Title of Study: The role of a new prosthodontics device in hard and soft tissue changing after subcrestal implant placement: 12 months parallel randomized clinical trial.

Type of Study: Clinical

Protocol No: PROTOCOL NABUT2020

Expected study start date: September, 2020 (study initiation)

Study Location/Country: Brescia, Italy

Study Originator(s)/ Contact (name, phone, fax): Magda Mensi, Piazzale Spedali Civili 1, 25123 Brescia, phone: +390303995784, email: magda.mensi@unibs.it

Test Products w/ PDM Numbers:
CE marked Medical Device to be used as a prosthodontics device after subcrestal implant placement in patients with monoedentulia (Confidential information).

Study Title:	The role of a new prosthodontics device in hard and soft tissue changing after subcrestal implant placement: 12 months parallel randomized clinical trial.
Study sites:	Dr. Magda Mensi (lead site) University-Hospital of Brescia Brescia, Italy.
Study Phase:	IV.
Name of Medical Device:	GFA® Gingival Former Abutment (**Advan S.r.l.** Via Linussio, 1 33020 – Amaro (UD) Italy)
Objective:	The objective of the clinical study is to assess the efficacy of a new prosthodontics device (GFA) in hard and soft tissue changing after subcrestal implant placement.
Patient Population:	40 patients, systemically healthy, male and female adults (18 – 75 years), with posterior monoedentulia at least 5 months.
Structure:	Parallel arms: Number of treatments: 1 (test group: subcrestal implant placement and GFA; control group: crestal implant placement and healing abutment). Duration of study: 27 months.
Number of Centers:	One.
Blinding:	Statistician
Method of Patient Selection:	Posterior monoedentulia intercalated with 11mm of residual bone
Total Sample Size:	40 adult subjects will be recruited (randomized) to participate in this study, with 34 expected to complete the study.
Primary Efficacy Variable:	Primary outcome measure will be the changing of radiographically MBL (marginal bone level) around implant.

The role of a new prosthodontics device in hard and soft tissue changing after subcrestal implant placement: 12 months parallel randomized clinical trial.
PROTOCOL #NABUT 2020

Protocol Date: March 16, 2020

Protocol Approval

Signature Page

_____

Dr. Magda Mensi
University-Hospital of Brescia, Italy

Date

ADDRESSES AND RESPONSIBILITIES

Addresses

Study Centres:	Section of Periodontics, School of Dentistry, Department of Surgical Specialities, Radiological Science and Public Health University of Brescia Piazzale Spedali Civili 1 25123, Brescia, Italy Dr. Magda Mensi (Principal Investigator) Tel. +390303995784 Email: magda.mensi@unibs.it
Study coordinator:	Dr. Magda Mensi Section of Periodontics, School of Dentistry, Department of Surgical Specialities, Radiological Science and Public Health University-Hospital of Brescia Brescia, IT
Data Management & Monitoring:	Dr. Magda Mensi Section of Periodontics, School of Dentistry, Department of Surgical Specialities, Radiological Science and Public Health University-Hospital of Brescia Brescia, IT
Statistician:	Prof. Stefano Calza Unit of Biostatistics and Bioinformatics, Department of Molecular and Translational Medicine University of Brescia Brescia, IT

Responsibilities

The **principal investigator's** responsibilities are described in detail in ISO norm 14155:2011 for the clinical investigation of medical devices for human subjects.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall be qualified by education, training and experience to assume responsibilities for the proper conduct of the clinical investigation. In particular, the principal investigator is responsible for:

- qualification of investigation site;
- communication with Ethics Committee;
- compliance with Informed Consent process;
- compliance with Clinical Investigation Plan.

Under the direct supervision of the Principal Investigator, certain duties may be delegated during the course of the study. These responsibilities will be documented on the transfer of responsibilities form maintained in the Investigator Site file.

The **Statistician** will be responsible for:

- sample size calculation;
- statistical plan;
- statistical section of the protocol;
- statistical evaluation;
- final statistical report.

