Shaping the Indications for Periodontal Adjunctive Antibiotics in Dental Practice: A PBRN Clinical Trial

NIDCR Protocol Number: 22-043-E

NIDCR Grant Number: UH3 DE031129-02

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Version Number: 4.0

17 June 2024

Draft/Version Number	Version Date	Summary of Revisions Made:
1.0	22AUG2023	Final version for submission to IRB
1.0	18OCT2023	Edits in response to IRB questions
1.0	01DEC2023	Edits in response to IRB questions
2.0	19DEC2023	Edits to study windows and operational procedures
3.0	08APR2024	Edits to remove reference to PerioCalc App, update to the safety reporting in section 9.4.2, the addition of expected allergic reactions in section 9.3.2, and edits to participant eligibility criteria and operational procedures
4.0	17JUN2024	Edits to allow for the participant 1 year follow up visit to start at 10 month mark, reference to appendix B in the MOP removed, and changes made to not require medication bottle return to practitioner

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (GCP) (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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Signed: _____ Date: 07/04/2023

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Title: Professor & Assistant Dean of Clinical Research

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AMXM	Amoxicillin/Metronidazole
BoP	Bleeding on Probing
CAL	Clinical Attachment Loss
CDT 4341	Code indicative of scaling and root planing 4 or more teeth in a quadrant
CEJ	Cementoenamel Junction
CSI	Clinical Site Investigator
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
DQMP	Data Quality Management Plan
eCRF	Electronic Case Report Form
FFR	Federal Financial Report
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IPP	Individual Patient participant Package
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention to Treat
MOP	Manual of Procedures
N	Number (typically refers to patient participants)
NCC	National Coordinating Center
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
NSPT	Non-Surgical Periodontal Therapy
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHIP	Oral Health Impact Profile
OHRP	Office for Human Protections
PAAS	Periodontal Adjunctive Antibiotics Study
PBRN	National Dental Practice-Based Research Network
PD	Probing Depths

PHI	Protected Health Information
PI	Principal Investigator
PNC	Principal Node Coordinator
PO	Program Official, NIDCR, NIH
PROM	Patient-Report Outcome Measure
PS	Project Scientist, NIDCR, NIH
Q8h	Every 8 hours
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SRP	Scaling and Root Planing
UP	Unanticipated Problem

PROTOCOL SUMMARY

Title:

Shaping the Indications for Periodontal Adjunctive Antibiotics in Dental Practice: A PBRN Clinical Trial (PAAS)

Précis:

Periodontitis is a bacterial inflammatory disease and antibiotic use is being empirically used as part of its treatment. However, a clinical practice guideline on periodontal treatment adjuncts published in 2015 identified weak evidence on the use of systemic antibiotics and large heterogeneity across small scale studies, suggesting that larger pragmatic clinical trials would benefit clinical decision making. This will be a prospective, randomized, placebo-controlled trial, stratified by practice and practitioner. The study will investigate the effectiveness of adjunctive antibiotics as adjunct to scaling and root planing (SRP) compared to SRP with placebo for the treatment of generalized stage II-III, grades A-C periodontitis in approximately 544 patient participants from about 34 National Dental PBRN practices. Periodontal data will be collected at baseline, re-evaluation (6 weeks), and final (12 month) study visits. Changes in periodontal clinical and patient-reported outcomes will be assessed to determine the effectiveness of SRP plus adjunctive systemic Amoxicillin / Metronidazole antibiotics (AMXM) versus SRP with Placebo.

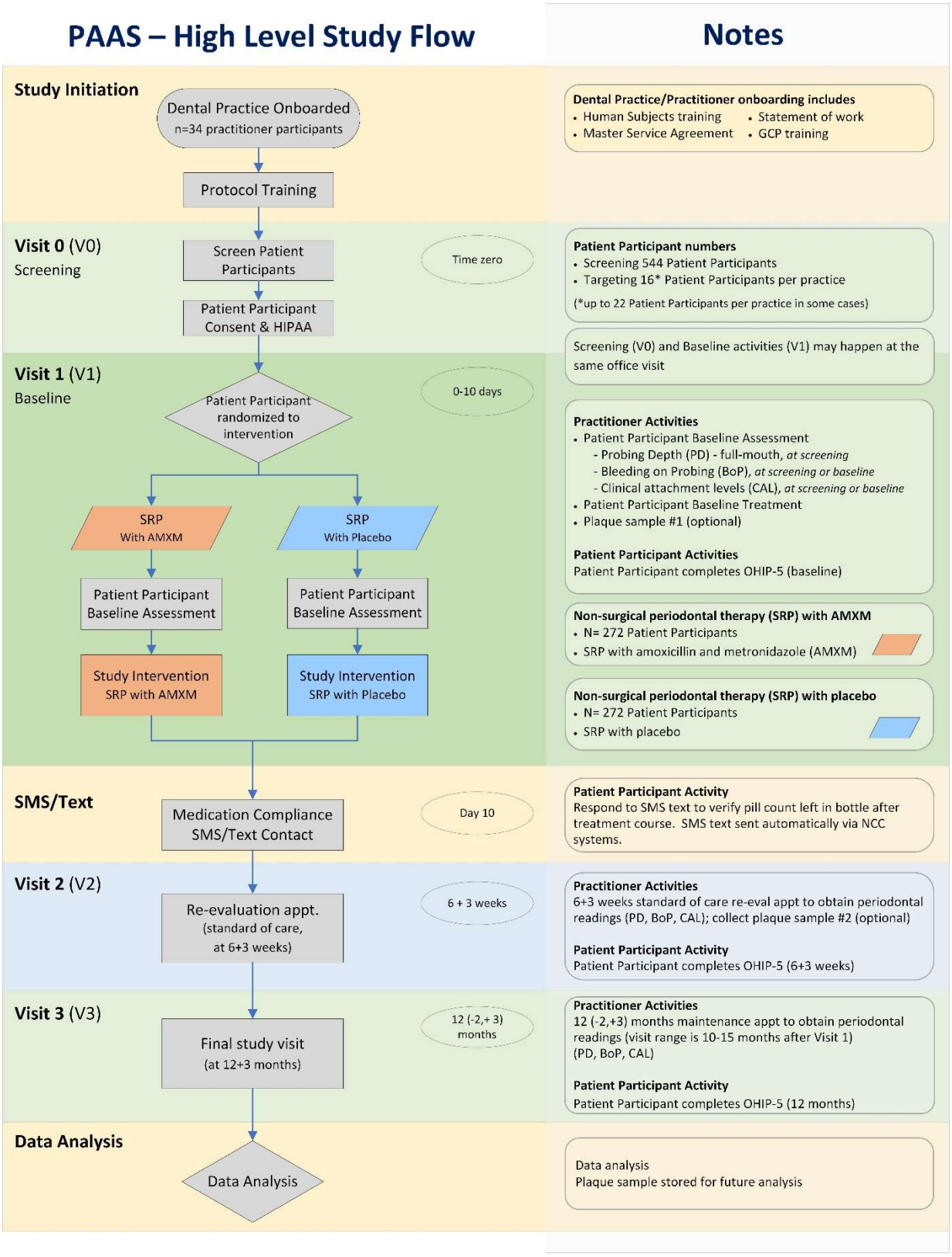
Objectives and Outcomes:

Primary: The primary objective will assess the effectiveness of SRP plus adjunctive antibiotics compared to SRP with placebo in periodontitis individuals from baseline to 6 weeks and 12 months following non-surgical periodontal therapy (NSPT) as determined by changes in site-level periodontal probing depth (PD).

Secondary: To assess changes in: i) gingival inflammation (measured by bleeding on probing (BoP)), ii) periodontal tissue attachment (measured by clinical attachment level (CAL)), iii) reduction in diseased sites (measured by remaining sites with maximum probing depth ≥5 mm), and iv) disease remission (measured by number of participants with ≤4 sites with PD≥ 5mm); comparing SRP plus AMXM to SRP with a placebo adjunctive in periodontitis individuals from baseline to re-evaluation (6 weeks) to final 12 month study visit following intervention. The patient-reported impact of periodontal treatment (measured by the Oral Health Impact Profile-5 (OHIP-5)) and treatment-related adverse events between groups will also be assessed.

Population:	The sample size will be a target of approximately 544 patient participants enrolled from approximately 34 National Dental PBRN practices. All patient participants are indicated to receive SRP and have been diagnosed with periodontitis stages II-III, grades A-C.
Phase or Stage:	Phase III Clinical Trial
Number of Sites:	Approximately 34 PBRN practitioner locations from across the Western, South Central, and Southwestern nodes.
Description of Intervention:	The intervention will involve either SRP, which is considered the standard of care treatment for debriding root surfaces, in conjunction with 500 mg Amoxicillin and 500mg Metronidazole orally every 8 hours (q8h) for ten days following SRP or SRP with placebo.
Study Duration:	34 months (including data system build and data analysis)
Participation Duration:	Approximately 12 months (range 10-15 months) - for patient participants, from baseline to final study visit.
Estimated Time to Complete Enrollment:	Approximately 6-8 months for patient participant enrollment.

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Periodontitis is among the most prevalent causes of years lived with disability among adults worldwide (GDB Collaborators 2020). Periodontitis is a bacterial inflammatory disease that has been reported to affect nearly 40% of Americans aged 30 years or older (GDB Collaborators 2020). If left untreated, periodontitis can lead to tooth loss and patient-perceived morbidity (Eke et al. 2018). Historically, antibiotic use has been an integral part of periodontal disease treatment. However, antibiotic stewardship calls for optimizing antibiotic prescribing to effectively treat infections, reduce antibiotic misuse, and prevent the development of antibiotic-resistant microbial strains (Dinsbach 2012, Doron & Davidson 2011, Sabtu et al. 2015). Since 2015, the American Dental Association (ADA) developed evidence-based guidelines limiting circumstances for prophylactic antibiotic use in dental practice (Sollecito et al. 2015, Lockhart et al. 2019); however, evidence regarding antibiotic use in the treatment of periodontal infections is considered weak because of substantial inconsistencies across small scale trials (Smiley et al. 2015). Further, existing trials are underpowered to assess the effects of disease- and patient-related factors to adjunctive antibiotic benefit, therefore, dentists are left to decide when adjunctive antibiotics are indicated, and which dental patients need them to achieve periodontal health (Smiley et al. 2015). In the context of periodontitis treatment, a biological rationale exists to support adjunctive antibiotic use to reduce periodontal pathogenic bacteria, but clinical trials assessing adjunctive antibiotic effectiveness have presented varying results depending on the study, sample population and disease characteristics (Hafajee et al. 2003, Hafajee et al. 2007, Teughels et al. 2020). Nonetheless, data from academic studies suggest that adjunctive systemic antibiotics may be beneficial for certain populations only, as the biological response to treatment is highly variable across individuals (Smiley et al. 2015). This marked variability warrants the identification of person and/or disease-related characteristics that are linked to maximum benefit from adjunctive antibiotic treatment. Consequently, guidelines may be established with tailored indications for their use with the goal of minimizing antibiotic misuse in periodontal treatment to avoid development of antibiotic resistance while optimizing outcomes (Garcia et al. 2013).

