Laser-Assisted Regenerative Surgical Therapy for Peri-implantitis: A Randomized Controlled Clinical Trial

NCT03127228

Version Date: 02-22-18

Laser-Assisted Regenerative Surgical Therapy for Peri-implantitis: A Randomized Controlled Clinical Trial

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Introductory Statement

Peri-implantitis is a serious emerging new disease with a prevalence of 22% in patients with dental implants. (Derks and Tomasi 2015). Although early stage mucositis may be controlled non-surgically, established peri-implantitis lesions are still a challenge to manage due to the unpredictable results (Suarez-Lopez Del Amo et al. 2016). Studies have evaluated the effectiveness of different methods for implant surface decontamination, as well as several bone grafting materials attempting to regenerate peri-implant bony defects (Claffey et al. 2008). Among the available approaches for decontamination, laser therapy (especially Er:YAG laser) has been proven to reduce bacterial load without damaging the implant surface (Goncalves et al. 2010; Yamamoto and Tanabe 2013). In animal models, there are several studies showing that with the Er:YAG laser treatment in preparation for bone grafting procedure, there is an increased regenerated bone-to-implant contact for a better regenerative outcome (Nevins et al. 2014; Takasaki et al. 2007) . Many studies also have shown the benefits of laser to improve wound healing, better hemostasis, and positive biostimulation effects (Aoki et al. 2015) . However, there is limited human randomized clinical trials assessing the clinical benefits of using Er:YAG laser (Schwarz et al. 2013; Schwarz et al. 2011). It is still of great interest to critically evaluate whether laser can assist in traditional mechanical debridement to promote regenerative therapy. The purpose of the study is to evaluate if Er:YAG laser can assist in mechanical debridement and enhance the outcome of a regenerative therapy for resolving peri-implant infection and restoring bony defects.

General Investigation Plan

This study involves one center and a double-blinded randomized controlled clinical trial is planned. Twenty-four adult patients in the need of surgical treatment due to peri-implantitis infections will be included. A signed written informed consent will be obtained after he or she has been given verbal and written information describing the nature and duration of the study. Subjects will not be screened or treated until an informed consent has been obtained. Subject information will be protected according to the privacy

regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Study Protocol

I. Introduction

Peri-implant diseases are similar to periodontal diseases and can be classified into two different entities, including peri-implant mucositis and peri-implantitis. Peri-implant mucositis corresponds to gingivitis and peri-implantitis corresponds to periodontitis in natural teeth. As defined by the American Academy of Periodontology, (Peri-implant mucositis and peri-implantitis: A current understanding of their diagnoses and clinical implications 2013) mucositis represents a disease in which the presence of inflammation is confined to the soft tissue surrounding an implant without signs of bone loss following initial bone remodeling during healing; while peri-implantitis is an inflammatory reaction around an implant, which includes both soft tissue inflammation and loss of supporting bone beyond biological remodeling. Regarding the treatment of these arising diseases, it has been proven that mechanical non-surgical therapy could be effective for peri-implant mucositis. However, when aiming to treat peri-implantitis, non-surgical treatment was found not to be effective (Renvert et al. 2008).

Dental implants are not immune from mechanical or biological complications (Aljateeli et al. 2012) and as implant therapy becomes more widely used, peri-implant diseases arise with it. It has been reported that 22-28% of implants patients had at least one implant with progressive bone loss and 12.4% had bone loss extend beyond 1/3 of the implant thread (Atieh et al. 2012; De Bruyn et al. 2013; Fransson et al. 2005; Marrone et al. 2012).

There are currently different techniques available for the treatment of peri-implantitis, including but not limited to: citric acid, chlorhexidine, local and systemic antibiotics, hydrogen peroxide, air powder abrasive treatment, laser and photodynamic therapy, as well as implantoplasty. Nevertheless, even though a great variety of studies attempted to evaluate the efficacy of these treatment options, no conclusions could be made due to most studies differed markedly in design and the surface debridement treatment that was performed in combination of various regenerative techniques

(Claffey et al. 2008). Nonetheless, one of the key steps to achieve a favorable outcome is to properly detoxify the contaminated implant surface.

Laser therapy in general, specifically Er:YAG laser has demonstrated to be an effective treatment in peri-implantitis, due to the high bactericidal potential without causing detrimental alterations of the fixture surface (Kreisler et al. 2002; Quaranta et al. 2009). More recently, it has been demonstrated that Er:YAG laser at 100 mJ/mm^2 irradiation power represents a safe and effective setting to remove the contaminated surface without alteration or melting the implant surface. In addition, implant temperature did not reach harmful levels when water was used during laser irradiation and thus osseointegration was proved to occur in an animal model after treatment (Yamamoto and Tanabe 2013) . Given its potential benefits from several in-vitro and in-vivo studies, a well-controlled randomized clinical trial is warranted.