OBJECTIVE

The study will be performed to assess the efficacy of a new prosthodontics device (GFA) in hard and soft tissue changing after subcrestal implant placement in terms of MBL and peri-implant tissues health.

INTRODUCTION

At present there is no scientific evidence in dentistry about the origin and treatment of perimplatitis and mucositis. These peri-implant pathologies can be partially prevented through periodontal diagnosis, correct implant placement and prosthetic loading.

In the literature, there is a physiological bone loss around implant after the placement (1 mm the first year and 0.2 mm each subsequent year). Different types of implants have been designed (laserization of the collar, platform switching..) to try to control this phenomenon with discordant results. Different surgical protocols for implant insertion have been created to minimize bone resorption: a subcrestal implant seems to partially overcome this problem even if this procedure increase the transmucosal tunnel: growing the risk of peri-implant soft tissue infection.

Tissue healing around the implants is not comparable to the natural dental element: the risk of inflammation and consequently of infection is higher around the implants because there is no stable seal between the two structures (tissue and implant).

The prosthetic structure of the GFA was created to overcome these problems: crestal bone reabsorption and transmucosal tunnel. Our objective is to validate or deny this claim.

STUDY OUTCOMES

a. Primary outcome measure: radiographically change in MBL
b. Secondary outcomes changes in the following clinical parameters:
    - PD (Probing Depth),
    - REC (Clinical Gingival Recession),
    - BOP (Bleeding on Probing),
    - PI (Plaque Index).

STUDY POPULATION

Forty (40) adults, aged 18-75 years, will be entered into study (randomized). It is expected that forty (34) subjects will complete the study.

Randomized subjects who deviate from the protocol (major protocol deviation) and, for this reason, are excluded from the analysis, will be replaced to guarantee that the sample required for the analysis (34) is reached.

Patients will be treated at the Department of Surgical Specialties Radiological Science and Public Health, School of Dentistry, Section of Periodontics, Brescia, Italy from 09/2020.

Inclusion Characteristics

- Comprehension and signed Informed Consent Form.
- Male and female subjects, aged 18-75 years, inclusive.
- Good general health (free of systemic diseases such as diabetes, HIV infection or genetic disorder, ongoing malignant disease of any type that could influence the outcome of the treatment and might interfere with the evaluation of the study objectives).
- Good oral health (no decay, periapical or periodontal lesions, PI and BOP < 25%).
- Patient with posterior monoedentulia:
    - at least 5 months,
    - mandibular or maxillary,
    - intercalated (distance between teeth more than 7.5 mm),
    - at least 11 mm of height residual bone (from bone crest to maxillary sinus or inferior alveolar nerve),
    - at least 5 mm of bone width (buccal – palatal/lingual).
- Availability for the 12-month duration of the study for an assigned subject.

Exclusion Characteristics

- Not willing to follow the agreed protocol.
- Presence of orthodontic appliances.
- Smokers more than 10 cigarettes per day.
- Chronic obstructive pulmonary disease and asthma.
- Tumors or significant pathology of the soft or hard tissues of the oral cavity.
- Current radiotherapy or chemotherapy.
- Pregnant or lactating women.
- Parafunctions like bruxism.
- Previous interventions to increase bone thickness in the implant area.
- Current or past assumption of medications that may influence surgical therapy and/or interfere with healing following surgical treatment.
- Systemic diseases that constitute a contraindication to surgical therapy and/or interfere with healing following surgical treatment.

A written informed consent will be obtained from each included patient after explanation of the risks and benefits of participating to this study. No change in the trial design will be made after approval of the Ethical Committee.