Persons diagnosed with periodontitis undergo non-surgical periodontal therapy (NSPT), a therapeutic regime that may include procedures such as scaling and root planing (SRP), adjunctive antibiotic prescription, and/or other antimicrobial treatments. Specifically, SRP alone is the most commonly employed form of NSPT and is considered standard of care treatment for periodontal disease (Badersten et al. 1981, Badersten et al. 1984, Cercek et al. 1983, Smiley et al. 2015). SRP entails the mechanical debridement of the root surfaces of teeth as part of periodontal treatment. The effectiveness of SRP is well documented, and a 2015 meta-analysis suggested that it leads to approximately a 0.5 mm average improvement in clinical attachment (Smiley et al. 2015). Nonetheless, in certain indications, such as in severe or aggressive periodontitis cases there may be a benefit to adjunctive systemic antibiotic administration in conjunction with SRP based on small-scale clinical trials (Bechara

Andere et al. 2018, Berglundh et al. 1998, Drisko 2001, Pihlstrom et al. 1984). These indications, however, are not compatible with the latest periodontitis classification system (Tonetti et al. 2018). Therefore, a gap in clinical translation exists.

Amoxicillin is a broad spectrum antibacterial of the penicillin family commonly used in the treatment of oral soft tissue infection. Metronidazole is also an antibiotic with higher efficacy for anaerobic bacteria associated with periodontal disease. In conjunction, AMXM have become the most used antibiotic adjunct in the treatment of chronic periodontal disease (Garcia Canas et al. 2015, Smiley et al. 2015). *In the present study, the test arm will receive SRP plus adjunctive systemic Amoxicillin / Metronidazole antibiotics (AMXM group); the control arm will receive SRP plus Placebo (Placebo group) without any active adjuncts.*

2.2 Rationale

Infection-related mortality caused by antibiotic-resistant bacteria has emerged as a leading cause of death for people of all ages, therefore appropriation of antibiotic usage only when they may be effective based on evidence-based clinical practice guidelines, is becoming a priority across medical disciplines (Doron et al. 2011). In 2019, the ADA developed evidence-based guidelines limiting circumstances for prophylactic antibiotic use for the management of endodontic infections (Lockhart et al. 2019). Nonetheless, a clinical practice guideline on periodontal treatment adjuncts published in 2015 identified weak evidence on the use of systemic antibiotics and large heterogeneity across small scale studies, suggesting that larger pragmatic clinical trials would benefit clinical decision making (Smiley et al. 2015, Oberoi et al. 2015). Two main limitations exist that impede the development of evidence-based guidelines with high level of certainty on the use of adjunctive antibiotics in the treatment of periodontitis. Firstly, existing trials assessing adjunctive antibiotic effectiveness have small sample sizes, primarily sampling from university clinic-based populations that may not fully reflect clinical practice conditions (Boia et al. 2019, Jentsch et al. 2016). Secondly, existing periodontal antibiotic effectiveness trials are based on older periodontitis classification systems that have now been superseded and were not designed to capture individual variability under the “umbrella” disease term of “periodontitis” (Tonetti et al. 2018). The current classification system of periodontitis was developed in 2017 at the World Workshop of Periodontics and it has been implemented in practice since 2018 (Tonetti et al. 2018). This system, now the only system recognized by the ADA and the American Academy of Periodontology (AAP), introduced an evidence-based periodontitis staging and grading system (Tonetti et al. 2018). Stages and grades of periodontitis capture individual variability within periodontitis phenotypes better and have paved the way for more personalized dental care (Papapanou et al. 2018).

To address limitations in evidence pertaining to adjunctive antibiotic use as part of NSPT, the study objective is to assess the effectiveness of systemic AMXM combination antibiotics as an adjunct to SRP (AMXM group) vs. SRP alone (Placebo group) in periodontal patients with Stages II-III, Grade A-C periodontitis who receive care in clinical practices within the National Dental PBRN. In brief, patient participants in

the AMXM group will receive a loading dose of Amoxicillin 500mg and Metronidazole 500mg followed by a self-administered dose (500mg) of the two drugs every 8 hours (qh8) for 10 days. This regimen was employed in a recent periodontitis clinical trial of forty-two adult patient participants and demonstrated a high safety profile with no drug-related adverse events (Ramón Gómez-Sandoval et al. 2020). Additionally, the present study will include effect modification analyses for sample subpopulations of interest, such as smokers versus non-smokers and groups with different rates of disease progression from more chronic (Grade A) to more aggressive (Grade C), in order to assess whether there may be benefit to adjunctive antibiotics targeted to specific populations.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks related to SRP

SRP is a non-surgical procedure that involves mechanical debridement of the roots of the teeth using dental instruments. This procedure may lead to root sensitivity, which may be transient or long term. It can also lead to gum recession and exposure of part of the root in the oral cavity. A periodontal abscess may form within days after SRP, which may cause pain and may require additional dental procedures for drainage. Patient participants will contact their dental practitioner if any adverse event including post-procedural pain, swelling, trauma, or bleeding has occurred.

Risks related to Amoxicillin and Metronidazole antibiotic intake

Antibiotic intake is associated with gastrointestinal adverse events such as fungal infections in the mouth or elsewhere in the body, nausea, and/or diarrhea. Women taking broad spectrum antibiotics are at increased risk of developing a yeast infection due to a reduction in healthy vaginal bacteria. Use of antibiotics may decrease the efficacy of hormonal contraceptives (birth control); use of a secondary method of birth control should be encouraged. It can also lead to adverse events including allergic / anaphylactic reactions. The possibility of adverse events (allergic reaction) will be mitigated with exclusion criteria that eliminate patients with a history of allergy or adverse effects associated with penicillin, Amoxicillin, or Metronidazole families of antibiotics.

Patient participants will also have a thorough review of their medication history to prevent adverse interactions with study medications.

After being administered antibiotics, patient participants will be monitored while in the office until treatment completion and discharge to determine if any adverse reaction has occurred. Patient participants who experience allergic or other adverse reactions due to study medications will be referred for immediate medical care as needed. The event of experiencing any severe adverse events with subsequent antibiotic doses is rare, and if that happens, the patients will call their dental provider. The research team will not routinely follow-up with the participants with a text or phone call. Drug-related adverse reactions will be a

reason for discontinuation of the drug as detailed in section 6. All prescribed treatments (outside of the study) will continue as planned.

Risks related to Placebo intake

This procedure (SRP) is routinely done using both methods tested in this trial: with or without antibiotics. Therefore, no physical risk is expected if the patients receive a placebo, as SRP is often done without antibiotics in clinical settings.

Risks related to subgingival plaque specimen collection

The collection of subgingival plaque for future microbiome analysis using paper points is minimally invasive since plaque is usually present and manipulated during SRP. No risks are expected beyond mild discomfort upon paper point insertion in the sulcus. All practitioners will undergo training on obtaining plaque samples with gentle pressure during insertion of paper points to mitigate risk. Samples will be kept in the study's repository in a -20 degrees Celsius freezer, which will include a temperature sensor with alarm to minimize any risk of sample loss due to bad storage.

Risks related to loss of confidentiality

As with any study, there is the potential for loss of confidentiality; however, appropriate precautions will be taken to mitigate this risk. These precautions include the use of unique study codes for patient participants, password-protected computers, and secure networks for data storage. Compliance with all Institutional Review Board (IRB) regulations concerning data collection, data storage, and data destruction will be strictly observed. Data will only be accessible to research study personnel and will be stored and coded according to Office for Human Research Protections (OHRP) guidelines.

2.3.2 Potential Benefits

The study patient participants will not have any direct benefit to their health beyond that of their planned periodontal therapy. The research may help advance periodontal care and may contribute to clinical guidelines for NSPT. No direct benefit to study practitioners is expected.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess the effectiveness of SRP plus AMXM compared to SRP with placebo in periodontitis individuals at baseline, re-evaluation (6 weeks), and final visit (12 months) following intervention.	The primary outcome of treatment effectiveness will be assessed by full-mouth probing depth (PD) at 6 weeks to 12 months post-intervention adjusted for baseline PD. These are considered universal, standard assessments used to determine periodontal status (Tonetti et al. 2018). A double-blinded patient participant-randomized design is used to assign patient participants to SRP plus AMXM versus SRP plus placebo prior to treatment.	**Outcome: Probing Depth (PD) in millimeters.** Full-mouth PD measurements (excluding 3rd molars) will be obtained utilizing a UNC 15mm periodontal probe. **Level of analysis: site** **Outcome Type: continuous**	Baseline, Re-evaluation (6 weeks), and Final study visit (12 months) after intervention.

3.2 Secondary

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess changes in periodontal tissue attachment comparing SRP plus AMXM to SRP plus placebo in periodontitis individuals at baseline, re-evaluation (6 weeks), and final visit (12 months) following intervention.	This secondary objective will be assessed by clinical attachment level (CAL) changes from baseline to 6 weeks to 12 months post-intervention, adjusting for baseline CAL. CAL is a disease-related characteristic. The assessment will employ a validated diagonal protocol (Vettore MV et al. 2007) including one maxillary and one mandibular quadrant to evaluate CAL.	**Outcome:** Half-mouth CAL in millimeters (excluding 3rd molars) will be obtained utilizing a UNC 15mm periodontal probe to measure base of pocket to cementoenamel junction (CEJ). **Level of analysis: site** **Outcome Type: continuous**	Baseline, Re-evaluation (6 weeks), and Final study visit (12 months) after intervention.

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess changes in the probability of bleeding on probing (BoP) at a given site comparing SRP plus AMXM to SRP with placebo in periodontitis individuals at baseline, re-evaluation (6 weeks), and final visit (12 months) following intervention.	This secondary objective will assess changes in the probability of observing BoP, a common surrogate for gingival inflammation, at 6 weeks to 12 months post intervention, adjusting for baseline BoP. The assessment will utilize a diagonal protocol (one maxillary and one mandibular quadrant) to evaluate BoP.	**Outcome:** BoP is assessed in conjunction with probing depths using a UNC 15mm periodontal probe and is recorded as a binary outcome per site, i.e., is the site bleeding? Yes/No **Level of analysis: site** **Outcome Type: binary (no/yes)**	Baseline, Re-evaluation (6 weeks), and Final study visit (12 months) after intervention.
Assess the reduction in diseased sites comparing SRP plus AMXM to SRP with placebo in periodontitis individuals at baseline, re-evaluation (6 weeks), and final visit (12 months) following intervention.	Reduction in diseased sites is a calculated variable from PD. We will assess the probability a site is observed with residual PD≥ 5 mm at 6 weeks to 12 months post-intervention, adjusting for its baseline PD. This is a common outcome related to the primary outcome (change in PD), which better reflects further treatment needs.	**Outcome:** PD≥ 5mm; The maximum probing depth per tooth will be recorded as ≥5 mm (yes/no). **Level of analysis:** site **Outcome Type:** binary (no/yes)	Baseline, Re-evaluation (6 weeks), and Final study visit (12 months) after intervention.
Assess disease remission between arms of SRP plus AMXM compared to SRP with placebo in periodontitis individuals at baseline, re-evaluation (6 weeks), and final visit (12 months) following intervention.	Disease remission is defined as the number of study patient participants who have ≤4 sites with PD≥5mm (Feres et al. 2020). This variable is calculated from PD≥ 5mm.	**Outcome:** Number of patient participants with ≤4 sites with PD≥ 5mm; Patient participants will be considered 'in remission' if they display ≤4 sites with PD≥ 5mm; This is a dichotomization from the summation of PD≥ 5mm within person. **Level of analysis:** person **Outcome Type:** binary (no/yes)	Re-evaluation (6 weeks), and Final study visit (12 months) after intervention.