II. Objectives

The primary objective of this study is to evaluate the effectiveness of using Er: YAG laser to assist in peri-implant defect debridement and implant surface decontamination prior to regenerative procedures in the treatment of peri-implant infections. To test this objective, three specific aims were developed and clinical measurements will be used as the primary outcome [including probing depths (PD), gingival index (GI), bleeding on probing (BOP), clinical attachment level (CAL), plaque-index (PI), radiographic bone fill (RBF), and 11 points Numeric Rating Scale (11-NRS), see Appendix A for more details]. Bacterial profile (BAC) and peri-implant crevicular fluid (PICF) biomarkers will be assessed as a secondary exploratory outcome to determine the dynamic change and the stability of the treatment.

Specific Aims/Hypothesis:

Specific Aim 1: To compare the clinical benefit of Er:YAG laser-assisted peri-implant defect debridement and surface detoxification with conventional mechanical debridement for regenerative therapy.

Null Hypothesis (H_0): Er:YAG laser-assisted surgical debridement combined with regenerative therapy significantly improves clinical outcomes (PD, BOP, CAL, RBF) compared to conventional mechanical debridement alone.
Alternative Hypothesis (H_1): Er:YAG laser- assisted surgical debridement combined with regenerative therapy does not give additional clinical benefits compared to conventional mechanical debridement alone.

Specific Aim 2: To evaluate whether Er:YAG laser-assisted regenerative surgical therapy can decrease bacterial load and alter microbial profile.
Null Hypothesis (H_0): Er:YAG laser-assisted surgical therapy significantly decreases bacterial load and alter microbial profile compared to mechanical debridement alone.
Alternative Hypothesis (H_1): Er:YAG laser-assisted surgical therapy does not significantly decrease bacterial load and alter microbial profile compared to mechanical debridement alone.

Specific Aim 3: To analyze whether Er:YAG laser-assisted regenerative surgical therapy can impact the molecular profile of the peri-implant crevicular fluid (PICF) and the stability of the treatment.
Null Hypothesis (H_0): Er:YAG laser-assisted regenerative surgical therapy significantly alter the molecular profile of the PCIF compared to mechanical debridement alone.
Alternative Hypothesis (H_1): Er:YAG laser-assisted surgical therapy does not alter the molecular profile of the PICF compared to mechanical debridement alone.

Specific Aim 4: To analyze whether the granulation tissue within the peri-implant defect can provide prognostic immunoscore for regenerative outcome and if Er:YAG laser has an impact on the landscape of the immunoscore.
Hypothesis: Peri-implant defect has a specific immunoscore that can predict the outcome and stability of the regenerative therapy

Significance

Treatment of peri-implantitis is still unpredictable, and one of the challenges is how we can detoxify the contaminated rough dental implant surface and restore osseous defect. Implant surface detoxification is of paramount importance in order to achieve re-osseointegration following bone regeneration. Peri-implant defect debridement could be easier with the aid of the laser and it could potentially stimulate better healing. A better understanding of the effects using laser therapy over the titanium surface and osseous defects, will help to establish an evidence-based protocol to manage peri-implantitis. Patients can benefit from reestablishing a healthy condition over a previously contaminated implant. This prospective randomized controlled clinical trial will allow us to potentially develop an effective new protocol for the treatment of peri-implantitis infections.

III. Materials and Methods

A. Trial design

There will be a total of 24 subjects (power calculation was establish at 10 patients per group, however, after considering the expected 20% dropout rate, 12 patients will be included in each group with at least one implant presenting peri-implantitis that meets the inclusion criteria. Twelve patients will be randomly allocated for each group. The control group will be treated with flap surgery, including implantoplasty of the implant surface above the interproximal bone level, debridement of osseous defect, and the implant surface with periodontal curettes; followed by human allograft placed in the defect and protected by collagen membrane. This procedure is the current standard of care. The test group will be treated the same as the control group with the aid of the laser application (Er:YAG), which is also routinely used in such treatment for clinicians who have access to dental lasers.

B. Study settings

This investigation will be conducted in the Department of Periodontics and Oral Medicine at the U-M School of Dentistry, Ann Arbor, Michigan, USA.

C. Eligibility

1. Pre-Screening Examination

In order to identify potentially eligible subjects, the electronic database will be screened for the procedure code D6010, which corresponds to surgical placement of endosseous dental implants. All electronic records initially retrieved with the automated query, will be manually reviewed by study team members for inclusion and exclusion criteria in order to confirm eligibility of each subject. If they qualify, the subjects will receive an invitation letter requesting that they contact the study coordinator by telephone for information regarding participation in the study. In addition, the study coordinator will conduct a follow-up telephone call approximately two weeks later to the subjects receiving the invitation letter to inquire their potential interest to participate in the study. The study coordinator will perform a brief telephone interview to determine whether or not the patient will qualify based on age and basic inclusion and exclusion criteria. Subjects indicating they may qualify would be scheduled for a screening examination appointment. In addition, a flyer will be posted in all of the clinics at the University of Michigan School of Dentistry.