1. STUDY DESIGN

The study design was chosen according to the current standards required by ISO, GCP and according to national requirements.

a. A Parallel-Arm, Statistician is blinded, RCT will be established;
b. The RCT will be run as mono-center;
c. A total of 40 subjects will be recruited to participate in the study. It is expected that all of 34 subjects will complete the study in total;
d. Admission into the study will be via rolling admission (estimated recruitment time: 12 months);
e. Each subject must have posterior monoedentulia (mandibular or maxillary) intercalated;
f. Each subject will follow the following treatment protocol:
    1. Visit 1: (Screening)
        a. Screening and entry into study.
        b. Verification of the eligibility of each subject by performing intraoral radiography.
        c. Explanation of the research protocol.
        d. Consent secured.
        e. Delivery of the medical request for CBCT (cone beam computed tomography) and for the antibiotic (Amoxicillin 1000mg 2cp/die every 12 hours for 6 days or Azithromycin 500mg 1cp/die every 24 hours for 6 days).
    2. When CBCT is ready the patient have to give it to the Principal Investigator to confirm the eligibility of each subject and to plan the surgery. Professional dental hygiene session is performed before surgery.
    3. Visit 2: (Treatment)
        a. Assessment of antibiotic prophylaxis, locoregional anesthesia and opening of a thickness flap limited to the intervention area.
        b. According to the list of randomization the patient will be allocated into one of the two arm of surgical treatment. Group A (control group): placement of the endosseous crestal implant through dedicated drills with 35N insertion torque and healing abutment. Group B (test group): placement of the endosseous subcrestal implant (2 mm under crestal bone) through dedicated drills with 35N insertion

torque and GFA (Gingival Former Abutment). Both group receive the same implant: TZero® (L= 9 mm, ∅ 3,6 mm or L= 7,5 mm, ∅ 4,3 mm) (Advan S.r.l. Via Linussio, 1 33020 – Amaro (UD) Italy)

c. Suture.
d. Execution of intra-oral and post-operative X-Rays.

After 7 days of the surgery suture removal.

4. Visit 3: (after 3 months from visit 2) (Treatment)
    a. Periodontal charting around the healing abutment or GFA (PD, BOP, PI) with calibrated periodontal probe.
    b. Impression taking for prosthetic finalization.
5. Visit 4: (after a week from Visit 3: Baseline – T0): (Treatment)
    a. Prosthetic finalization and loading.
    b. Periodontal charting around the new prosthetic crown (PD, BOP, PI, REC).
    c. Take a standardized x- Ray (Bite Block).
6. Visit 5 (6 months from baseline – T1): (Follow-up)
    a. Control.
    b. Periodontal charting around the prosthetic crown (PD, BOP, PI, REC).
    c. Take a standardized x- Ray (Bite Block).
    d. Professional dental hygiene session.
7. Visit 6 (12 months from baseline – T2):
    a. Control.
    b. Periodontal charting around the prosthetic crown (PD, BOP, PI ,REC).
    c. Take a standardized x- Ray (Bite Block).
    d. Professional dental hygiene session.

g. All treatments are made by the same clinician;
h. Data collection:

- Standardized X- Ray: control periapical radiographs is performed using a long-cone paralleling technique and an individual X-ray holder (bite block) to ensure reproducibility. Built thanks to impression material.

- A calibrated periodontal probe (Click-Probe™ Kerr Dental) is used on six sites per tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual and disto-lingual) with a standard probing force by the same clinician. Measurements are rounded to the nearest millimeter;

j. Clinical and radiographical assessment data will be recorded via hard copy CRFs. CRFs will be submitted to a data entry staff member for entry into the statistical database. At the conclusion of the study, such statistical database will be submitted to the statistician for the preparation of the statistical analysis and the final study report.

k. Prosthetic finalization is given to the dental laboratory.

2. TREATMENTS

Implant kit, implants and every component will be delivered to the study center prior study start by Advan S.r.l. Via Linussio, 1 33020 – Amaro (UD) Italy:

- Surgical Kit PRO: GKC13

- Set countersink GFA: GKM10

- Kit stop drills: GST11

- Implant: TZero - T3609 (D3,6 L9,0) - T4307 (D4,3 L7,5)

- GFA: 04GFX03 (D4,0 H3,5) - 04GFX04 (D4,0 H4,5) - 04GFX05 (D4,0 H5,5)

- component GFA: 01GFT01 (healing stopper H1) - 01GFT03 (healing stopper H3) -01GFT05 (healing stopper H5) - 01TGF10 (transfer pick-up) - 01AGF10 (analogo GFA) -01CGF40 (moncone calcinabile con base in cobalto-cromo)

- for control group: 05OMG12 (healing abutment H2) - 05OMG13 (healing abutment H3) - 05OMG14 (healing abutment H4) - 01OTR10 (transfer pick-up) - 41CCN40 (moncone calcinabile con base in cobalto-cromo)

Radiographically Analysis

Specification of software analysis

Peri-apical x-ray examinations will be performed using phosphor image plates (FONA™ Dental Image Plates) and then acquired through a digital scanner device (FONA ScaNeo™).

