PROTOCOL TITLE: Effect of Non-Surgical Periodontal Therapy With and Without Minocycline HCl Microspheres, 1 mg on Bacterial Load and Systemic Markers of Inflammation
VERSION DATE: September 26, 2022

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| **Protocol Title** | Effect of Non-Surgical Periodontal Therapy With and Without Minocycline HCl Microspheres, 1 mgon Bacterial Load and Systemic Markers of Inflammation |
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| **Version Number/Date:** | Version 1.4<br>April 8, 2020 |

**PROTOCOL COVER PAGE**

**REVISION HISTORY**

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 1.2 | September 8, 2019 | Page 9 was revised to state patient charts that are pre-screen and have a email address will be emailed to subjects instead of sent by mail. Page 9 was also revised to state the study information will be posted on the U of M OHCRC website. | No |
| 1.3 | February 21, 2020 | Page 7 was revised to include the use of de-identified data for future research. | Yes |
| 1.4 | April 8, 2020 | COVID-19 plan to mitigate risks on page | No |
| 1.5 | September 8, 2022 | Add MMP-8 to GCF and serum biomarkers | No |
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**ABBREVIATIONS/DEFINITIONS**

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| FDA | Food and Drug Administration |
| ICH | International Conference on Harmonisation |
| IRB | Institutional Review Board |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SCR | Scheduled Continuing Review |
| US | United States |
| SRP | Scaling and Root Planing |
| GCF | Gingival Crevicular Fluid |
| hsCRP | High Sensitivity C-Reactive Protein |
| Hp | Haptoglobin |
| Hgb Alc | Hemoglobin A1c |
| MMP-8 | Matrix metalloproteinase-8 |
| TNF-α | Tumor Necrosis Factor alpha |
| IL-1 | Interleukin 1 |
| IL-6 | Interleukin 6 |
| CVD | Cardiovascular disease |
| U of M | University of Minnesota |
| School of Dentistry | SoD |

## 1.0 Study Intervention(s)/Investigational Agent(s)

*1.1* Description:

The primary goal of this study is to investigate the qualitative and quantitative effects of SRP with and without minocycline HCL microspheres, 1 mg on periodontal pathogens and overall bacterial load.

A randomized controlled clinical trial of a control (scaling and root planing) (SRP)) group and an experimental (SRP with minocycline HCl microspheres, 1 mg) group is planned.

The intervention of minocycline HCl microspheres, 1 mg will be administered in the experimental group at baseline and the three month periodontal maintenance visit. Saliva samples, gingival crevicular fluid (GCF), and blood serum will be collected at four time points (baseline, 1, 3, and 6 month follow up). Saliva will be analyzed for overall pathogen burden. GCF will be analyzed for IL-1, IL-6, TNF-α, MMP-8. Serum will be analyzed for C-reactive protein (hsCRP), haptoglobin (Hp), hemoglobin (Hgb) Alc, IL-1, IL-6, TNF-α, and MMP-8.

Primary: Investigate the pathogenic burden and overall bacterial load utilizing the MyPerioPath® salivary test as a measure of the effect of SRP with and without minocycline HCl microspheres, 1 mg.

Secondary: Evaluate the effects of SRP with and without minocycline HCl microspheres, 1 mg on serum biomarkers of systemic inflammation, including IL-1, IL-6, TNF-α, MMP-8, hsCRP, Hp, and Hgb A1c and GCF levels of IL-, IL-6, TNF-α, MMP-8.

*1.2* Drug/Device Handling:

Minocycline HCl microspheres, 1 mg are approved by the Food and Drug Administration (FDA) as an adjunct to SRP procedures for reduction of pocket depth in patients with adult periodontitis. Minocycline HCL, 1 mg is a subgingival unit dose of 4 mg of drug containing 1 mg of minocycline and 3 mg of poly (glycolide-co-dl-lactide) (PGLA). The drug is in a powder form and prepackaged in a disposal plastic cartridge tip. The tip is loaded into a stainless steel spring- loaded cartridge handle to deliver subgingivally. The packaging is clearly labeled for the administration of the drug.

Minocycline HCL, 1 mg will be stored in a locked cabinet in the U of M SoD Oral Health Clinical Research Clinic (OHCRC) at room temperature ($68^{O}$ to $77^{O}$ F). The product will not be exposed to heat or pressure.