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Evaluate patient-reported changes in oral health-related quality of life comparing SRP plus AMXM to SRP with placebo in periodontitis individuals at baseline, re-evaluation (6 weeks), and final visit (12 months) following intervention.	To evaluate oral health-related quality of life, the Oral Health Impact Profile (OHIP-5) will be utilized. The OHIP-5 is an abbreviated patient-reported outcome measure (PROM) that gauges oral-health related quality of life status (John 2022). This provides insight on the patient participant's perception of their individual oral health status.	**Outcome:** OHIP-5 sum score based upon self-reported responses. **Level of analysis:** person **Outcome Type:** continuous	Baseline, Re-evaluation (6 weeks), and Final study visit (12 months) after intervention.
Evaluate treatment - related adverse events. (Safety outcome)	The number and severity of adverse events related to SRP plus AMXM versus SRP plus placebo will be recorded to assess the safety of the intervention.	**Outcome:** Number of serious adverse events (SAEs) and adverse events (AEs) identified by practitioners at each study visit, or at unscheduled encounters related, probably related, or possibly related to study participation, during the study period. Documentation of SAEs and AEs will identify if the event was unexpected/expected and unrelated/related to study participation or the intervention, following relevant OHSP reporting procedures for SAEs and AEs.	Continuously throughout the study.

4 STUDY DESIGN

This is a patient participant-randomized, double-blinded clinical trial that will be conducted in three National Dental PBRN Nodes: Western, South Central and Southwestern Nodes. About 53% of fully participating (level 3) dentists in the National Dental PBRN are located in these three regions and reflect the wide demographic and practice setting diversity of the national membership. Currently, there are 451 active Level 3 dentists in the South-Central region, 540 in the Western region, and 716 in the Southwest region.
This research study will be conducted in the National Dental PBRN and will involve approximately thirty-four practitioners who will enroll a target of N=544 patient participants (a target of n=16 patient participants per practice). Patient participants will be randomly assigned to either AMXM or placebo, in conjunction with SRP as a single intervention. Randomization will be performed in blocks and stratified by practice to mitigate any inter-practice effects. AMXM is the most employed periodontal adjunctive antibiotic therapy based on existing studies (Smiley et al. 2015) and will be compared to non-active placebo.

Brief description of the study design:

- Intervention model: parallel arm, placebo-controlled, randomized clinical trial. Test arm (~N=272): AMXM group; control arm (~N=272): placebo group.
- Masking: practitioner- and patient participant-level masking. Statistician assessor will also remain blinded; a separate biostatistician will remain unblinded in order to implement randomization.
- Allocation: patient participant-randomized with randomization stratified by practitioner to mitigate inter-practitioner effects.
- Timepoints: Baseline visit* (intervention), re-evaluation visit (6 weeks post-intervention), and final study visit (12 months post-intervention).

**In case time does not permit completion of SRP at one visit, an optional second baseline visit may occur within 10 days of the first baseline visit.*

4.1 Practitioner recruitment

Practitioners will be recruited from three National Dental PBRN Nodes based on specific enrollment criteria including confirmation that they routinely treat patient participants with periodontal disease and have previously administered adjunctive antibiotics with SRP. Most state licensures require that a dentist diagnose periodontal disease, while a dentist or hygienist may perform SRP. Therefore, dentists and hygienists may be recruited and trained for the study depending on the division of care at each practice site (refer to study training slides for more information). Multiple practitioners may be

recruited from the same practice. Case report forms (CRFs) will indicate the type of provider (DDS vs. RDH).
Recruitment and rolling enrollment of practitioners is estimated to take approximately 3-6 months. Once trained, practitioners and office staff will begin to recruit and enroll patient participants. It is expected that each practitioner will enroll a target of 16 patient participants (up-to 22 patient participants) over a 4-6-month period of time. The entire data collection period for each practitioner is expected to be approximately 16-21 months. The study participation duration for patient participants is expected to be approximately 12 months (the expected range is from 10 months to 15 months). Study appointments (baseline, re-evaluation, and final study visit) are expected to add no more than 15 minutes to a typical appointment length of its type.

4.2 Patient participant recruitment

The patient participant population will be enrolled from National Dental PBRN practices without regard to sex, race, or ethnicity. Periodontitis diagnosis will follow the criteria established by the 2018 Classification of Peri-implant Diseases and Conditions. The study will enroll a target of N=544 adult patients aged 40 years, or older with an existing or new diagnosis of Generalized Stage II-III, Grade A-C periodontitis (previously Generalized Moderate to Severe Periodontitis) requiring periodontal treatment. At the time of screening periodontal status will be assessed to determine eligibility based on periodontal examination including probing depth, clinical attachment levels and patient participant characteristics, such as age, smoking and diabetic status according to the classification guidelines (Papapanou et al. 2018).

Intervention: Patient participants will receive conventional SRP (standard of care) with or without adjunctive antibiotics depending on group allocation (AMXM group versus Placebo group respectively). SRP refers to the procedure of mechanically debriding the root surfaces of teeth as part of periodontal treatment (Badersten et al. 1981).
The SRP procedure will be provided by the PBRN practitioners or their practices' hygienists. All patient participants will receive SRP; either the entire mouth will be treated at the baseline visit (visit 1) or if determined by the practitioner a second optional baseline visit (visit 1B) may be scheduled within 10 days of visit 1 to complete the SRP. In conjunction with SRP, the patient participants will receive adjunctive AMXM or placebo as the study intervention based on randomized allocation. AMXM is a combination antibiotic comprised of Amoxicillin 500mg and Metronidazole 500mg in two separate capsules. The intervention will be administered in-office starting with a loading dose (1g Amoxicillin and 1g Metronidazole, i.e. two capsules of each medication, or equivalent placebo) of AMXM or placebo followed by a self-administered 10-day course (See Section 6.2). The AMXM or placebo will be provided to participating practitioners in Individual Patient participant Packages (IPPs), labeled and shipped to participating

practices by the PI's local study team. The IPPs are packages containing all study supplies required for each patient participant including the study drugs, plaque collection supplies and shipping supplies (see MOP).

Data Collection & Analysis: Following randomization, practitioners will obtain periodontal clinical measurements and optional baseline plaque samples, and then proceed with the intervention; i.e., an antibiotic (or placebo) regimen will be initiated, and standard SRP will be performed. Changes in periodontal clinical and patient-reported outcomes (see protocol section 3 for description of outcome) will be assessed at re-evaluation (6 weeks + 3 weeks) and at the final study visit (12 months -2,+3 months; range is 10-15 months) post-intervention. Both disease-oriented clinical outcomes (probing depth changes, attachment level changes, bleeding on probing) and an abbreviated oral health-related quality of life patient-reported outcome (Oral Health Impact Profile-5 (OHIP-5)) will be assessed at all timepoints.

In terms of the dependent variables employed in the analyses, overall there are 5 recorded variables (PD, BoP, CAL, OHIP-5, and AE) and the rest of the variables are calculated from these variables. As discussed in section 3, reduction in diseased sites is a calculated variable from PD by PD≥ 5mm; the maximum probing depth per tooth will be recorded as ≥5 mm (yes/no). Further, the disease remission variable is defined as the number of study patient participants who have ≤4 sites with PD≥5mm (Feres et al. 2020). This variable is calculated from PD≥ 5mm as the patient participants that display ≤4 sites with PD≥ 5mm; this is a dichotomization from the summation of PD≥ 5mm within person. All analyses will be data-level, and changes in site-level dependent variables at each timepoint will be assessed using mixed models to account for the clustering of longitudinal observations (level1) within tooth site (level 2) within patient participants (level 3) and will include a random intercept to account for multi-practitioner effects. Additional information is detailed in section 12.

4.3 Biospecimen Collection

At the baseline visit, for practitioners who choose to do plaque sample collection, patient participants will be given the option to consent for plaque sample collection. Two subgingival plaque samples obtained from the periodontal sulcus will be collected at the baseline visit prior to SRP and at the re-evaluation (6 weeks +3 weeks) using paper points (DiaDent, BC, Canada), via a study-specific collection kit (additional sampling time: 2-3 minutes).

5 STUDY POPULATION

5.1 Inclusion Criteria

Practitioner criteria:

To be eligible to participate in this study, a National Dental PBRN **practitioner** must meet all the following criteria:

- Practice in the U.S. and possess a sufficiently stable patient population such that the practitioner estimates he/she can recruit approximately 16-22 patient participants within the enrollment period who are expected to remain in the practice for the 12-month study duration.
- Routinely perform periodontal assessments and therapy, periodontal care in their practices, and have prescribed a periodontal treatment adjunctive antibiotic at least once during the previous 12 months.
- Affirm that the practice can devote sufficient time for patient participant scheduling and treatment such as longer appointment times to complete study procedures in addition to routine care, or the option of a second baseline appointment within a week of the first baseline visit in case treatment / study procedures cannot be completed in a single session.
- Affirm to have available clinical personnel who can treat the patient participants, auxiliary personnel who will support the study administratively, and office personnel who will undergo human subjects training and study specific training as defined by their role.
- Does not anticipate retiring, selling the practice, leaving the study, or moving during the duration of the study.
- Agree to set aside space in the office during the study for secure storage of study materials and biological samples.
- Affirm office can connect iPad to wireless internet for data collection.
- Affirm that during the course of the study, the practitioner will not add any additional type of adjunct periodontal therapy to patients who participate in the study beyond those described in the protocol. This includes but is not limited to laser therapy, local antibiotic, or periodontal surgery.

Patient participant criteria:

The study will recruit a target of 544 patient participants presenting for periodontal treatment within the National Dental PBRN practices participating in this study.