All radiographical images will be later analyzed by the same external examiner, which will measure marginal bone level parameter (MBL) around placed endosseous implants using an image analysis software (ImageJ™).

In particular bone levels will be determined, both mesially and distally the dental implant, using the "Measure" function of the software, which records the distance between the most apical bone point and the most coronal bone point in 0.3 mm range from the implant.

Measurements will be all recorded to allow the observation of bone level changes over time.

Concomitant Therapy

A necessary concomitant medication or therapy is permitted as long as it is not excluded in the exclusion criteria. Every medication has to be reported in the CRF (Appendix 1) and in the Concomitant Medication form (Appendix 2). All changes during the study are to be reported in the CRF. Usage of prohibited therapy will lead to the exclusion of the subject.

Blinding and Randomization

Blinding:

The statistician and the patient will be blinded to the group identification. The operator will know the treatment allocation. Knowledge of the randomization list will be limited to the persons responsible for creation of the randomization list, provider of randomization numbers to study site, and delivery of the test/control treatment until the last subject (i.e. final examination of the last subject), quality control and verification of the CRFs is completed.

Randomization and allocation concealment:

The randomization of the study protocols will be performed by a staff member who is not further involved in this study. This will be done based on a computer-generated table (using R package *randomizeR*) that links each patient to one of the treatment groups. Treatment allocation will be delivered in sealed envelopes.

Implementation: The Principal Investigator will be informed immediately of Serious Adverse Events (SAEs), regardless of the causality relationship between the administration of the investigational treatment and the SAE.

3. PROCEDURE

Screening and Selection of Subjects

Patients visiting the U.O. Odontostomatology of ASST Spedali Civili of Brescia will be asked to participate in this study. Subjects will report to the clinical facility and be screened by the dental examiner to identify those subjects who meet the inclusion/exclusion characteristics. The findings of this initial screening procedure will be recorded on the CRF. Subjects who meet the inclusion/exclusion characteristics and sign an Informed Consent Form will be entered into the study.

Baseline Oral Soft and Hard Tissue Assessment

All subjects will receive an evaluation of their oral soft and hard tissues. This examination will include an evaluation of the soft and hard palate, gingival mucosa, buccal mucosa, muco gingival fold areas, tongue, sublingual and submandibular areas and the tonsillar and pharyngeal areas. The results of this evaluation will be recorded on the CRF.

CBCT

All patients receiving a CBCT to confirm the eligibility of each subject and to plan the surgery at Complex Operative Unit of Diagnostic Radiology 2.

Treatment

Patients who have been identified for treatment receive an implant placement and prosthetic finalization will be randomized according to a randomization table generated.

Clinical Periodontal Evaluation

All patients receiving treatment will be evaluated by the dental examiner for the following assessments (see Study Flow Chart):

- Full Mouth Plaque Score (PI);
- Periodontal Inflammation (BOP);
- Probing Pocket Depth (PD);
- Recession (REC);

All parameters will be recorded in the CRF.

Radiographically Evaluation

All patients receiving control reproducible periapical radiographs for evaluation of MBL (mesial and distal) (see Study Flow Chart)

All parameters will be recorded in the CRF.

Follow up

Following completion implant placement and prosthetic finalization, the study start. Radiographically and clinical evaluation will be done at baseline (T0), 6 and 12 months (T1 and T2) in the test and control site. At 6 and 12 months a dental hygiene session and OHI will be done.