2. Screening Examination V0

Study personnel will provide each study candidate with a written informed consent form at the initial visit prior to administration of any research related procedures. Prior to enrolling a subject, study personnel will explain to each subject, the protocol, procedures, and objectives of the study, before obtaining consent. Subjects will be given the opportunity to read the informed consent and ask questions. Study personnel will answer all questions that the subject may have and ensure that the subject understands all aspects of the study by utilizing the teach-back method. When the subject understands and is willing to participate in the clinical trial, he/she must sign and date the Institutional Review Board (IRB) approved Informed Consent Form.

This screening visit will consist of the following procedures:

- Perform Informed consent regarding the study

- Medical history will be reviewed by system, using the School of Dentistry medical history questionnaire.
- Vitals of blood pressure and heart rate will be taken.
- Clinical measurements including PD, BOP, CAL, GI, PI will be taken. Also, a peri-apical radiographic will be performed on the affected implant if inclusion and exclusion criteria cannot be determined by the existing radiograph.

If requested by the subjects, information concerning the study and their participation will be shared with their healthcare provider (general dentist or physician). Study personnel will obtain consent from the subject to release all pertinent information (Appendix B). This study protocol will conform with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in obtainment of approval by the University of Michigan's human subjects research review committee.

Potential subjects will be carefully screened according to the inclusion and exclusion criteria as follows:

Inclusion Criteria
• Subjects, aged 18 - 85 years • Physical status according to the American Society of Anesthesiologists (ASA) I or II, which includes patients who are systemically healthy or suffer under mild to moderate, but well controlled systemic diseases. • Subjects having a minimum of 1 dental implant with peri-implantitis. • Dental implants with peri-implantitis ≥ 2 threads (or ≥ 2mm) exposed (infrabony defect) identified on the radiograph and pocket probing depth (PPD) ≥ 5mm, with bleeding on probing (BOP) and/or suppuration (pus) • The implants are in function for at least 6 months • Only rough surface implant will be included in this study
Exclusion Criteria

- Long-term use of antibiotics > 2 weeks in the past two months
- Obvious malpositioning of the dental implants
- Subjects taking medications known to modify bone metabolism (such as bisphophonates, corticosteroids, Hormone replacement therapy for menopausal women, parathyroid hormone, Denosumab, strontium ranelate)
- Pregnant females or those planning to become pregnant
- Subjects with a history of major diseases, oral cancer, sepsis or those having adverse outcomes to oral procedures in the past, will be excluded
- Mobility of dental implants
- History of alcoholism or drug abuse
- Current smokers
- Diseases of the immune system or any medical condition that may influence the outcome (uncontrolled diabetes (HbA1c >8)
- Uncontrolled systemic disease or condition known to alter bone metabolism, like Osteoporosis, Osteopenia, Hyperparathyroidism, Paget's disease

Premature Exclusion Criteria

- The researcher believes that it is not the best interest of the subject to stay in the study
- If the subject becomes ineligible to participate based on the exclusion criteria
- If the subject's medical condition requires interventions which preclude involvement in the study (radiation therapy, chemotherapy, etc)
- If the subject does not follow study related instructions
- The study is suspended or canceled.

D. Randomization

Subjects will be randomized into one of the two groups. Twelve subjects will be allocated to the test group and another 12 subjects to the control group. The subject will not know which group he or she belongs as blinded allocation. Randomization will be determined by the last digit of the chart number (odd number goes to Group A and even number goes to Group B) but if one group has two subjects more than the other group, the next subject will automatically be enrolled in the lesser number group to ensure timely even distribution. The assignment of control or experimental group to Group A or B will be written by the primary surgeon (Principle Investigator) in a concealed envelop before recruiting patients. This ensure the clinical examiner be blinded throughout the study. This randomization will prevent any operator bias.

E. Pre-surgical Preparation V1

Prior to the surgical visit, the subject will be asked if they are still willing to participate in the study and their medical history will be reviewed. Clinical measurements of PD, BOP, CAL, PI and GI will be recorded and peri-implant bacterial and crevicular fluid samples will be collected. A prophylaxis or a periodontal maintenance will be completed based on the subject's prior diagnosis. In addition, a set of intraoral photographs will be taken, one standardized peri-apical radiograph, and maxillary and mandibular impressions will be taken. Articulating paper will be used to check the occlusal contact of the implant crown, if there is obvious heavy contact or lateral interference, occlusal adjustment will be made.