To be eligible to participate in this study, a potential **patient participant** must meet all the following criteria:

- Adult who is at least 40 years old.
- Presence of ≥ 20 permanent teeth excluding 3rd molars.
- In good general health as evidenced by medical history (ASA Class I or II) per the practitioner.
- Planned to receive periodontal care for Generalized Stage II-III, Grade A-C periodontitis (previously Generalized Moderate to Severe Periodontitis) and a minimum of two quadrants of SRP (CDT code 4341) in practices participating in the National Dental PBRN.
- Willing to comply with all study visits and be available for the duration of the study (10-15 months)
- Willing to provide contact information for self, including a cellular phone number, and one to two emergency contacts to be reached for the follow-up visits and any other study-related matters for the duration of the study.

5.2 Patient participant Exclusion Criteria

A patient participant who meets any of the following criteria will be excluded from participation in this study:

- Known drug allergy to any antibiotics or anesthetics.
- Use of systemic antibiotics taken within the previous 3 months prior to enrollment.
- Medical condition which requires antibiotic prophylaxis prior to dental treatments/visits.
- Current use of medications that, in the opinion of the practitioner, may cause adverse effects with AMXM (such as disulfiram, warfarin, and oral contraceptives).
- History of any periodontal therapy (including SRP D4341, D4342) within the last 6 months prior to enrollment.
- Planned to receive any other type of adjunct periodontal therapy for the duration of the study (10-15 months). This includes but is not limited to laser therapy, local antibiotic, or periodontal surgery.

- Is currently pregnant or lactating per patient participant self-report.
- Is considered immunocompromised, in the opinion of the practitioner (including diseases and conditions such as HIV/AIDS, immunosuppressive drug therapy and/or radiation), or has chronic mucosal lesions (e.g. pemphigus vulgaris) affecting the gingiva.
- Has Diabetes mellitus with an HbA1c score of >/= 10% within the past 3 months as per patient participant self-report.

5.3 Strategies for Recruitment and Retention

Practitioner recruitment and retention

Practitioner recruitment: Practitioners enrolled in the National Dental PBRN who express interest in the study and meet eligibility criteria will be invited to participate. Eligible practitioners are recruited using multiple outreach methods used by the National Dental PBRN Administrative and Resource Center (ARC) and regional Node staff. Methods include but are not limited to Network social media posts announcing the study, email outreach to network members, targeted outreach from Node staff (such as group and individual emails, personal phone calls) to practitioners who provide periodontal services. Interested practitioners will be made “research ready” by being oriented to the Network and completing any institutionally required human subjects research protection training.

ARC and Node staff may also recruit dentists who are not currently enrolled in the Network who may be interested in the study, through presentations and conversations at professional meetings, and through mailed and email recruitment. Practitioners recruited in this manner will also be required to enroll in the Network and complete “research ready” requirements before participating.

Practitioner retention: Practitioner retention for the duration of their participation is addressed as part of study eligibility including sufficient and ongoing remuneration after completion of study milestones as described in the baseline, re-evaluation and through contacts and support from NC staff during the study.

Patient participant recruitment and retention

Patient participant recruitment: The study population will be enrolled from participating practices in the Western, South Central, and Southwestern regions of the National Dental PBRN. Our recruitment target is to enroll a sample population that is representative of the participating practices’ patients being treated for periodontal disease, by using a consecutive recruitment strategy during enrollment periods in each participating practice. Prospective patient participants may be recruited at any dental

appointment in a participating practitioner's office when it is determined that a patient participant will need periodontal care for Generalized Stage II-III, Grade A-C periodontitis.

The participating practitioners will screen eligible patient participants on a continuous basis using the PAAS Patient participant Screening process as follows:

Step 1: Identify periodontal patients who need to receive a minimum of two quadrants of SRP for periodontal treatment.

Step 2: Evaluate medical history (ASA status) and age inclusion requirements.

Step 3: Confirm that the rest of the eligibility criteria are met, via an electronic screening questionnaire, and as per the screening table below.

Patient participant eligibility Criteria

- At least 40 years of age
- ASA Class I or II
- ≥ 20 teeth, excluding third molars
- Needs periodontal care for Generalized stage II-III, Grade A-C periodontitis
- Indicated to receive SRP in a minimum of 2 quadrants with CDT code 4341
- If diabetic, HbA1c is ≤ 10%
- Willing and able to provide informed consent
- Is NOT currently pregnant or breastfeeding
- Does NOT have a known drug allergy to antibiotic or anesthetics
- No systemic antibiotics within the last 3 months
- No medical condition that requires antibiotic prophylaxis prior to receiving dental treatment

Patient participant Retention: We have estimated for 20% attrition at 12 months. Because the primary endpoint occurs 12 months following treatment and because periodontal patients are usually lifetime patients where maintenance visits are an integral part of periodontitis management, we believe the attrition rate is reasonable. To minimize loss to follow-up, we will work with the study management team at the NCC and regional Node staff to increase retention including study visit reminders to practitioners and patient participants.

5.4 Treatment Assignment Procedures

The treatment assignment procedures will be as follows:

1) The NCC unblinded statistician will create the randomization sequence, stratified by practitioner at each practice (AMXM versus Placebo groups). The allocation ratio between the two groups will be 1:1.

2) The NCC will e-mail the randomization lists to the PI's local packaging team to prepare the Individual Patient participant Packages (IPPs) according to the randomization sequence using sequential IPP IDs for each practice and the practice ID. The IPPs will include: 1) the active drug (AMXM) / placebo in

identical drug-safe vials, 2) plaque collection kits and 3) shipping packages for the return of the plaque samples, and 4) pre-paid return envelopes for unused drugs.

3) The PI's local study team will organize IPPs in the randomization order generated by NCC and ship the IPPs to the practices, ensuring that practitioners and their office staff are blinded. Patient participant packages will be assigned to enrolled patient participants when they present for SRP therapy within each practice. When the patient participant is registered into the PAAS data system, the link between the patient participant ID and the IPP ID will be established.

4) The PI and statistician will remain blinded to randomization procedures.

5.4.1 Randomization Procedures

Patient participants will be randomly assigned to the AMXM or placebo groups within each practice and stratified by practitioner at a 1:1 ratio. Randomization will occur prior to SRP treatment. A permuted block randomization scheme using blocks of 2 and 4, stratified by practitioner within each practice, will be employed. Practitioner-specific randomization lists will be generated by the NCC using "Sealed Envelope Ltd. 2022" (Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists software). The randomization code will be generated by the unblinded statistician at the NCC and provided to the PI's local team to prepare the IPPs, so that each IPP will be prepared and labeled with the packet identification number according to the randomization sequence. The individual randomization codes for each practitioner will be stored electronically at the NCC in secure password-protected database within the NCC system in accordance with NCC best practices. Access to the files will be restricted to the NCC biostatistician and designated NCC analysts. The NCC biostatistician will have access to group assignment in the event unblinding is required due to an emergency.

With a total of approximately 34 practitioners, each practitioner will enroll a target of N=16 patient participants to reach the final sample size of N=544 randomized patient participants. Based on experience with recruitment within the National Dental PBRN, the expectation is that some practitioners will not meet the target recruitment number. To account for this possibility and meet the target enrollment, the randomization list will be prepared by the NCC for N=22 patient participants per practitioner. The use of permuted blocks of 2 & 4 will promote balance both for randomization of either N=16 or N=22 patient participants per practitioner. The study team will be tracking patient participant enrollment and randomization and, in communication with the Node coordinators, practitioners who enroll and randomize the first N=16 patient participants will be invited to enroll N=6 additional patient participants for a total of N=22 patient participants, which will be the maximum enrollment per practitioner. Practitioners who

are willing to continue to participate in the study will receive an additional shipment of N=6 IPPs (see MOP for additional details).

After having completed study-specific training, all practitioners will receive N=18 IPPs corresponding to the sixteen patient participants that will be enrolled plus two "rescue" IPPs (one per treatment arm) to account for package corruption or misplacement. In case an IPP is missing, there will be a secondary randomization list available to identify the correct "rescue" IPP, wherein a matching packet in the auxiliary list will be assigned and allocated. The secondary randomization list will randomize four rescue IPPs; two will be included in the initial shipment and the remaining two will be shipped to the practitioner as needed with the shipment prompt being the use of a "rescue" IPP.

5.4.2 Masking Procedures

Patient participants will have a study ID assigned and will be randomized to AMXM or Placebo groups. All patient participants will receive SRP mechanical therapy based on treatment needs. All patient participants will receive AMXM/placebo in identical drug-safe vials with capsules identical in appearance to maintain practitioner- and patient participant-level masking. The AMXM will be provided in two separate drug-safe vials; bottle “A” with the Amoxicillin 500 mg (green capsules), and bottle “B” with the Metronidazole 500mg (blue capsules). Similarly, placebo will be provided in two separate vials, which will be identical to the AMXM vials; bottle “A” with the Amoxicillin Placebo (green capsules), and bottle “B” with the Metronidazole Placebo (blue capsules). The antibiotic bottles will be placed in the IPPs without any group allocation identifiers. Information on quantity and dosage is provided in section 6.

The instructions for using the investigational product will be the same for both treatment groups, ensuring the patient participant, practitioner and practice personnel will be blinded.

Key NCC study personnel (unblinded biostatistician, analyst, data manager and study manager) will be unblinded in order to implement randomization. The PI’s local study team will create and distribute the IPPs, but the NCC will hold the crosswalk to the patient participant ID numbers thereby maintaining blinding to the practitioners, patient participants, and the study team members and National Dental PBRN personnel who are blinded. Further, a research coordinator part of the PI’s local study team will be unblinded in order to put the investigational products in the IPPs and label the packets, while ensuring that the PI maintains blinding.

Group assignment will be traceable only by the key NCC study personnel who will be unblinded. Practitioners and office staff, patient participants, local study team members, and National Dental PBRN personnel will remain blinded unless unblinding is required for a specific participant due to an emergency.

Most emergency situations can be addressed by discontinuing the study drug without disclosure of group assignment. However, in rare circumstances for which knowledge of

the drug assignment is necessary for the treatment of a serious adverse event, the PI must discuss the situation with the NCC unblinded key personnel, prior to deciding whether or not to disclose treatment assignment. If disclosure of individual group assignment occurs, it must be made by the NCC unblinded key personnel who will communicate directly with the practitioner.

5.5 Patient participant Withdrawal or Discontinuation from Study Procedures/Intervention

5.5.1 Reasons for Patient participant Withdrawal or Discontinuation from Study Procedures/Intervention

Patient participants are free to withdraw from participation in the study at any time upon written request.

Patient participants may choose to discontinue the intervention or study procedures but continue to be followed for treatment in the practice.

The PI's study team may discontinue an individual's participation in an intervention but continue to be enrolled and provide trial data if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the intervention would not be in the best interest of the patient participant.
- The patient participant meets an exclusion criterion (either newly developed or not previously recognized).

The PI's study team may withdraw a patient participant from the study if:

- The patient participant fails to maintain appointments within a reasonable timeframe, i.e. If the second baseline visit has not happened within 30 days from the time of medication the patient participant is discontinued from study, and this will be considered as missing data.
- The patient participant can no longer be contacted, or patient participant has moved.