The drug is prepackaged and no preparation is required. The prepackaged drug is located inside a disposal plastic cartridge tip to ensure exact dosage delivered. The tip is loaded into a stainless steel spring-loaded cartridge handle to deliver subgingivally.

*1.3* Biosafety: N/A

*1.4* Stem Cells: N/A

## 2.0 Local Procedures Involved and Local Requirements

*2.1* Local Procedures:

All study procedures are located on page 14-16 of the protocol.

*2.2* Individually Identifiable Health Information:

Identifiable information from the PHI will be used for recruitment. PHI information used for research purposes will be age and gender. See the HIPCO Survey and permission to use PHI for research and HIPAA authorization form uploaded in ETHOS. Subjects who agree to participate in the study will also sign the HIPAA authorization.

*2.3* Use of radiation*:* N/A

*2.4* Use of Center for Magnetic Resonance Research*:* N/A

## 3.0 Provisions to Monitor the Data to Ensure the Safety of Participants

*3.1* Data Integrity Monitoring.

The specimen collect, data, and monitoring plan is located on page 21-24. Additionally the use of de-identified data for future research. The adverse events definitions are located on page 20. Additional information is on page 20 under the header ASSESSMENT OF SAFETY.

*3.2* Data Safety Monitoring.

This study does not include a DSMA or DSMC. However, the data safety plan is on page 20-24 of the protocol and can be found on the HIPCO Survey.

*3.3* See page 5-6 of the protocol for the plan to mitigate COVID-19 risks.

## 4.0 Data and Specimen Banking

*4.1* Storage and Access: N/A

*4.2* Data: N/A

*4.3* Release/Sharing: N/A

## 5.0 Sharing of Results with Participants

*5.1* The results of this study could be published in an article, but results will not be disclosed to participants. If the participants elects a portfolio of their oral pathogenic bacteria burden and inflammatory markers a written request will be obtained. See page 16 of the protocol.

## 6.0 Local Study Population

The inclusion and exclusion criteria is on page 9 of the protocol. The premature exclusion criteria, handling of participant withdrawals, and premature termination or suspension is located on page 11. The screening procedures are found on page 14.

Vulnerable Populations:

- ☐ Children
- ☐ Pregnant women/Fetuses/Neonates
- ☐ Prisoners
- ☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
- ☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
- ☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
- ☐ Serious health condition for which there are no satisfactory standard treatments
- ☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
- ☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
- ☐ Undervalued or disenfranchised social group
- ☐ Members of the military
- ☐ Non-English speakers
- ☐ Those unable to read (illiterate)
- ☐ Employees of the researcher

☒ Students of the researcher

☐ None of the above

*6.1* Additional Safeguards:

Students and patients of study team members will have equal opportunity to participate if they elect to enroll and meet the inclusion criteria.

## 7.0 Local Number of Participants

*7.1* Local Number of Participants to be Consented:

A sample size of 30 in each group will have 80% power to detect a difference in means of 0.736 standard deviations using a two group t-test with a 0.05 level of significance. In addition, with an estimated 20% attrition rate, we may enroll up to 75 participants.

## 8.0 Local Recruitment Methods

*8.1* Recruitment Methods:

A U of M Institutional Review Board (IRB) for full or partial waiver of HIPAA and protected health information (PHI) will be requested for pre-screening.

As part of the pre-screening process, charts of patients of record at the U of M SoD will be reviewed for inclusion criteria. Participants who may be eligible to participate will have an invitation letter mailed to them or emailed requesting participation.

In addition, a follow-up phone call will me made 1-2 weeks after the invitation letter is mailed or emailed. All potential participants will have the option to opt out of participation.

Flyers will be posted on each floor of the U of M SoD with study participation and contact information. Also, patients currently receiving oral healthcare in the dental clinics may be approached by a study team member, their assigned student provider, or the attending faculty with a flyer inviting them to participate in this study.

Email may be used only after initial contact or with enrolled participant permission to use their email for questions or scheduling. Also, email communication may be used if an interested person contacts the PI first via email from the letter or the flyer.

The study will also be posted on the U of M Oral Health Clinical Research Clinicwebsite. This will allow recruitment of subjects from the surrounding

cities near Minneapolis or subjects that may be interested and are not patients of record at the U of M SoD.