Study Flow Chart

Study phase	Enrolment	Treatment	Treatment	Treatment	Follow-up	Follow-up
Study visit	Visit 1	Visit 2	Visit 3	Visit 4 (T0)	Visit 5 (T1)	Visit 6 (T2)
Study Time	- X days	0	3 months	3 months and 1 week	6 months form visit 4	12 months form visit 4
Selection criteria	+					
Informed consent	+					
Demographics, ethnics	+					
General health status	+	+	+	+	+	+
Medical & dental history	+					
Concomitant therapy/treatment	+	+	+	+	+	+
Safety (adverse events and serious adverse events)			+	+	+	+
Data collection (PD,REC, BOP, PI)	+			+	+	+
X- Rays and CBCT	+	+	+	+	+	+
Randomization		+				
Professional Oral Hygiene session	+				+	+
Prosthetic Finalization			+	+		
Implant Placement		+				
GFA or healing abutment		+				

4. STATISTICAL ANALYSIS

Sample size determination

Sample size was compute assuming a two parallel groups design with balanced groups and an independent sample t-test. We assumed a single implant and a single measurement for patient, a standard deviation of 0.5 mm and an average difference of at least 0.5mm. A total sample size of 34 patients will provide a power of at least 80% at a 5% significance level. Assuming a 15% drop-out , the total sample size will be N=40 patients.

Statistical Analysis

Data will be described using standard statistics such as, mean, median standard deviation and IQR for quantitative variable, and counts and percentages for qualitative variables.

Variation in MBL will be modelled using both a simple t-test for independent samples (after averaging values within patients) as well as a multilevel model using GEE (Generalised Estimating Equations) on individual site measurements and accounting for within subject correlation.

Secondary continuous outcomes will be modelled using GEE with ad hoc error distribution according to outcome (Gaussian for PPD, CAL, REC, binomial for BOP).

Results will be expressed as estimates and relative 95% confidence intervals. A significant level of 5% will be used for all the comparisons and all analysis will be performed using R (version 3.6.3 or higher).

Evaluation of Safety

The following safety variables will be used for the evaluation of safety:

- Adverse events (AE);
- Adverse reactions (AR).

The total number of AEs and the total number of AEs at least possibly related to the study treatment, as well as the total number of patients affected by at least one adverse event will be calculated per treatment group.

The type of AE classified by organ system (according to MedDRA terminology) will be tabulated.

Serious and/or unanticipated adverse events and AEs resulting in discontinuation or reduction/withdrawal of the study treatment will be presented separately.

Safety analysis set

Safety summaries will be based on the safety analysis set which will consist of all patients who received the test/control treatment.

5. MONITORING AND AUDIT

Study Monitoring

The study will be monitored by the Principal Investigator at periodic intervals during the course of the study to ensure that the study is being conducted according to Good Clinical Practice.

The Investigators will be contacted by the PI on a regular basis. On this occasion, the progress of the study will be discussed with the Investigator and the CRFs will be checked for completeness and consistency and to verify compliance with the study protocol.

6. SUBJECT TERMINATION/WITHDRAWAL PROCEDURES

All efforts will be made to determine the reason(s) why a patient is withdrawn from the study. Subjects could be withdrawn from the study if any of the following occur:

1. Subject fails to substantially comply with the protocol requirements;
2. Subject develops a serious adverse reaction. The Study Investigator will immediately notify the PI and information will be recorded on a Serious Adverse Event Form (Appendix 3);
3. Subject elects to terminate participation in the study. Participation in the study is voluntary. A subject has the right to withdraw from the study at any time for any reason.

The Investigator may terminate the study at any time if the risk-benefit ratio is no longer favourable. Before discontinuation, the Investigator should inform the PI and ask for advice. If the Investigator is concerned about continuation of the study, his/her concerns should be transmitted immediately to the PI.

7. DOCUMENTATION AND DATA MANAGEMENT

Data collection in the case report form (CRF)

All study data will be recorded in the case report forms identified by the subject number. Only the principal investigator, co-investigators, or designated study personnel may make entries in the case report forms.

The Investigator has to identify all data that were directly recorded into the CRF and to be considered to be source data.

The CRFs will be checked for completeness and plausibility by the PI. The Investigator will resolve any queries.