5.5.2 Handling of Patient participant Withdrawals from Study or Patient participant Discontinuation of Study Intervention

In the event that a patient participant chooses to withdraw or is withdrawn from the study, a patient participant termination form will be used to capture the date and reason for the withdrawal with no additional study data recorded. Patient participants who are withdrawn may continue to receive routine clinical care as a patient of record for the

treating dentist, but additional study data will not be collected. Data collected prior to study withdrawal will be used for the intention-to-treat analysis.

In the event that the intervention is discontinued, e.g., patient participant develops a persistent drug-related symptom such as diarrhea, prior to completing the intervention, the patient participant will continue to be enrolled in the study and the deviation from the intervention plan will be noted.

Patient participants who are withdrawn from the study after randomization will not be replaced.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documentation of the reason for study suspension or termination will be provided by the PI to all pertinent parties with an explanation for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patient participants.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6 STUDY INTERVENTION

6.1 Study Product Description

This trial will utilize the following products:

Amoxicillin 500mg: Amoxil (trade name; GlaxoSmithKline Pharmaceuticals, Philadelphia, PA) will be used in this trial. Amoxil received FDA approval in 02/27/1992 for treatment of bacterial infections. It belongs to the penicillin category, and it is a commonly prescribed broad-spectrum antibiotic.

Metronidazole 500mg: Flagyl (trade name; Pfizer, New York, NY) will be used in this trial. Flagyl received FDA approval in 9/9/2011 as an antibiotic for treatment of bacterial infections. Metronidazole is effective against anaerobic bacteria, and it is often combined with Amoxicillin for an enhanced antimicrobial effect.

Placebo: Capsules filled with inactive white powder, such as sugar or starch, compounded by Oakdell Pharmacy, and designed to produce a similar taste, texture, and color with the active drug. A separate placebo will be constructed for each of the active study drugs, i.e., one placebo identical to Amoxicillin and another identical to Metronidazole.

Product information from the package inserts is provided in the appendix.

6.1.1 Acquisition

Oakdell Pharmacy, 7220 Luis Paster Dr., San Antonio, Texas 78229 will provide Amoxicillin 500mg (green), Metronidazole 500mg (blue), and their matching placebo [Amoxicillin Placebo (green), Metronidazole Placebo (blue)] capsules. The compounding, filling, packaging, and labeling of study drug placebos will be done according to applicable regulatory requirements.
The compounding pharmacy will prepare the bottle “A” with the green capsules and bottle “B” with the blue capsules. The antibiotic bottles will be placed in a box labeled as “Antibiotics box” and the placebo bottles will be placed in a box labeled as “Placebo box”. The boxes will then be shipped to the PI and his study team, where they will insert the appropriate bottles into the IPPs based on the randomization sheet. The IPPs will be safely stored in a locked cabinet until they are ready for shipment.

6.1.2 Formulation, Packaging, and Labeling

6.1.2.1 Amoxicillin 500mg

Oakdell Pharmacy will procure Amoxil capsules, will empty the contents and then re-package the powder into non-identifiable green capsules that will match the placebo. The pharmacy will prepare 272 airtight drug-safe bottles containing 32 green capsules and will label them as bottle “A”.

6.1.2.2 Metronidazole 500mg

The compounding pharmacy will procure Flagyl capsules, empty the powder and re-package the powder into non-identifiable blue capsules that will match the placebo. The pharmacy will prepare 272 airtight drug-safe bottles containing 32 capsules and will label them as bottle “B”.

6.1.2.1 Placebo for Amoxicillin and Metronidazole

Placebo will be a matching non-identifiable capsule, green for the Amoxicillin 500mg Placebo and blue for the Metronidazole 500mg Placebo. The pharmacy will prepare 272 airtight drug-safe bottles containing 32 capsules of each placebo and will label the bottle with the green Placebo as bottle “A” and the one with the blue Placebo as bottle ”B”.

6.1.3 Product Storage and Stability

All products including placebo should be stored at room temperature (68° to 77°F) in an airtight container away from heat, moisture, and direct sunlight. The bottles will be provided to each practitioner inside the IPPs. Practitioners will be provided with instructions to store the IPPs until use and to keep away from direct sunlight.

6.2 Dosage, Preparation and Administration of Study Product

Study drugs will be formulated as capsules (green capsules for Amoxicillin 500mg and blue capsules for Metronidazole 500mg) and dispensed in two separate identical bottles, one of each drug (Bottle A and Bottle B, respectively) as mentioned above. Placebo capsules for Amoxicillin 500mg will be green, identical to the Amoxicillin 500mg capsules and Placebo capsules for Metronidazole 500mg will be blue, identical to the Metronidazole 500mg capsules, and will be dispensed in two separate bottles, similar to AMXM group to maintain care provider and patient participant masking. Two green capsules of Amoxicillin 500mg and two blue capsules of Metronidazole 500mg **(AMXM group)** or two green capsules of Placebo and two blue capsules of Placebo **(Placebo group)** will be given to the patient participants as a loading dose 30-60 minutes prior to initiation of the SRP procedure, because of evidence supporting greater benefit when antibiotics are given in conjunction with SRP (Kaner et al. 2007). A loading dose for the AMXM group will equate to 1g of Amoxicillin and 1g of Metronidazole. After the loading dose, each patient participant will be instructed to take one green capsule and one blue capsule every 8 hours for 10 days, in both AMXM and Placebo groups. Medication

bottles will not include any identifiers related to group allocation in order to maintain masking.

The identical labeling of the bottles between the two groups will ensure proper masking for the patient participants, the study staff, and practitioners administering the products.

6.3 Modification of Study Product Administration for a Patient participant

There will be no dose modification of the study product. If a participant is experiencing drug-related adverse events, they will be instructed to stop the drug and may continue to be followed for the remainder of the study.

6.4 Accountability Procedures for the Study Product

The PI's local study team will prepare the IPPs and label them with sequential IPP IDs for each practice as well as the practice ID. The IPPs will include the study product. The PI will then mail the IPPs to each of the participating practices with tracking numbers; shipment will be tracked by the PI's study team. The IPPs will include a paid return envelope for the practices to mail back the leftover study product to the PI, with the instruction to return the whole amount of leftover product to the PI when the 6-week re-evaluation visit for all patient participants within a practice has been completed. The PI will then safely dispose of the leftover product in a biohazard bin.

6.5 Assessment of Patient participant Compliance with Study Product Administration

Patient participants will be asked to return the medication vials to the dental office at their next visit (6-week re-evaluation) upon completion of the antibiotic / placebo regimen, at which time the practitioner will perform and record a capsule count and will safely store any unused capsules (see additional instruction in Section 6.4 above). For fidelity monitoring regarding compliance with product administration, patient participants will also receive a text inquiry regarding the number of remaining capsules in each bottle on day 10 and reminded to return the medication vials to the office at the re-evaluation (6 week) visit. The text response will be recorded by NCC and in case of a discrepancy between self-reported and practitioner-assessed capsule counts, the practitioner-assessed count will be considered as final data. If the patient participant misses returning their bottle at the re-evaluation visit, then a self-reported capsule count will be used for data entering. The training slides will emphasize the need to schedule the second baseline visit within 10 days of initial medication dispensing to ensure antibiotic coverage. Data may be collected within a 30-day time frame from initial medication dispensing, this will not be a protocol violation. If the second baseline visit occurs beyond 30 days from the time of the antibiotic / placebo administration, then the patient participant will be withdrawn from the study. The number of remaining capsules will be recorded, and all patient participants will be analyzed in the originally randomized group consistent with Intention-To-Treat (ITT) analyses principles.

6.6 Concomitant Medications/Treatments

Amoxicillin and/or Metronidazole may interact with other antibiotics, alcohol, disulfiram, and warfarin to cause adverse events. Practitioners will receive training to advise the patient participants during enrollment regarding the potential of interactions and discuss prohibited medications based on known contraindications (e.g., Lithium, disulfiram as well as substances such as alcohol). Patient participants taking the concomitant medications listed above will be excluded from the study (see exclusion criterion #4) prior to enrollment. Patient participants will also be advised to refrain from initiating a prohibited medication during the 10 days of the antibiotic intervention. After the 10-day intervention, the risk of an adverse event from a concomitant medication is extremely low. Therefore, concomitant medications/treatments will not be tracked for research purposes. No rescue medications will be given in this study.

6.7 Study Procedural Intervention(s) Description and Administration

The procedural intervention in this trial is SRP. As described above, SRP entails the mechanical debridement of the root surfaces of teeth as part of periodontal treatment (Badersten et al. 1981). The same procedural intervention will be applied to both arms by operators who will be blinded to the arm allocation of each patient participant. Based on state licensure and routine clinical practice of each dental practice site the SRP may be performed by either the dentist practitioner or by their hygienist. The “PAAS Baseline Visit Checklist” will capture data on whether a dentist or hygienist is completing the visit.

In the training slides it is suggested that all SRP procedures are performed with local dental anesthesia or Topical anesthetic (e.g., Oraqix); this information will be also captured in the “PAAS Baseline Visit Checklist”. Adequate completion of SRP will be determined with an appropriate calculus explorer as per standard clinical procedures, and relevant training is provided in the training videos. The intervention will be applied once at each involved quadrant either at the baseline visit or the optional second baseline visit with at least one quadrant completed at the first visit. The drug / placebo loading dose will be performed prior to SRP for the 1st baseline visit, regardless of the number of baseline visits. The second baseline visit should occur within 10 days of the initial baseline visit. If the second baseline visit has not happened within 30 days from initiation of the investigational product (drug / placebo), the patient participant is discontinued from study, and this will be considered as missing data.

7 STUDY SCHEDULE

Practitioner Training
Node staff will provide practitioners with the study information and instructions including the patient participant selection procedures, methods for approaching patient participants and obtaining informed consent (according to regional approvals), methods for data collection, and other study procedures. In addition, NCs will conduct remote or in-person protocol training with practitioners and staff prior to initiating the study. The training ensures that the practitioner and staff understand the study procedures and receive instruction on the consent process, electronic data capture systems, safety event ascertainment, recording and reporting, and other relevant procedures. The NCs will maintain close contact with the practitioners prior to and throughout the study implementation period.

The study schedule will proceed in the following stages on a rolling basis:
1) Each participating Node will enroll practitioners into the study to obtain a total of approximately 34 across three participating nodes. A reasonable balance across Nodes is preferred but not required. For each of the three Nodes, participating practitioners will be enrolled over a period of approximately 4-6 months.
2) NCC will create randomization schedules and the PI's local study team will put together the IPPs based upon the randomization schedules created by the NCC and mail them to the practices.
3) Practitioners will complete activities to be deemed study ready.
4) Practices will screen and enroll eligible patient participants into the study.