F. Surgical procedure V2

The subject will be asked if they are still willing to participate in the study and their medical history will be reviewed. The subject's vitals of blood pressure and heart rate will be taken. During this visit, intraoral photos will be taken and all surgeries will be performed under local anesthesia using one or more of the following medications:

- Lidocaine with epinephrine, (Xylocaine 2%®-Epinephrine 1:100,000 and 1:50,000, Dentsply Pharmaceutical, York, PA, USA).
- Articaine (Septanest 4%®-Epinephrine 1:100,000, Dentsply Pharmaceutical, York, PA, USA).
- Mepivacaine (Polocaine 2%®-Levonordefrin 1:20,000, Dentsply Pharmaceutical, York, PA, USA).

After local anesthesia, the width of the keratinized tissue around the implant will be measured by periodontal probe and the thickness of the peri-implant mucosa will be measured with endo file and stopper.

1) Test and Control group procedures

Open flap debridement and regenerative approach will be the treatment of choice for both groups. Intrasulcular incisions will be performed with a 15-C scalpel around the

implant to expose the contaminated surface. All the suprabony implant surface will be debrided with implantoplasty procedure as a standard of care and the specific treatment and outcome will be focused on the infrabony component of the defect. The experimental group will have the same treatment as the control group, but the laser will be used as a tool to aid in tissue debridement. In control group, the laser will also be set up for a fake application.

(A) Control group:
After the reflection of the flap, removal of the granulation tissue and mechanical debridement of infrabony defect and the implant surface with mechanical scalers will be performed.
(B) Test group:
The same protocol for the control group will be completed with the addition of the Er:YAG laser application to assist in mechanical debridement of the osseous defect and detoxify the implant surface.

The granulation tissue within the peri-implant defect will be collected during the surgical debridement will be stored for Immunoscore analysis:
Next-gen RNA sequencing will be performed on the peri-implant granulation tissue. This additional protocol serves two important scientific goals. First, we have built a novel machine learning tool, characterization of immune cell subsets using RNA-Seq data (Ci-Seq). We will utilize Ci-Seq to comprehensively annotate the immune landscape of the granulation tissue. Specifically, we will resolve the percentages of different immune cell subsets and determine the weighted impact of each immune subset on the overall regenerative potential. Second, we will perform Gene Set Enrichment Analysis (GSEA) and differential genes expression profiling to identify key pathways that modulate patients' response to regenerative treatment.

2) Bone Graft and Membrane Placement (Both groups)

After detoxification of the implant surface, mineralized bone allograft will be applied to both groups to fill the peri-implant defects. After the graft material is properly placed, an

absorbable cross-link collagen membrane will be trimmed to an appropriate size and shape to completely cover the implant site, and extend about 3-5mm beyond on the facial aspect. The membrane will be tucked under the sub-periosteal flap. Care will be taken to ensure that the membrane is resting on bone. Bone grafting and membrane placement for peri-implant infrabony defect is a standard of care procedure.

3) Site closure

Soft tissue will then be sutured with PTFE sutures (Cytoplast - PTFE suture) using either a simple interrupted technique or a criss-cross technique. Primary closure of the site will be attempted. The main objective of the sutures will be the stabilization of the wound. Sutures will be removed 10-14 days after.

5) Post-Operative Care

All subjects will be prescribed 500mg of amoxicillin to take 3 times a day for ten days. If the subject is allergic to Amoxicillin, they will be prescribed 250 mg of Zithromax 6 tablets total /sig. 2 tablets the 1st day and Q.D. (1 x per day) until gone. In addition, the subject will be prescribed 600 mg of ibuprofen, taken as needed, for pain control. Subjects will be instructed to rinse twice daily with chlorhexidine for 1 minute, 2 times per day for the first week. Following the first week, the subject will apply chlorhexidine with a Q-tip for another 3 weeks. They will also avoid brushing or touching the area of implant placement for 2 weeks. Subjects will be informed that the sutures will be removed 2 weeks following the surgical appointment.

G. Outcomes

The primary outcome examined in this study will be the clinical results. Secondary measurements will include radiographic assessments and post-op pain assessment. Exploratory measures will include biomarker profile and microbiological examination.

2 (± 1) Week Follow-Up (V3)

The subject will return in 2 weeks (±1 week) for follow up care. The subject will be asked if they still are willing to participate in the study and their medical history will be reviewed. The removal of the sutures or partial removal will be determined depending on the healing.. The intensity and duration of post-operative pain assessment will be based on patient-reported days and scores using a 11-point numeric pain rating scale (NRS-11) (Jensen et al. 1989; Matys and Dominiak 2016). In addition, a standardized radiograph and intraoral photographs will be taken, BAC and PICF will be collected, and clinical measurements of GI and PI will be taken.

