performance, including malfunction, user errors, and inadequate information supplied by the manufacturer.

Malfunction (ISO14155)
Failure of an investigational device to fulfill its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency with Serious Adverse Device Effect (SADE) potential (Art. 80 Abs 1 letter c MDR; ISO14155)
Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, if the intervention had not occurred, or if circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155)
Adverse event that is possibly, probably, or causally related to the use of an investigational device or procedure.

Serious Adverse Device Effect (SADE) (ISO14155)
Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event (SAE).

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)
Serious adverse device effect (SADE) which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Causal Relationship of SAE (MDCG 2020-10/1)
Causal relationship with the medical device or the investigational procedure should be rated by the principal investigator as follows:

- **Not related:** A relationship with the device or procedure can be excluded.
- **Possible:** A relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** A relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond a reasonable doubt.

10.2 Adverse events categorization

The adverse events are categorized by the PI using the following algorithm:

Does the AE meet the seriousness criteria?

- No, it is not serious:
  - Is the relationship to the device or the procedure possible, probable, or causal?
  - No: unrelated AE
  - Yes: ADE

- Yes, it is serious:
  - Is the relationship to the device or the procedure possible, probable, or causal?
  - No: non-related SAE
  - Yes: SADE

- Is it anticipated (within expected type, severity, and frequency of the complications)?
  - No: unanticipated SADE (USADE)
  - Yes: anticipated SADE (ASADE)

10.3 Documentation and reporting in medical device category A clinical investigations

Device deficiencies (DD) and all adverse events (AE) including all serious adverse events (SAE), will be recorded, fully investigated, and documented in the source document and corresponding case report form (eCRF) throughout the investigation period (from patient consent to the last CIP-specific procedure).

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, date of onset and end of the event, treatment, resolution, severity assessment, and causal relationship to MD and/or investigation procedure (Art. 32 ClinO-MD, ISO14155).
- Documentation of DDs by the PI includes a description of the dysfunction, date of onset, investigational device information, any action taken regarding the investigational device, and whether the DD led to an AE. The principal investigator shall review all DDs and determine and document in writing whether they could have led to an SAE (DD with SADE potential) (Art 32. ClinO-MD, ISO14155).
- The information on AEs is systematically collected by clinical safety assessment at the regular visits
- no safety follow-up is required based on the benefit-risk profile and lack of known long-term adverse effects with this medical device

Safety and protective measures

If immediate safety and protective measures must be taken during the conduct of this clinical trial, the investigator must notify the CEC of these measures and the circumstances necessitating them, within 2 days.

Annual Safety Report

(As indicated under 10.3.2)

10.3.1 Foreseeable adverse events and anticipated adverse device effects

Based on the available data, there are no known foreseeable serious adverse events and anticipated adverse device effects for the medical device investigated in this study.

10.3.2 Reporting of safety related events

Reporting to the sponsor-investigator:
All SAEs, DDs, and health hazards requiring action will be reported to the sponsor-investigator by the investigators within 24 hours of becoming aware of the events. DDs will be assessed regarding their potential to lead to an SAE. Reporting on pregnancies is not required for this study.

Reporting to the Competent Ethics Committee:
The principal investigator will immediately report to the CEC any serious adverse event which has a causal relation with the MD or for which a causal relationship appears possible (Art. 33 ClinO-MD). To ensure rapid reporting, the sponsor-investigator may initially submit an incomplete report. If measures must be taken immediately to address safety and health hazards in the conduct of the investigation, the principal investigator will report these measures and the circumstances necessitating them to the CEC within 2 days (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):
An Annual Safety Report (ASR) will be submitted annually to the CEC by the principal investigator. The ASR includes a list of all SADEs and DDs and a report on their severity, their causal relationship to the MD and procedure, and on subject safety.

Other reports are made according to the MD vigilance provisions as per Art. 87-90 MDR and Art. 67 MedDO.

All device malfunctions will additionally be recorded in the University Hospital's materiovigilance system according to the hospital guidelines.

11. STATISTICAL METHODS

Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Department of Biostatistics, University of Zurich.

11.1 Hypothesis

The two-sided null hypothesis to be tested is that nasal cavity photodisinfection by aPDT (intervention) as an add-on treatment to 0.2 % chlorhexidine gluconate has no effect on local microbial colonization in a perioperative setting compared to 0.2 % chlorhexidine gluconate and non-light activated methylene blue (control). The corresponding alternative hypothesis is that the two treatments differ. The research hypothesis is, that the intervention will reduce local microbial colonization compared to control (superiority of the intervention).