7.1 Screening/Enrollment

Screening/Enrollment Visit (Visit 0, Day 0)

Prior to consent we will assess the following information that already exists and/or is generally collected as part of a standard of care dental appointment; this information may be used to aid in identifying a potential patient:

- Review medical/dental and medication history to determine initial eligibility based on the existing demographic data, medical health history (including vitals and medications)
- Existing radiographs – to confirm periodontal bone loss
- Existing periodontal charting – to assess periodontal status (if previous chart exists)

If a patient is identified as a possible candidate for the study, the practitioner and/or staff may introduce the study. At the screening examination consent must occur prior to data collection and the initiation of any study-specific procedures. The practitioner and potential patient participant will complete the screening process. Once the potential patient participant passes inclusion/exclusion criteria, the practitioner and / or trained practice staff will complete the consent process and HIPAA authorization with the patient and provide patient participants with copies of patient participant information and HIPAA authorization sheets. If the patient meets the criteria and accepts enrollment, the contact form and the Patient Participant Demographics form will then be completed via the electronic tablet.

Subsequently the practitioner will complete a periodontal examination with periodontal charting. If the practitioner only records the probe depths (PD), they should also collect gingival recession (GR) at the deepest probing site to help determine periodontal staging and grading, which is necessary to ascertain study eligibility. Guidance on periodontal staging and grading can be found in the training slides.

The following sequence of activities will take place at the screening visit after obtaining consent:

- Obtain patient participant contact information and preferred method of contact to include at least a cellular phone number, e-mail and postal mailing address along with an alternate method of contact (e.g., alternate postal mail, email, telephone,).
- Obtain demographic information, medical/dental history, medication history, alcohol, and tobacco use history.
- Record history of allergy to medications including antibiotics.
- Record full-mouth Probing Depth (PD) at 6 sites: mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual per tooth using a UNC-15 periodontal probe. PD will be recorded in the practitioner's electronic health record system.
- OPTIONAL: Record half-mouth (Upper right and Lower Left quadrants) Gingival Recession (GR) at 6 sites: mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual per tooth using a UNC-15 periodontal probe either at this screening or at the baseline visit. In the case that GR is not completed at screening, GR charting must be completed prior to SRP at the baseline visit (see baseline visit section).
- OPTIONAL: Record half-mouth (Upper right and Lower Left quadrants) Bleeding on Probing (BoP) at 6 sites: mesiobuccal, buccal, distobuccal, mesiolingual,

lingual, distolingual per tooth using a UNC-15 periodontal probe either at this screening or at the baseline visit. If time does not permit, completion at screening, BoP charting has to be completed prior to SRP at the baseline visit (see baseline visit section).

- Verify study eligibility status and schedule / perform baseline study visit for individuals who are eligible and available for the duration of the study.
- Provide patient participants with instructions needed to prepare for first study visit. Patient participants will be allowed to continue using their toothbrush and toothpaste of choice as recommended by their dental provider.

The patient participant will then be scheduled for the baseline study visit. However, if time permits, the baseline visit may be combined with screening visit.

7.2 Baseline

Baseline Visit (Visit 1, Day 0 + 30 days*)

- Randomize the patient participant by selecting next IPP packet and recording assignment in the EDC system. (NCC)
- Access IPP and randomized drugs/placebo. (Office staff / practitioner)
- Record the patient participant ID (PPT ID) on the IPP box label for future use and cross-check in the EDC system. (Office staff / practitioner)
- Practitioner provides patient participant with the drug/placebo loading dose (1g of each drug / placebo). (Practitioner). Recommended time is 30-60 minutes prior to procedure. The dental office personnel will monitor patient participants for any symptoms after receiving the first study medication dose for the duration of the dental appointment.
- Patient participant completes baseline OHIP-5. (Self-reported)
- Practitioner collects optional subgingival plaque specimen. (Practitioner)
- In case they were not collected at the screening visit, practitioner records periodontal measurements (Practitioner):

  BoP will be recorded at 6-sites per tooth at half mouth using a prespecified half-mouth diagonal protocol and measured dichotomously as “0” (no bleeding), or “1” (bleeding).

  Gingival Recession (GR) will be recorded at 6-sites per tooth at half mouth using a prespecified half-mouth diagonal protocol and measured from the CEJ to the gingival margin in mm. Areas of gingival overgrowth above the CEJ will be

recorded as negative ("-") recession (see training videos). Clinical attachment levels (CAL) will be indirectly calculated by the formula CAL=PD+GR.

- Administer anesthetic and perform mechanical debridement (SRP) intervention on all study patient participants. (Practitioner)
- Record adverse events as reported by patient participant or observed by practitioner. (Practitioner)
- Practitioner hands the antibiotics / placebo drug-safe vials to the patient participant and provides instructions to take one capsule from each bottle every 8 hours (q8h) until gone. (Practitioner)

If the intervention is not completed in one visit, the practitioners will be asked to complete treatment within 10 calendar days of the initial baseline visit in an optional second baseline visit (1B) where SRP will be performed in any remaining quadrants.

Second Baseline Visit (Visit 1B, Visit 1 + 10 days)**

Second baseline visit should occur within 10 days of the initial baseline visit. If the second baseline visit has not happened within

days from initiation of the investigational product (drug / placebo) the patient participant is withdrawn from the study.

- Administer anesthetic and perform remainder of mechanical debridement (SRP) intervention on all study patient participants.
- Instruct to continue taking the antibiotics / placebo as prescribed every 8 hours until gone.

7.3 Medication Check (SMS text; Day 10)

An SMS/text will be sent to all patient participants 10 days from the baseline appointment with the following information:

- A request for a reply with capsule count.
- A reminder to return the bottles with remaining capsules at the next visit, which would be the re-evaluation.

7.4 Intermediate Visits

Re-evaluation (Visit 2, 6 weeks + 3 weeks)

- Record adverse events as reported by patient participant or observed by practitioner.

- Patient participant completes OHIP-5.
- Record patient participant's compliance with medication schedule by capsule count in the medication bottles. Practice will collect any returned leftover pills and mail them back to the PI's team in a provided pre-paid envelope after the practice has completed re-evaluation visits for all patient participants.
- Practitioner collects optional subgingival plaque specimen using paper points.
- Practitioner records periodontal measurements:
    - Probing Depth (PD) (full-mouth)
    - Bleeding on Probing (BoP) (half-mouth diagonal)
    - Gingival Recession (GR) (half-mouth diagonal)

      After the re-evaluation visit, the patient participant will continue care for their periodontal disease as is typical for the practitioner. During training, all practitioners will be asked to perform q3-4month maintenance visits as per their practice standards. The number of maintenance visits will be recorded on the Final Visit Checklist eCRF.

7.5 Final Study Visit

Final Study Visit (Visit 3, 12 months -2, + 3 months) (visit range 10-15 months)
Record adverse events as reported by patient participant or observed by practitioner.

- Patient participant completes OHIP-5.
- Practitioner/office staff records patient participant's compliance with standard of care maintenance visits (D4910).
- Practitioner records periodontal measurements:
    - Probing Depth (PD) (full-mouth)
    - Bleeding on Probing (BoP) (half-mouth diagonal)
    - Gingival Recession (GR) (half-mouth diagonal)
- Practitioner/office staff provides final instructions to patient participant (e.g., follow-up on ongoing adverse events)

7.6 Withdrawal Visit

If a patient participant withdraws from the study, the following is completed:

- Record date and reason for withdrawal.

- Record information needed to address a safety event that may have led to the patient participant's withdrawal from the study.
- No further information will be recorded after patient participant withdrawal request. Any information collected until that time will be used for the ITT analysis.

7.7 Unscheduled Visit

If a patient participant presents for an unscheduled visit as it pertains to the study (e.g., abscess or severe pain following SRP) except for maintenance visits (D4910), the following should be recorded: the date of the visit, the patient participant's chief complaint, and how the chief complaint was addressed.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

Prospective patient participants may be recruited at any dental appointment in a participating practitioner's office when it is determined that a patient will need periodontal care for Generalized Stage II-III, Grade A-C periodontitis. The practitioner or staff member will introduce the study to the potential patient participant and review inclusion and exclusion criteria via a study-issued tablet. If eligible and interested in the study, the potential patient participant will undergo the consenting process via the tablet, pursuant to IRB requirements. If an eligible potential patient participant declines participation in the study, this is noted on the eligibility form, and the informed consent process will not be completed.

All baseline, re-evaluation (6 weeks), and final study visit (12 months) data will be collected electronically via REDCap. At the end of each visit oral hygiene instructions will be provided to participants based on each practitioner's routine clinic practices. Periodontal charting data will be entered in each practitioner's preferred electronic health record software and a screenshot of the periodontal chart will be obtained as a digital file. The image file of the periodontal chart will then be uploaded on a secure HIPAA-compliant password-protected electronic image upload system through REDCap established by the NCC. Study staff will enter data from the periodontal chart image into the PAAS Electronic data capture system.

Practitioners

No practitioner data will be gathered beyond a practitioner eligibility checklist (Practitioner Screening Tool), which is only used to aid recruitment and is not entered into the EDC system. We will use existing or updated practitioner and practice data from the Enrollment Questionnaire, which resides in the practitioner database located on the NCC HUB. If needed to enhance recruitment, the NC's will extract practitioner information to identify likely eligible practitioners enrolled at Level 3 (full participation) for each Node.

For participating practitioners, we will collect information from the practitioner database on practitioner demographics (age, gender, race-ethnicity), primary practice setting (e.g., solo private practice, group practice, managed care, academic, public health, etc.) and location (region, state, zip code), practice type (general dentist, specialist, and dental hygienist), specialty training, year of dental school graduation, and frequency of NSPT performed. We also will collect available practitioner-reported percentages of patients by age group, race-ethnicity, and dental insurance type. Practitioners will be asked to review and update, if necessary, their practice information as part of becoming research ready.

Each participating practitioner is assigned a practitioner identification number (PID) in the database, which will be used to register practitioners in the study. The PID will then enable linkage to each practitioner's demographic and practice data for analysis.

Patient participants

Participant data recorded by the practitioner / office staff: medical/medication history and clinical data will be captured on eCRFs and through a periodontal software application, which will be screen shot and uploaded to the EDC, to include:

- Medical history: medical history at baseline appointment, to include allergies to antibiotics and anesthetics. Subsequent study visits- review and report any new issues as part of AE process. Counsel patient participants on the need for secondary forms of birth control for females, and the possibility of GI distress, fungal and/or yeast infections based on antibiotics used in the study. Current cigarette smoking and confirmation via self-report of last known HbA1c score at or above 10% , harmonized to groupings used by the AAP (Tonetti et al. 2018).

- Medication history: listing of current medications, both prescription and over the counter; recent antibiotic use, history of allergy to antibiotics. Only changes to medications related to AEs will be tracked and reported after the Baseline visit. Discuss prohibited medications based on known contraindications (e.g., Lithium, as well as substances such as alcohol). In case the patient participant is unaware of their complete list of medications at screening they will need to provide that at the baseline visit.

- Evaluate and assign ASA classification based on current guidelines at baseline.