4 (± 1) Week Follow-Up (V4)

The subject will return in 4 weeks (±1 week) for follow up care. The subject will be asked if they still are willing to participate in the study and their medical history will be reviewed. If sutures are present, they will be removed. Intraoral photographs will be taken. BAC and PICF will be collected and clinical measurements of GI and PI will be taken. The subject will be mailed a compensation of a $40 check from HSIP at the conclusion of this visit.

12 (±1) Week Follow-Up (V5)

The subject will return in 12 weeks (±2 week) for follow up care. The subject will be asked if they still are willing to participate in the study and their medical history will be reviewed. Intraoral photographs will be taken. A prophylaxis or a perio maintenance will be completed. In addition, BAC and PICF will be collected and clinical measurements including PD, BOP, CAL, PI, and GI will be taken. The subject will be mailed a compensation of a $40 check from HSIP at the conclusion of this visit.

Re-evaluation (±2) 24 Week Follow-Up (V6)

The subject will return in 24 weeks (±2 week) for follow up care. The subject will be asked if they still are willing to participate in the study and their medical history will be

reviewed. A standardized radiograph and intraoral photographs will be taken. A prophylaxis or a periodontal maintenance will be completed. In addition, BAC and PICF will be collected and clinical measurements including PD, BOP, CAL, PI, and GI will be taken. Peri-implant mucosal thickness and the width of the keratinized tissue will be measured. A final impression will also be taken. The subject will be mailed a compensation of a $40 check from HSIP at the conclusion of this visit.

Radiographic assessment of the alterations in alveolar bone fill and crestal level will be done through the use of standardize peri-apical x-rays. One peri-apical x-ray may be taken at the screening visit (V0), if there is no current x-ray to reference or if inclusion and exclusion criteria cannot be determined. Standardized peri-apical x-rays will be obtained at three different time points (before surgery (V1), two weeks post-surgery (V3), and at the re-evaluation 24 week visit (V6). The ridge dimensions obtained from these x-rays will then be compared to the baseline measurements to identify changes.

II) Microbial profile (BAC) and Peri-implant crevicular fluid (PICF) analysis

PICF samples will be obtained at Pre-surgical Preparation (V1), 2 week (V3), 4 week (V4), 12 week (V5) and re-evaluation-24 week (V6). These samples will be used for bacterial DNA and biomarker analysis. Samples will be collected with sterile paper point and strips. The sites sampled will be isolated with cotton rolls to keep the area dry and free of salivary contamination. A gentle air blow will be applied perpendicularly before sampling. For biomarker analysis, a perio strip will be inserted into the crevice until mild resistance is felt and left for 30 seconds. For microbial profile, a paper point will be inserted for 10 seconds. Two sampling per assays will be collected with 90-second intervals. The paper point and paper strip will be carefully removed to avoid contamination from contact with other tissues and to avoid trauma to the site. The samples will then be transferred to sterile micro centrifuge tubes containing protease inhibitors and stored at – 80 °C until further processing of the biomarkers analysis. All

the sampling procedures are established and published by our group (Kinney et al. 2014; Wang et al. 2016).

Examiners calibration

Calibration of the examiner will be performed through a training exercise with a calibrated examiner prior to the beginning of the study. The calibrated examiner will observe and confirm the accuracy of the clinical measurements of PI, GI, and PD of the study examiner (>0.8 agreement between examiners will be considered calibrated).

IV. Statistical Analysis:

Sample Size

This study will have a sample size of 24 subjects, 12 in each of the groups.

The study power was calculated using the software nQuery Advisor v7.0 (Statistical Solutions, Saugus MA, USA). A difference of 2.0mm between groups was considered as clinically significant. The power value was evaluated for probing depths at 6 months after the surgery. A “p” value of less than 0.05 will be considered statistically significant.

Data Analysis

Mean values, standard deviations, and medians will be calculated for clinical and radiographic measurements. We will examine the univariate association of the probing depths with the detoxification method used. We will also attempt to examine the association of bacterial load with various combinations of clinical and radiographic parameters using multiple logistic regression, but acknowledge that we will be restricted by our sample size to at most two or three predictors in any model. Changes of the parameters over time within each group as well as differences between groups will be analyzed using the repeated measure of analysis of variance.

V. Regulatory Considerations

Surgeries and related procedures would be performed at no cost for the patients included in the study. Three free dental cleaning and $120 compensation will be given to the patients.