11.2 Determination of sample size

The sample size was calculated to show the superiority of the intervention compared to the control regarding the primary outcome with a power of 90 % at a significance level of 5 %. We calculated the sample size for a Wilcoxon-Mann-Whitney test, but did this via the sample size for a two-sample t-test and by increasing the sample size using the Asymptotic Relative Efficiency (ARE) of the Wilcoxon-Mann-Whitney test (compared to the t-test), which is never less than 0.864 (17,18). The power was estimated for a range of sample sizes $n_{i=1,...,61}$ = 50,...,350 with the R package sse (19). Moreover, to assess how the calculation is affected by the mean difference, θ, we varied θ from 1.5 to 4.5. For each combination of n_i and θ, we calculated the power for a two-sample t-test.

Figure 1 shows that for showing a mean difference in the primary outcome of 3 with a standard deviation of 6, a total of 170 evaluable patients would be required for a two-sample t-test. For a Wicoxon-Mann-Whitney test we increased the sample size, dividing 170 by 0.864, which resulted in 198 patients (rounded up to an even number). Assuming a drop-out rate of 5 %, 208 patients need to be enrolled.

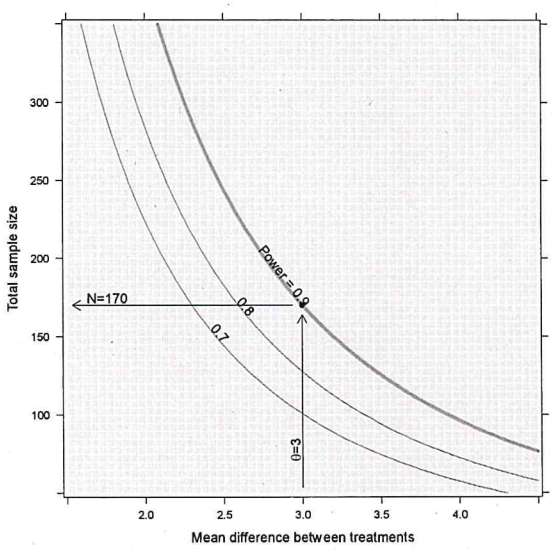


Figure 1: Dependence of the sample size on the mean difference between treatments, θ, assuming a standard deviation of 6. An example is shown for θ=3 and a power of 90 %. The curves are smoothed and shown for illustration only.

11.3 Statistical criteria of termination of the investigation

None.

11.4 Planned analyses

11.4.1 Datasets to be analyzed, analysis populations

The full analysis set (FAS) includes all patients randomized to the trial who underwent aPDT.

11.4.2 Primary analysis

The primary outcome, bacterial colonization 5 minutes after aPDT across the nine analyzed microbe groups, expressed as a score (range 0–27), will be compared between the randomized groups (intervention vs. control) by an exact Wilcoxon-Mann-Whitney test, as implemented in the function of wilcox_test from the R package coin (20), for an improved handling of ties (compared to other implementations of the test). We will also estimate the Mann-Whitney parameter, $\varphi = Pr[X < Y] + 0.5Pr[X = Y]$ (with X and Y being the ordered primary outcome in the intervention and control group), a natural effect parameter associated with this test with a corresponding 95 % confidence interval. In addition, we will apply a proportional odds logistic regression model, in order to adjust for the baseline measurement of bacterial colonization and the type of surgery used for stratifying the randomization. The primary outcome will be analyzed as ordinal outcome with type of surgery and randomized treatment (intervention vs. control) as explanatory variables. This model will estimate proportional odds ratios with 95 % confidence intervals.

11.4.3 Secondary analyses

Analyses of secondary outcomes: The secondary outcome, bacterial colonization 14 days after aPDT (measured otherwise the same way as the primary outcome) and bacterial colonization 2 days after for the ORIF midface group will be analyzed in a similar way as the primary outcome (see Section 11.4.2). The proportional odds logistic regression model will additionally adjust for concomitant treatment with nasal rinse therapy, antibiotic therapy, steroid therapy, and nasal decongestant therapy, which are prescribed depending on the surgical intervention, and may also influence bacterial colonization after 14 days. To compare bacterial colonization 5 minutes after aPDT 2 days (only ORIF midface) and 14 days after aPDT (short- and long-term), we analyze these measurements as repeated measurements together in one model. We fit a mixed-effects proportional odds logistic regression model on bacterial colonization, with treatment (intervention vs. control) and time (14 days vs. 5 min and 2 days (only ORIF midface)) as explanatory variables. In an additional model, we will add the interaction between treatment and time, in order to test for a difference in the change over time between the treatment groups.

The colonization with individual types of bacteria (9 types) at baseline, and 5 minutes and 2 days (only ORF midface) and 14 days after aPDT will be descriptively analyzed and summary statistics (frequency and percentage of each category) will be reported by treatment group.