- Periodontal assessment will be recorded at all study visits:

  - Probing Depth (PD) will be recorded at 6-sites (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual) around all teeth using a UNC-15 periodontal probe provided to all practitioners and measured as the distance from the gingival margin to the depth of the pocket in mm rounded to the largest integer (i.e., 4.5 reading will be recorded as 5 mm). If an examination within the last two months has been completed and documented, the PD will be verified with the UNC-15 probe.

  - Bleeding on Probing (BoP) will be recorded at 6-sites per tooth at half mouth using a prespecified half-mouth diagonal protocol and measured dichotomously as “0” (no bleeding), or “1” (bleeding).

  - Gingival Recession (GR) will be recorded at 6-sites per tooth at half mouth using a prespecified half-mouth diagonal protocol and measured from the CEJ to the gingival margin in mm. Areas of gingival overgrowth above the CEJ will be recorded as negative

("-") recession.

- Subgingival Plaque Specimen Collection (optional) will be collected from those who consent to specimen collection at the baseline and re-evaluation follow-up appointments. Firstly, the area will be isolated with a
- cotton roll and visible supragingival plaque will be removed from the sampling tooth with a sterile cotton pellet. Then, sterile paper points will be inserted at the bottom (junctional epithelium) of the mesio-buccal periodontal sulci of the upper right first and second molars for 15 seconds. If molars are absent, the first/second premolars are substituted. Samples will be placed in 1.5mL Eppendorf tubes and placed immediately in the pre-paid envelope for shipment to the study core lab, where plaque DNA will be logged, harvested, and stored.
- Safety events: Adverse events and unanticipated problems as reported by a patient participant or observed by a practitioner will be recorded on the appropriate safety event eCRF.

- Practitioners will attest that study medications and written instructions for their use were dispensed prior to patient participant dismissal.

Patient-reported data: Patient participants will complete an electronic version of OHIP-5 at all study visits. The OHIP-5 is a validated (Naik et al. 2016, John 2022), abbreviated patient-reported oral-health related quality of life measure.

8.2 Laboratory Procedures/Evaluations

8.2.1 Special Assays or Procedures

Optional collection of subgingival plaque will be performed to establish a periodontal plaque repository by adding a simple plaque collection step to the patient participant workflow. These samples will undergo DNA extraction and quality control at the PI's lab and will be used to form a periodontal plaque repository curated for future studies. The plaque samples will not be analyzed for the purpose of the present RCT. As a result, plaque sampling is optional for all patient participants and is not a requirement to participate in this study.

For plaque collection, following a previously employed method (Boutin et al. 2017) subgingival plaque will be sampled from the mesio-buccal site of the first and second molar of the upper right quadrant (substitution by first / second premolar, if absent). Briefly, the area will be isolated with a cotton roll and visible supragingival plaque will be removed from the sampling tooth with a sterile cotton pellet. Then, sterile paper points will be inserted at the bottom (junctional epithelium) of the mesio-buccal periodontal sulci of the sampling teeth. All paper points from a patient participant at a data collection visit will be placed in the same 1.5mL Eppendorf tube (Eppendorf North

America, Enfield, CT) and shipped ambient to the study core lab, where plaque DNA will be logged, harvested via bacterial DNA extraction, and stored.

8.2.2 Specimen Preparation, Handling, and Storage

After collecting plaque samples (if applicable) on paper points, they will be placed in 1.5 ml Eppendorf tubes and placed in a pre-paid envelope for shipment to the study core lab. The buffer is room temperature safe for up to one week to account for unforeseen shipping delays, but it is recommended to keep in a 4°C fridge.

Practitioners/office staff will be asked to ship the specimens in the prepaid envelopes within 48hours of receipt. Upon receipt, samples will be stored in -20°C until high throughput DNA extraction for quality control and long-term storage in the -80°C biorepository.

8.2.3 Specimen Shipment

Optional plaque sample collection will occur at the baseline visit and at the re-evaluation (6 week + 3 weeks) visit. Practitioners will be asked to ship samples with the provided pre-paid envelope within 48 hours of collection in the individual pre-labelled tubes and processed by the study lab facility. Confirmation of shipment will include the tracking number from the prepaid envelope.

Shipments are accepted Monday through Friday during business hours 8AM-5PM EST.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety monitoring for this study will focus on unanticipated problems (UPs) involving risks to study patient participants, including UPs that meet the definition of a serious adverse event (SAE). The practitioner will inform the patient participants about the risk and nature of adverse events during the consent process. In case of a SAE (anaphylactic reaction to antibiotics), the patient participants will be instructed during the consent process to call 911. The practitioner will also exclude patients if they meet the following exclusion criteria to minimize the risk of adverse events:

1. Potential participant has a known drug allergy to antibiotics or anesthetics.
2. Potential participant currently uses medications that may cause adverse effects with Amoxicillin/Metronidazole (AMXM) such as disulfiram, warfarin, oral contraceptives

Patient participants will contact their practitioner in case of an AE and the practitioner will address any patient participant needs or concerns regarding the AE. In addition, the practitioner will record adverse events (AEs) using a designated form and inform the node coordinator. The PI will monitor these events to grade severity, relationship to the study intervention and procedures, and assess whether the nature, severity, or frequency is unexpected. Safety data will be collected at all study visits through solicitation of adverse events from patient participants. Practitioners will record safety data on the Adverse Events eCRF and any questions should be directed to the Node coordinator.

Safety events will be recorded and reported into the National Dental PBRN safety event reporting system maintained by the NCC. Study PI will be informed via the safety event system when events are reported.

9.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to patient participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the patient participant population being studied.
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places patient participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with participation in the research, whether or not considered related to the patient participant's participation in the research.

Practitioners will record information about the adverse event from the patient participant. The study PI should review the report and confirm the practitioner's assessment on whether it identifies the adverse event as being:

1. unexpected
2. related or possibly related to participation in the research
3. serious or otherwise one that suggests that the research places patient participants or others at a greater risk of physical or psychological harm than was previously known or recognized

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the patient participant at immediate risk of death from the event as it occurred)
- Results in in-patient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Based upon appropriate medical judgment, the event may jeopardize the patient participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Details of UPs and AEs, including SAEs, will be recorded by the practitioner/trained office staff on eCRFs throughout the study. All events will be recorded with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) calendar days or 30 calendar days (for SAEs) after the last day of study participation. At

each study visit, the practitioner/trained office staff will inquire about the occurrence of AE/SAEs since the last visit. If a safety event has occurred, the practitioner/trained office staff will initially complete the safety event eCRF and then contact the NC, who can assist the practitioner in completion of the eCRF. Events will be followed for outcome information until resolution or stabilization.

9.3 Characteristics of an Adverse Event

Each event will be recorded on an appropriate case report form that includes assessment of the characteristics defined below. These characteristics, along with the frequency of an event's occurrence, will be considered in determining if the event is a UP.

9.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention, and/or
    b. There is a temporal relationship between the intervention and event onset and/or
    c. The event abates when the intervention is discontinued, and/or
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset, and/or
    b. An alternate etiology has been established

9.3.2 Expectedness

The Study PI and/or study-appointed, clinically/medically responsible individual will determine whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

The following are expected AEs that may occur with this research study:

a. Post procedural tooth sensitivity: Sensitivity is defined as specific or generalized tooth sensitivity or pain to air, temperature, or pressure that is a unique experience directly related to the previous procedure and may become apparent when local anesthesia is cleared.
b. Post procedural pain: This post-procedural pain is related to tissue discomfort or pain directly related to the previous procedure and may become apparent when local anesthesia is cleared.

c. Periodontal abscess: post-procedural deep pocket abscess can occur where epithelial (surface gingival) heals more quickly than deeper periodontal tissue causing a stricture (collar) to tighten around the tooth trapping sulcular fluid and building up pressure.

d. Nausea associated with antibiotic use: This can occur within several hours of the first dose of medication and may continue during dosing.

e. Allergic reaction: rash or itching

f. Allergic reaction: difficulties breathing

9.3.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number.
- a detailed description of the adverse event, incident, experience, or outcome.
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem.
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB as soon as possible or within 5 working days of the investigator becoming aware of the event.

- Any other unanticipated problem will be reported to the IRB within two weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made to NIDCR's centralized reporting system via Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: *rho_productsafety@rhoworld.com*

General questions about UP reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

9.4.2 Serious Adverse Event Reporting

Serious Adverse Events (SAEs) that meet the UP definition will be reported to NIDCR at the time of routine Medical Monitor Oversight Reports (MMOR) submission.

Any SAEs that also meets the definition of an Unanticipated Problem (UP) will be promptly reported to NIDCR. SAEs that also meet the definition of a UP will be submitted on an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: *rho_productsafety@rhoworld.com*

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231

- International: 919-595-6486

The node coordinator will work with the practitioners to complete a Serious Adverse Event Form and submit via fax or email as soon as possible or within 5 working days of the investigator becoming aware of the event. All SAEs will be followed until resolution or stabilization.

9.4.3 Reporting of Pregnancy

In the event an enrolled patient participant reports pregnancy during the intervention period when AMXM or placebo is being administered, they will discontinue the intervention and will remain enrolled in the study (e.g., will not be withdrawn) to allow for collection of outcome data including safety event data.

9.5 Halting Rules

No halting rules are planned for this protocol.

10 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the NIDCR Medical Monitor. The PI will submit a report every 6 months to the NIDCR Medical Monitor for review. This report will include data regarding enrollment and retention, unanticipated problems and protocol deviations, disposition of biospecimens, outcome measures, quality management findings and other relevant parameters. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

11 CLINICAL SITE MONITORING

No outside clinical site monitoring will be employed for this study. The Principal Investigator(s) and staff will closely monitor the subjects as they progress through the study. They will monitor and evaluate study processes and documentation based on the International Council for Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP), and internal quality management plans. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

Hypothesis: The use of AMXM as periodontal adjuncts will result in improved effectiveness of periodontal treatment as compared to placebo from baseline to re-evaluation (6 weeks) to final (12 month) study visit following intervention.

Secondary Hypotheses: The use of AMXM as a periodontal adjunct will result in improvements in measures of periodontal disease severity including clinical attachment loss, bleeding on probing, residual disease sites, remission (as defined in outcomes), as compared to placebo from baseline to re-evaluation (6 weeks) to final (12 month) study visit following intervention.

12.2 Sample Size Considerations

For the primary outcome, changes in site-level PD at each timepoint, preliminary estimates of the adjunctive effect of systemic antimicrobials are reported in the meta-analysis of studies that informed Clinical Practice Guidelines on the non-surgical treatment of periodontitis (Smiley et al. 2015). In this analysis, the estimated adjunctive effect of the intervention was approximately 0.4 mm. This is a relatively large clinical effect size (on par with the estimated effect of SRP alone). However, more modest effects could also prove clinically significant and as such, this study will be powered to detect an adjunctive effect of 0.2 mm.