Study reporting

1. Adverse events

Any adverse event, including both observed or volunteered problems, complaints, or symptoms, are to be recorded on the Adverse Event Case Report Form. The intensity of the adverse event will be characterized as mild, moderate or severe as follows:

- MILD events are usual transient, requiring no special treatment, and do not interfere with the subjects daily activities.
- MODERATE events traditionally introduce a low level of inconvenience of concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- SEVERE events interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

When intensity changes occur more frequently than once a day, the maximum intensity for the event should be listed. If the intensity category changes over a number of days, then these mini-events or changes should be recorded separately (i.e. having distinct onset days).

The investigator will determine the relationship of the adverse event to the study test material.

One of the following determinations will then be used to document the relationship of the adverse event to the study test material:

- NOT RELATED
- POSSIBLE
- PROBABLE

ANY SERIOUS AND UNEXPECTED ADVERSE EVENT INCLUDING HOSPITALIZATON OR DEATH DUE TO ANY CASE, WHICH OCCURS DURING THIS INVESTIGATION, WHETHER OR NOT RELATED TO THE STUDY, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO THE PRINCIPAL INVESTIGATOR.

Reports of serious or unexpected adverse events will be made immediately by telephone or fax to: **Dr. Jeff Wang (734)-647-6175**

This telephone report or fax must be followed within 5 days by a written summary fully documenting the event in order to permit the Principal Investigator to file a report which satisfied regulatory guidelines.

All serious and unexpected adverse events associated with the use of the study test material will be immediately reported to appropriate regulatory agencies by the Principal Investigator.

Adverse events reporting will proceed according to the University of Michigan guidelines for standard AE reporting.

2. Discontinuation and replacement of subjects

- Any subject found to have entered the study in violation of this protocol will be withdrawn from the study after discussion with the Principal Investigator

- An effort will be made to determine why any subject discontinues the study prematurely. This information should be recorded on the appropriate case report form.
- As stated in the informed consent, all subjects reserve the right to withdraw from the study at any time.
- Any female subject that becomes pregnant during the study will be withdrawn from the study.
- Any subject whose condition changes after entering the study, so that he or she no longer meets the inclusion or exclusion criteria, will be withdrawn from the study.
- Any subject who requires the use of an unacceptable concomitant medication will be withdrawn from the study.
- The investigator will discontinue any subject from the study if, in the investigator's opinion, it is not in the subject's best interest to continue.
- The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the case report form.
- When a participant is lost to follow-up, that is, fails to return for study visits, a reasonable effort should be made to contact the participant in order to determine why the subject failed to return. This information will be documented on the case reporting form (CRF). When a participant is withdrawn from the study, regardless of the cause, all evaluations required at the scheduled end of study day should be performed.
- Subjects discontinued for adverse events will not be replaced.

3. Data reporting and case report forms (CRFs)

Data reflecting participant experience with the protocol under investigation will be reported to the Principal Investigator and the data recorded on CRFs

CRFs will be signed and dated by the investigator or a designated representative and filled out in black ink. If an entry on a CRF requires change, the correction will be made as follows:

a. A single line will be drawn through the incorrect entry.

b. The date will be entered and the change initialed. White-out or erasure on CRFs will not be permitted under any circumstance.

All fields and blanks must be completed. The following abbreviations will be used when values or answers cannot be provided: NA=not applicable; ND=not done, UNK=not known

Completed original CRFs will be collected by the Principal Investigator. CRF must be submitted for each subject.

Data entry will proceed directly from the case report form. The data, as well as group/subject identification, will be made available to the investigator at the conclusion of the study.

4. Study monitoring

The investigator will periodically audit all CRFs and corresponding portions of U-M School of Dentistry records of each study participant and has a monitoring plan with the U-M Institutional Review Board. The monitoring will provide the Principal Investigator the opportunity to evaluate the progress of the study and to verify the accuracy and completeness of the CRFs; assure that all protocol requirements, applicable FDA regulations and investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records. The Principal Investigator may stop the study if it is observed that the protocol or sound clinical practices are not being followed. The Principal Investigator may exclude subjects from the study if review of their records indicates violations of the protocol or if there are other reasons to believe that their inclusion would jeopardize the validity of the study.

B. Regulatory Considerations

1. Institutional Review Board (IRB)

The protocol and informed consent for this study must be reviewed and approved by an appropriate IRB before enrollment of participants into the study.

It is the responsibility of the investigator to assure that all aspects of the institutional review are conducted in accordance with current Federal Regulations. A letter with IRB approval for the protocol must be received by the Principal Investigator before the initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol. At each annual protocol renewal, an updated report of the numbers of participants and any adverse events will be provided to the IRB.

After completion or termination of the study, the investigator will submit a final report to the IRB. This report should include any deviations from the protocol, the number and types or participants evaluated, the number of participants who discontinued, including reasons, results of the study, adverse events, and a conclusion summarizing the results.