Investigator Site File (ISF)

The ISF includes all documents that are required for the clinical study. During monitoring, the ISF will be checked regularly for completeness and actuality. After the clinical trial is finished or stopped, the ISF has to be stored 15 years in the study center.

Data Management

Data extraction from CRFs into a single, electronic database is performed by examiners. Discrepancies are to be clarified and corrected by authorized persons by means of documented data queries between Statistician and Investigator(s).

After the study is finished and before data are analyzed, a blind data review meeting will be held between the investigator and the statistician. When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after this procedure can only be made by joint written agreement among the clinical trial leader, the trial statistician, and the co-investigators.

8. ADVERSE EXPERIENCES/EVENTS

Subjects will be informed of any possible adverse reactions which they could experience and will be instructed to immediately report any event to the investigator. The investigators will record any and all adverse reactions and report this documentation to the Principal Investigator. In the event of an adverse experience, emergency or other problems or questions regarding participation in this study, the subject can contact the following investigators:

Dr. Magda Mensi (Principal Investigator) – tel. +39 030 3995784.

Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined by the ICH Guideline Medical Device Directive 93/43/EEC and Guidelines on Medical Devices MEDDEVG 2.7/3rev. 3, May 2015 Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385/EEC and 93/42/EEC for Good Clinical Practice (ICH GCP) as follows:

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

With respect to intensity, adverse events are classified as follows:

- Mild Some awareness of symptoms, but easily tolerated;
- Moderate Symptoms causing enough discomfort to interfere with usual activity;
- Severe Incapacitating event causing inability to work or to perform usual activity.

Adverse events are classified as either non-serious or serious.

Serious Adverse Event (SAE) is an adverse event that:

a) led to a death;

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness or
- injury or permanent impairment to a body structure or a body function.

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Device deficiency: inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

AEs include any clinically significant deterioration of a subject's medical status, after being enrolled and signing an informed consent form. The AE may involve any organs or systems and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change from baseline, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring after the administration of investigated treatments is an adverse event. All such occurrences must be recorded and reported accordingly, whether they appear causally related to the study medication, or not.

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

Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or investigator's brochure (IB).

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report or IB.

The following events are considered reportable:

- any SAE;
- any Device Deficiency that might have led to a SAE if:
  a) suitable action had not been taken or
  b) intervention had not been made or
  c) if circumstances had been less fortunate;
- new findings/updates in relation to already reported events.

Reportable events have to be reported by clinical investigators.

Assessment of Causality

The following criteria are to be used for the assessment of the causal relationship to the test/control treatment. For classification, all criteria of one of the following categories must be met:

related, if

- a timely correlation exists and
- dechallenge and/or rechallenge and
- a biological plausibility exists and
- other factors are clearly excluded
- a medical report or clinical proof exists;

possibly related, if

- a timely correlation exists and
- dechallenge and/or rechallenge and
- a biological plausibility exists and
- a medical report or clinical proof does not exist;

unrelated, if

- a timely correlation does not exist or is uncertain and
- dechallenge and/or rechallenge does not exist and
- a biological plausibility exists and
- a medical report or a clinical proof does not exist;

unknown, if

- not enough information exists for evaluation

- no further contact with reporter possible.

Sound medical/clinical judgment will be applied when assessing the causality and seriousness of the adverse events.

Adverse Event Reporting

The study center will provide the study participants with emergency telephone numbers for study related support and feedback. The emergency telephone number is operated by either an investigator of the study or by a qualified person designated by the principal investigator. The schedule of reachability of the emergency telephone number will be defined prior to start of the study.

Serious Adverse Events

The Investigator shall immediately after awareness (and in any event, not later than within 24 hours after awareness) inform the PI. The Investigator will send the SAE report to the following email address: magda.mensi@unibs.it. Appendix 3 has to be used for SAE reporting. Form has to be completed electronically and in English.