Subgroup analyses: For the primary outcome, subgroup analyses will be performed for the following subgroups: bacterial colonization at baseline (> median vs >= median), type of surgery and sex. For each subgroup variable, a proportional odds logistic regression model will be fitted to the primary outcome, with treatment, the subgroup variable, and the interaction between the subgroup variable and treatment as explanatory variables. A statistically significant interaction between one of the subgroup variables and treatment would indicate a different treatment effect in the corresponding subgroups. We will also estimate group-specific treatment effects (with 95 % CI), fitting a separate model for the corresponding subgroups, which will be reported together with the interaction p-value.

11.4.4 Interim analyses

None.

11.4.5 Safety analysis

Adverse effects (inquired by standardized survey on first day post intervention and on day 14 (+/- 1d) during regular postoperative follow up will be analyzed descriptively, with summary statistics reported by treatment group.

11.4.6 Deviation(s) from the original statistical plan

If substantial deviations of the analyses as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analyses from the protocol or from the detailed statistical analysis plan will be listed and justified in a separate section of the final statistical report.

11.5 Handling of missing data and drop-outs

For the primary outcome, which is measured 5 min after aPDT, we do not expect any missing values since loss to follow-up is very unlikely. We plan to do complete case analyses of the primary and the secondary outcomes. Should more than 5 % of the primary outcome measurements be missing, we would use multiple imputation of the missing primary outcome data. The final number of imputations per missing value would be determined by the fraction of missing information (21).

12. QUALITY ASSURANCE AND CONTROL

The principal investigator implements and maintains quality assurance and quality control systems with written SOPs and work instructions to ensure that study conduct, data generation, documentation, and reporting follow the protocol, GCP, and applicable regulatory requirements. Monitoring and audits will be conducted during the investigation for quality assurance purposes.

12.1 Data handling and record keeping / archiving

The collection, transmission, storage, and evaluation of personal data within the scope of this project is carried out in accordance with the applicable Swiss data protection regulations. All investigation-related documents will be archived.

12.1.1 Case Report Forms

The investigators will use electronical case report forms (eCRF; REDCap, Vanderbilt University), one for each enrolled study participant, in which all relevant data of the participant are entered during the study (according to parameter table eCRF). All participants who were either enrolled in the study or deemed ineligible or were eligible but not enrolled in the study will additionally be documented in a screening log. The investigator will document the participation of each patient on the enrollment log.

All clinical data will be stored in medical history of the patient in KISIM. For study specific data collection and storage eCRF will be used. In case of premature discontinuation or withdrawal the reason will be documented in the eCRF.

All data are protected on a secure clinical network only allowing access for study staff according to staff list. It is the responsibility of the principal investigator to ensure that all data are entered completely and correctly in the respective database during the investigation. Corrections in the eCRF may only be done by the principal investigator or by other authorized persons. In case of corrections, the original data entries will be archived and can be made visible if needed. For all data entries and corrections, the date, time of day, and person making the entries will be logged automatically by the eCRF.

The eCRFs must be kept up to date to reflect participant status at each phase of the study process. Participants must not be identified by name in the eCRF. Appropriate coded identification (participant number and year of birth) will be used.

Care will be taken to identify each authorized investigator who may make data entries and changes in the CRF. A list of signatures and initials of all authorized individuals will be placed in the study site file and the trial master file, respectively.

Documented medical histories and reports of participant progress during the study will be maintained. These records will include originals or copies of laboratory and other medical test results (microbiology test results) to be maintained in each participant's eCRF.

The investigators assure to make a complete and accurate documentation of the participant data in the eCRF. All data entered in the eCRF will also be available in the individual participant file.

12.1.2 Specification of source data and source documents

The following documents are considered source data, including but not limited to:

- SAE worksheets
- Nursing staff records, records of clinical coordinators

Source data are available at the site to document the existence of the study participants and demonstrate the integrity of the study data collected. Source data includes the original documents relating to the study, as well as the participant's medical treatment and medical history.

The following information will be included in the source documents:

- Demographic data (age, gender)
- Inclusion and exclusion criteria details
- Participation in the study and signed and dated Informed Consent Forms (ICF)
- Visit dates
- Key efficacy and safety data (as specified in the protocol)
- SAEs (related) and concomitant medication
- Results of the microbiological analysis

12.1.3 Archiving of essential clinical investigation documents

All documents of this investigation will be archived for a minimum of 10 years after a regular or premature termination of the investigation in accordance with Art. 40 ClinO-MD. All data will be stored securely at the department of oral and maxillofacial surgery, University Hospital Zurich. The principal investigator is responsible for the secure storage of all documents.