2. Informed Consent

A signed, written informed consent must be obtained from each subject before he or she enters the study after he or she has been given verbal and written information describing the nature and duration of the study. Subjects are not to be screened or treated until an informed consent has been obtained. The signed informed consent will be retained with the study records. Each subject will also be given a copy of his/her informed consent.

As long as patient information is kept within the University of Michigan, it will be protected by the Health System's privacy policies. Information about these policies, are available at http://www.med.umich.edu/hipaa/npp.htm. Patient information will be protected according to the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

3. Access of Records

The investigator understands that the office and hospital records of subjects entered in this study will be required to be available under the supervision of the investigator or a designated representative for inspection by the FDA. All subject related information provided to the FDA will be done so without subject names or other identifying information.

4. Retention of Data

The investigator will maintain adequate records for the study including participant's CRF, medical records, informed consent forms, safety reports, information regarding participants who discontinued, and any other pertinent data. All records will be maintained in a locked fireproof storage room to which only study investigators have access.

These records will be available to copying and inspection if requested by a properly authorized employee of the Department of Health and Human Services, under the supervision of the investigator or a designated representative and in accordance with federal regulations.

5. Deviation from the Protocol

The investigator will not deviate from the protocol without obtaining written approval from the IRB. In medical emergencies, the investigator will use medical judgment and will remove the participant from immediate hazard, then notify the IRB regarding the type of emergency and course of action taken. Any other changes or deviation in the protocol will be made as an amendment to the protocol and must be approved by the IRB before being implemented.

6. Reports

The investigator will make an accurate and adequate written progress reports to the IRB at appropriate intervals not exceeding one year.

The investigator will make an accurate and adequate special report to the IRB on any serious unexpected or life-threatening adverse event or death occurring in relationship to the study whether regarded as study-related or not.

On completion of the study, the investigators will prepare a final report of the study results.

APPENDIX A

Clinical Measurements and Outcomes

A periodontal probe will be used for all clinical measurements. PD will be measured from the gingival margin to the base of the pocket in millimeters. All PD measurements will be rounded to the nearest millimeter. Bleeding on probing will be recorded dichotomously as 0 or 1 (0=no, 1=yes). Patient –reported outcome will also be assessed using the 11 points Numeric Rating Scale (NRS-11) for the post-operative pain assessment.

PD and BOP will be recorded at six sites per implant (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual). A bleeding index for each patient will be determined by dividing the total BOP score of each individual by the number of sites examined

The PI (O'Leary et al 1972) will be measured at six surfaces of each tooth. A PI for each patient will be determined by dividing the total plaque score of each individual by the number of teeth examined

The GI will at midfacial mucosa tissue will be assessed according to Löe (Löe 1967) with the following scores:

- Score 0: Normal gingiva.
- Score 1: Mild inflammation, slight change in color, slight edema, no bleeding on probing.

- Score 2: Moderate inflammation, redness, edema, glazing, bleeding on probing.
- Score 3: Severe inflammation, marked redness, edema, ulceration and tendency to spontaneous bleeding.

APPENDIX B

Consent to Release Information To The Subject's Dentist

Patient's Initials/Number:_____

Date:_____

Title of Study: Laser-Assisted Regenerative Surgical Therapy for Peri-implantitis: A Randomized Controlled Clinical Trial

University of Michigan School of Dentistry
Department of Periodontics and Oral Medicine
Principal Investigators: Jeff Wang, DDS, DMSc
Study Coordinator: Michelle Arnett, RDH, MS

CONSENT OF THE SUBJECT
By signing this document, you are agreeing that we inform your general dentist that you are participating in this study. Information regarding the surgical treatment and other pertinent information will be given. This information will be given by mail or by phone. You will be given a copy of this document for your records and one copy will be kept with the study records. Be sure that all your questions concerning the study have been answered and understood.

I have read of the information of the information given above. I understand the meaning of this information. I hereby voluntarily consent to release my information to my general dentist.