Adverse Events

Adverse events will be assessed by the investigator or designee within 24 hours for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification to the PI. For data collection purposes, the outcome of all adverse events recorded on the Adverse Reaction section of the CRF will be designated as of the completion of the final evaluation or examination. However, the investigator is responsible for following all adverse events until resolution or until no longer of clinical concern, and providing these data to the PI. At the end of the study, the investigator will report all adverse events (serious and non-serious) to the PI on CRFs. Forms have to be completed electronically and in English.

Pregnancy

No pregnant women (according to medical history) will intentionally be enrolled in this study. In the event a woman enrolled in this clinical research study becomes pregnant during the course of the study, participation in this study will be terminated upon the clinical staff's notification of the event.

The subject's medical records used in this study will be updated to reflect the pregnancy and there will be follow- up contact until the end of the pregnancy to record the outcome in the clinical file.

9. ADHERENCE TO PROTOCOL/AMENDMENT(S)

The Investigator will be required to adhere to the final protocol. Any changes to the protocol, except those necessary to eliminate apparent hazards, will require prior approval by the local reviewers through the submission of a protocol amendment. In the event of emergency, the Investigator shall engage any medical procedures that he/she deems appropriate. However, all such procedures must be promptly reported to the PI and Ethical Committee.

The Ethical Committee which granted approval for the study must be notified of all changes in the protocol and must provide written approval if changes are substantial (e.g. increase the risk to the subject, and/or affect the rights of the subject or validity of the investigation, change of/within study population, number of participants or changes of patients' age group).

Departures from eligibility requirements may be allowed on a case-by-case basis by the medical monitor or other authorized sponsor representative. Such departures must be medically and scientifically justified, must be pre-authorized, and must be documented in the CRF and tracked as official eligibility waivers.

10. ADMINISTRATIVE ASPECTS

Final Report

Following the completion of the study, the PI shall prepare a final study report. The final report will include a general description of the conduct of the study including protocol deviations, subject withdrawals, discussion of any adverse events, safety and efficacy data, and statistical analysis of the data. This report will be shared with the Co-investigator at the Participating Centre by the Principal Investigator, and agreed upon parts before being sent to the Sponsor.

Data Retention

The information in this and any further document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

The files pertaining to this study will be kept by the University-Hospital of Brescia for a period of 15 years from the day of delivery of the final report and will be available for consultation by competent authorities at any time.
The Investigators will retain originals of the approved study protocol, copies of completed CRFs, subjects' participation agreements, relevant source documents and all other supporting documentation related to the study for a period of 5 years. These files must be made available for inspection upon reasonable request by an authorized representative of EMS or the competent authorities.

11. ETHICAL ASPECTS AND REGULATIONS

Ethical Conduct of the Study

This study is to be conducted in accordance with the ethical principles of the Declaration of Helsinki and according to local laws and regulations.

Independent Ethics Committee (IEC) and Relevant Authorities

Before starting the study, the study protocol will be subject to review by the Ethical Committee of the University-Hospital of Brescia. As required by law, the study will be notified to authorities if applicable. No subject should be admitted to the study before the Ethical Committees issue their written favourable opinion of the study. Periodic status reports must be reported to the ethics committee at least annually as well as notification of the completion of the study. The investigator must maintain an accurate and complete record of all reports and documents submitted to and received from the ethics committee according to the ISO 14155:2011 Clinical Investigation of Medical devices for human subjects.

Subject information and Informed consent form

The purpose and description of the study in lay language, possible adverse reactions, risks and benefits of participation and the subject’s right to withdraw without prejudice at any time must be explained to each subject. Each subject must read, understand and sign the informed consent form provided before any study-related procedure.

Subject data protection and Confidentiality

The name of the subject as well as all other personal data will be kept strictly confidential by the Investigator. If due to medical reasons, it is necessary to identify the subject during the study course, this will be done under medical secrecy.

The subject has given his/her consent before the beginning of the study. In case of withdrawal of this consent subject has to leave the study.
All subjects will agree to verify, by letter, that they participated in this study, if called upon to do so.

New Findings

Subjects will be informed of any significant new findings related to study products or procedures when they become known during the course of this clinical research study. Such information may affect the subject's decision to continue participation in the study.