12.2 Data management

Only authorized personnel will have access to the data. Data will be entered from the source documents into the eCRF on the day of participant registration. After statistical analysis, data will be anonymized by destroying the key (the document linking identifiable data to the pseudonymized participant number).

12.2.1 Data management system

For data and query management, monitoring and reporting a digital data acquisition will be done (eCRF, REDCap). It is the responsibility of the principal investigator to ensure that all data are entered completely and correctly in the respective database during the investigation. Appropriate training will be provided by the Clinical Trials Center.

12.2.2 Data security, access, and back-up

Only authorized personnel will have access to the data, this includes the investigators and designated members in case of monitoring or audits.

12.2.3 Analysis and archiving

Data entry will be done by authorized personnel at the site. Data from the laboratory-results will be available and collected over the clinical information system, anamnestic data collected by authorized personnel and patient questionaries' will be transferred to the eCRFs. After the data collection period, the data will be transferred to local storage provided by the investigator. The collected data will be stored for 10 years after completion of the trial at the investigator's facility.

12.2.4 Electronic and central data validation

All Data will be stored in the Study Files. Access will be limited to personal involved in collection, analysis, maintenance or safety monitoring and hospital personal involved in treatment of the study patients. Where data is stored or transferred electronically it will be done according to Swiss data protection laws. Completion checks and validation of the data in the eCRFs will be done by personal authorized from the investigator periodically.

12.3 Monitoring

Monitoring visits at the investigator's site prior to the start of the study and during the study will help to track the progress of the clinical trial, ensure utmost accuracy of the data, and detect possible errors at an early stage. The principal investigator organizes professional, independent monitoring for the study.

All original data including all patient records, progress notes, and copies of laboratory and medical test results must be available for monitoring. The monitor will review a part of the eCRF and written informed consent forms. The accuracy of the data will be verified by reviewing the above-referenced documents. The investigator's site will collaborate with the Clinical Trials Center (CTC) of the University Hospital Zurich to ensure monitoring. In accordance with the CTC's Monitoring SOP, the extent and nature of monitoring activities based on the objective and design of the study is defined in the study-specific monitoring plan. Source data will be accessible to the monitors, and questions will be answered during monitoring by the principal investigator and site personnel.

12.4 Audits and Inspections

The CEC or the competent authorities may conduct a quality assurance audit/inspection of this study. The quality assurance auditor/inspector will have access to all medical records, study-related files, and investigator correspondence, as well as informed consent documentation relevant to this clinical trial. This process is independent of the sponsor-investigator.

The investigator will provide access to the source data/documents to those responsible for the audit or the inspection and will answer any questions that arise. All parties involved will keep patient data strictly confidential.

12.5 Confidentiality, data protection

Direct access to source documents will be permitted for purposes of monitoring, audits, and inspections according to chapters 12.3 and 12.4. During the investigation, only authorized study personnel will have access to the documents of this investigation.

12.6 Storage of biological material and related health data

Samples will be destroyed after analysis according to the standards of practice of the respective laboratory. No data or samples will be stored in a biobank. There are no plans for secondary evaluations in other trials with the collected data.

13. PUBLICATION AND DISSEMINATION POLICY

After the statistical analysis of this study, the sponsor-investigator will make every effort to publish the data in a medical journal. In the case of results of public interest, a summary will be provided in lay language. The sponsor-investigator will have final authority over all activities. In this study, an analysis of gender effects will be conducted, and the respective results will be published in the final study report.

14. FUNDING AND SUPPORT

14.1 Funding

The study is financially supported by the **Innovationspool of the University Hospital Zurich,** which has awarded competitive money for the funding of this study. The funding will be used to cover expenses such as monitoring, additional supporting staff, material and logistics.

14.2 Other Support

Consumables and the aPDT medical devices (Steriwave™) are provided free of charge by **Ondine Biomedical Inc.**

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888-1100 Melville Street
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Carolyn Cross
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15. INSURANCE

Category A1 studies are exempt from compulsory insurance. Nevertheless, insurance coverage is provided by the "Versicherung für klinische Versuche und nichtklinische Versuche" by Zurich Versicherungs-Gesellschaft AG (Policy no.: 14.970.888).

Any damages incurred in connection with study participation are covered by this insurance. So as not to forfeit their insurance coverage, the participants themselves must strictly follow the instructions of the study personnel. Participants may not undergo any other medical treatment without the permission of the principal investigator (emergencies excluded). Emergency medical treatments must be reported immediately to the principal investigator. The principal investigator must also be informed instantly in the event of health problems or other damages occurring during or after the study treatment.

The principal investigator will allow delegates of the insurance company access to the source data/documents as necessary to resolve a claim related to study participation.

A copy of the insurance certificate will be placed in the investigator's site file.

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