_____
Name of Adult Subject of Research (Print)

_____ _____
Signature of Adult Subject of Research **Date**

_____ _____

Study Investigator/Coordinator Signature **Date**

Name of dentist: _____

Address: _____

_____

Phone number: _____

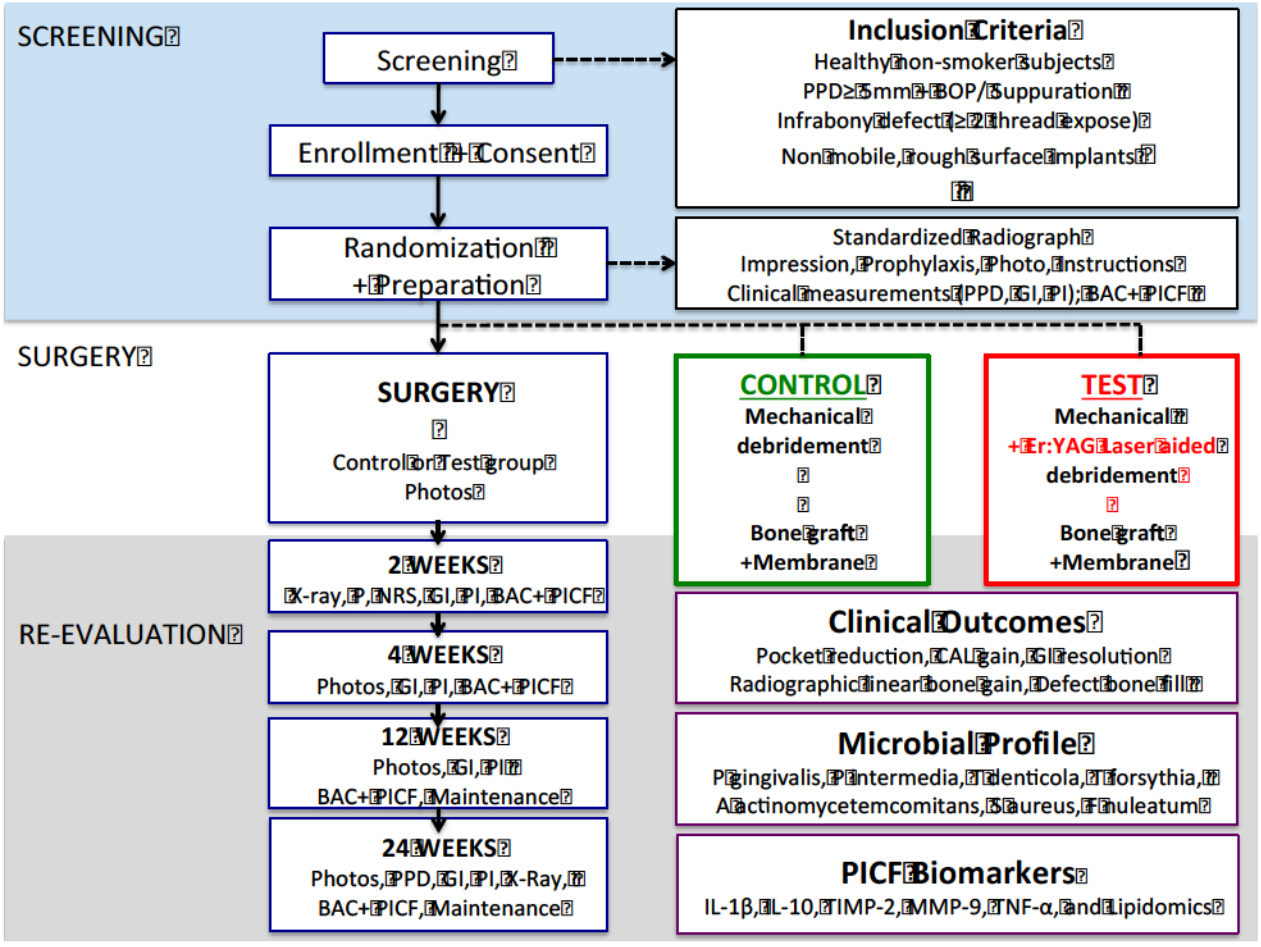
TABLE I
Schedule of events

VISIT	Screening & Enrollment	Pre-Surgical Preparation	Surgery Day	Post-op			Re-evaluation 24wk
				2wk	4wk	12wk	
Visit no.	V0	V1	V2	V3	V4	V5	V6
Timeline	Prior to V1	before BL	Baseline (BL)	2±1wks from BL	4±1wks from BL	12±2wks from BL	24±2wks from BL
Informed consent	**Sign**	**X**	**X**	**X**	**X**	**X**	**X**
Medical history	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood pressure and heart rate	**X**		**X**				
X-ray *S(standardized)	**X (If needed)**	**X(S)**		**X(S)**			**X(S)**
Suture removal				**X**	**X** *If present		
Pain assessment (NRS-11)				**X**			
Prophylaxis/Perio Maintenance		**X**				**X**	**X**
Impressions		**X**					**X**
Photograph		**X**	**X**	**X**	**X**	**X**	**X**
Granulation tissue sampling			**X**				
BAC + PICF		**X**		**X**	**X**	**X**	**X**
Clinical measures (PD, BOP, PI, CAL, GI)	**X**	**X**		**X** *Only GI & PI	**X** *Only GI & PI	**X**	**X**
Peri-implant mucosal thickness			**X**				**X**

Subject compensation					**X**	**X**	**X**

FIGURE 1

Study outline and sequence of events



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