See page 9-10 of the protocol.

*8.2* Identification of Potential Participants:

A U of M Institutional Review Board (IRB) for full or partial waiver of HIPAA and protected health information (PHI) will be requested for pre-screening. A HIPCO survey will be submitted. As part of the pre-screening process, charts of patients of record at the U of M SoD will be reviewed for inclusion criteria. Participants who may be eligible to participate will have an invitation letter mailed to them requesting participation. In addition, a follow-up phone call will me made 1-2 weeks after the invitation letter is sent. All potential participants will have the option to opt out of participation.

Interested participants may also self-identify in response to the flyer or invitation letter (Page 11 of the protocol).

- Information contained in private/protected records (mailing address) will be obtained from AxiUm only after IRB confirm PHI and HIPAA waiver to use for recruitment purposes.
- The PI will make initial contact with potential participants.

*8.3* Recruitment Materials:

Recruitment materials are described on page 10 of the protocol and uploaded in ETHOS.

*8.4* Payment:

A $50 prepaid ClinCard will be given to each participant at the conclusion of the one month and three month follow up visits. At the last visit, a $100 will be loaded in the ClinCard for completing all study visits. This is noted on page 15-16 of the protocol and in the schedule of events on page 29.

## 9.0 Withdrawal of Participants

Participant withdrawal and termination is outline in the premature exclusion criteria/participant withdrawal on page 11 of the protocol.

## 10.0 Risks to Participants

There are no risks greater than the risk of a regular dental visits. Risks are described on page of the protocol and in the informed consent form on page 6. In addition, research activities are in the protocol on page 14-16. All activities are the standard of care and minocycline HCl microspheres, 1 mg will be used in the context of the standard of care and FDA approved administration.

## 11.0 Potential Benefits to Participants

The potential benefits are on page 5 of the protocol.

## 12.0 Confidentiality

*12.1* Protecting Privacy:

Protections for confidentiality are on page 22 of the protocol. Protection of data are described in the protocol on page 22-24.

*12.2* Access to Participants*:*

Having access to dental records of enrolled/consented participants is needed to conduct the study and maintain the standard of care.

## 13.0 Compensation for Research-Related Injury

*13.1* Compensation for Research-Related Injury:

This study is not greater than minimal risk, however, details regarding a research injury is described on page 8 of the informed consent.

*13.2* Contract Language:

Below is the language from page 8 of the protocol:

What happens if I am injured while participating in this research?

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away.

## 14.0 Consent Process

The consent process is on page 14 of the protocol. The consent process and all study visits will take place at the U of M SoD Oral Health Clinical Research Clinic (OHCRC).

*14.1* Consent Process (when consent will be obtained): N/A

*14.2* Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

*14.3* Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

*14.4* Non-English Speaking Participants: N/A

*14.5* Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

*14.6* Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

*14.7* Adults Unable to Consent: N/A

## 15.0 Setting

*15.1* Research Sites:

A convenience sample of up to 75 participants from the University of Minnesota (U of M) School of Dentistry (SoD) or outside of the university (U of M StudyFinder website) will be invited to participate in this study. The goal is two groups of 30 participants. Participants in both groups will have four clinical visits over a 6 month period in the U of M SoD Oral Health Clinical Research Clinic (OHCRC). Page 13, 14 and 29 of the protocol.

*15.2* International Research: N/A

## 16.0 Multi-Site Research

N/A

## 17.0 Resources Available

*17.1* Resources Available:

It is feasible to recruit up to 75 periodontal patients from the U of M SoD. There is an abundance of patients of record that meet the inclusion criteria. In addition, patients from the U of M StudyFinder may participate.

The PI will have one full clinic day (8 am- 5pm) for research activities. The research assistant will have one and half days to recruit, manage study documents, and assist in research activities.

The OHCRC is located at the U of M SoD. It is a dental clinic and has a private room to conduct the informed consent process if potential participants elect a private room instead of a cubicle.

https://www.dentistry.umn.edu/research/centers-institutes-labs/oral-health-clinical-research-clinic

The U of M SoD is equip if a medical emergency occurred.

The M Health Clinical Research Unit (CRU) is located on the second floor and participants will be escorted to the blood draw visit.

There will be regular study team meetings on a monthly basis. See the monitoring plan on page 17-18 of the protocol.