Given the complexity of the correlation structure present in periodontal PD data, the variability in the number of probing sites a given patient participant presents with, and the variability of the correlation in sites depending on which teeth are present, a custom simulation was conducted to further explore the power of this design. In the simulation, patient participants are added to the study with a random number of existing teeth ranging from twenty to twenty-eight, with anterior teeth being added with greater probability than posterior teeth. In order to assign baseline PDs, a correlation structure was constructed in which sites on the same teeth are more highly correlated with each other and sites on different teeth are assigned a correlation based on the distance between them. Simulated baseline PDs are then added with an average depth of 4.5 mm. Similarly changes from baseline were simulated using a similar correlation structure with an average change of 0.3 mm being assumed for the placebo group, a 0.5mm in the AMXM group), and a standard deviation of 1 mm for both groups. This difference of 0.2 mm was chosen as it was determined to be a small but clinically meaningful difference. This synthetic data was then analyzed using the hierarchical model described in section 12.4. The simulation suggested that a sample size of N=220

per arm would be sufficient to achieve 90% power for detecting an average reduction of PD=0.2 mm. Sensitivity analyses were conducted which suggested that by choosing to design the study to a relatively high power of 90%, the design is likely to have adequate power of >80% even if the observed correlation in the study, observed average number of teeth remaining, or the positioning of remaining teeth deviate from that which was included in our initial simulation by a moderate amount. After accounting for a potential dropout rate of 20% and to distribute an even number of patient participants across thirty-four practitioners, the final total sample size would be N=544 or 272 per arm.

With a total of thirty-four practitioners, each practitioner will enroll N=16 patient participants to reach the final sample size of N=544. Based on experience with recruitment within the National Dental PBRN, the expectation is that some practitioners will under- or over-enroll. Thus, to account for this possibility and meet the target enrollment, the randomization list will be prepared by the NCC for N=22 patient participants per practitioner. The use of blocks of 2 & 4 will promote balance both for recruitment of either N=16 or N=22 patient participants per practitioner.

12.3 Planned Interim Analyses (if applicable)

No interim analyses are planned for this protocol.

12.3.1 Safety Review

No safety analyses are planned for this protocol.

12.3.2 Efficacy Review

No efficacy review is planned for this protocol.

12.4 Final Analysis Plan

Analysis Population: All analyses will be intent-to-treat, i.e., all participants who provide data at baseline will retain their original assignment regardless of the treatment received. All statistical tests will be evaluated using a two-tailed alpha level of .05 and will express precision using 95% confidence intervals.

Center Effects: The Primary analysis will account for variation between centers using a mixed effects model. The empirical Bayes estimate of center effects resulting from this model will be analyzed to assess the degree of heterogeneity between centers by assessing the magnitude of the variance of the random effects. This assessment will consist of a formal statistical test to determine if the variance of the random effect is greater than zero as well as an assessment of its estimated magnitude. If a clinically meaningful amount of variability between centers is detected, exploratory analyses will be conducted to attempt to identify covariates related to center effects including

geographic information, demographic information, and disease-related information. If these analyses identify meaningful subgroups among the centers, subgroups of sites will be created based on the potential for differential effectiveness. These subgroup analyses will be considered secondary and will be conducted in a manner identical to the primary analysis provided that the subgroups are of sufficient size to merit such an analysis. The specific data related to the characteristics of these subgroups, should they prove to exist, will be reported separately.

Primary Outcome Analysis: We will test the primary study hypothesis, which posits the AMXM intervention to be more effective than placebo in reducing periodontal probing depths, using a hierarchical linear model (HLM; aka mixed models, random coefficients regression). This analysis will account for the correlation between longitudinal observations within tooth site, within participants, and by practitioner, each of which can be represented within the model by a random intercept. The primary outcome measure, PD in mm, is effectively continuous, within a fixed range being necessarily positive and bounded above by the anatomy of the tooth in question. The model will include the fixed effect of time by using two dummy indicators representing re-evaluation at 6 weeks and final study visit at 12 months. The model will also include a binary indicator for arm (AMXM vs placebo) and an interaction between the indicators for time and study arm. Significance of either interaction term will represent a difference between the treatment and control arm at that timepoint, with the 6-week time representing efficacy and the 12-month time representing long-term efficacy/durability. No transformation of these variables is likely to be necessary.

It is not presently anticipated that boundary value problems or deviations in the residual distribution of the primary outcome will negatively impact the proposed analysis' operating characteristics due to the large size of the study. However, sensitivity of the analysis to these factors will be assessed using residual plots. In addition, potential site effects and the impact of any overly influential sites will be investigated by assessing the cluster-bootstrap stability of the analysis. Resampling analysis will be conducted stratified by person and site. The analysis will be conducted within each replication and the variability will be assessed in terms of statistical significance, clinically meaningful effect size, and the distribution of observed treatment effects. Any deviations impacting performance will be mitigated by modification of the primary analysis potentially to an approach utilizing the Huber-White sandwich estimator for the variance.

Analysis of Secondary Measures: The analysis of all secondary outcome measures will use similar hierarchical generalized linear models to those described in the primary analysis above. Analyses of all secondary measures enhance and further characterize any effect demonstrated by the primary endpoint as opposed to alternative efficacy measures. Therefore no adjustments for multiple comparisons are necessary nor planned.

For continuous outcome measures of CAL and OHIP-5 we will use the same analytical framework described for the primary outcome, consisting of a mixed effects linear model with random effects for site, patient and provider and fixed effects for time (indicators for 6-week, 12 months) and treatment including a treatment by time interaction. Significance of either interaction term will represent a difference between the treatment and control arm at that timepoint, with the 6-week time representing efficacy and the 12-month time representing long-term efficacy/durability. No transformation of these variables is likely to be necessary.

For the secondary binary outcomes of BOP and the presence of residual disease (tooth level), we will use the generalized extension of the HLM using a logit link and binomial family (aka multilevel logistic regression, random coefficients logistic regression). The terms included in the model will be identical to that described for the continuous outcomes above.
The secondary outcome of remission (participant level) differs from the others in that it is measured at the person level and that the model is not longitudinal given that there is no variability at baseline (i.e., all participants at baseline meet the criteria of this outcome as it is part of the inclusion criteria for participation). Thus, outcome will be evaluated using mixed effects logistic regression, with a random effect for provider and a fixed effect for treatment assignment. This will be conducted separately at re-evaluation (6 weeks) and final study visit (12 months). A significant and positive term for arm would indicate an effect of the treatment.

Key Subgroup Analyses & Analyses by Sex, Race and Ethnicity: In order to determine whether any key differences exist by age, sex, or race and ethnicity, analyses of each outcome will be conducted to assess if differences in the intervention effect are to be expected. For our regression analyses, this will take the form of the addition of an interaction term between treatment and subgroup, with a significant p-value suggesting a statistically meaningful difference between the effects experienced by the subgroups. Any significant differences will be examined to determine whether they are of a clinically significant magnitude and comparison of intervention effects will be achieved by reporting intervention effects and their confidence intervals separately for each sex and

for each race/ethnicity group. Further, the raw data will be summarized using boxplots (continuous) or bar charts (binary), stratified by subgroup to visually represent key differences should any be found. These analyses are supported by our randomization scheme which should result in relative balance of treatment assignment across subgroups resulting in unbiased effect estimates.
We will also perform secondary evaluations of the primary outcome measure to assess whether there is effect modification based on age and periodontitis stage and grade, which are key variables associates with periodontitis.

The analysis will consider the following variables:

- Race/ethnicity: non-Hispanic White, non-Hispanic Black, Mexican American, Other Hispanic, Other Race
- Age: continuous variable
- Sex: male or female
- Periodontitis Stage: II, III
- Periodontitis Grade: A, B, C

To test these potential moderators, we will adapt the model described for the primary outcome to include the moderator and product of the moderator and arm in the third level of the model for predicting all level 1 terms. A significant omnibus test based on a contrast would provide support for effect modification. We will probe the nature of any significant interaction by examining the pairwise differences in differences of the change (i.e., moderator X arm X time) and by plotting these values to facilitate interpretation.

Sensitivity of the analysis to model misspecification and potential site (provider) effects will be investigated by assessing the cluster-bootstrap stability of the analysis. Any deviations impacting performance will be mitigated by modification of the primary analysis potentially to an approach utilizing the Huber-White sandwich estimator for the variance.

Missing data

For all patient participants, we will attempt to gather follow-up information and reasons for dropout regardless of protocol completion and censor at the point of drop out. PBRN studies routinely attempt to collect reasons for dropout. We will compare baseline data between those with and without missing data and examine whether there are variables that are related to missingness. For each independent variable in the data set, the degree of missingness will be assessed. For key independent variables (demographics, and variables directly relevant to the analyses outlined above), variables with missingness will be dealt with using multiple (greater than or equal to 10) imputation by

chained equations and an appropriate variance will be derived using Rubin's rules (Azur et al. 2011).

Missing outcome variables will not be imputed for analysis. If for a given outcome variable less than 5% of the observations are missing, the missing observations will be dropped. If more than 5% of the outcome variables are missing and the study is positive (demonstrates a benefit for the treatment group over the control), subsequent tipping point analyses will be conducted to determine the potential influence of the missingness on the analysis. Tipping point analyses are used to determine how contrary to the observed data the missing data would need to be in order to reverse the findings of the study. This analysis will be conducted by fitting a predictive model to the observed study data and then using a modified version of that model to impute missing outcomes under progressively increased pessimism until the positive effect observed in the study is countered. This gives the reader an idea of how extremely contrary the missing outcomes would need to be in order to have been influential.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

NCC Study staff, dental practices and the PI's local study team will maintain appropriate medical/dental and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of patient participants. NCC Study staff, dental practices and the PI will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Data will generally be collected on eCRFs entered directly into the electronic data capture system, and consequently the eCRF will serve as the source document.

A summary of Source Data/Documents includes:

- Plaque biospecimen data will be entered into a registry maintained by the PI including the participant ID, collection timepoint and when available bacterial DNA extraction information. This registry will serve as the source document for the biospecimen data
- Consent forms via EDC
- Registration / Contact forms via EDC
- Medical/Dental History
- Study case report forms via EDC
- Periodontal measurements extracted from uploaded periodontal charts and entered into the EDC.
- Protocol deviation logs
- Safety event forms via EDC
- Participant withdrawal form via EDC

14 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Management (QM) is the overall process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control (QC), and quality assurance (QA) activities. Quality management processes involve review of consent procedures and CRFs for completeness, timeliness, and accuracy; if irregular trends or other ongoing issues are identified, virtual or in-person monitoring visits may be conducted. The NCC, with input from the study team and ARC, has developed a study-specific Data Quality Management Plan (DQMP) that sets up a continuous quality control process with the goal of reducing the turnaround time between error detection and correction. Refer to the DQMP for further details on the quality management plan.

The NCC will develop a data management system for study data collection and safety event reporting. Study progress and safety will be reviewed monthly by the PI utilizing reports provided by the NCC. The PI will maintain primary responsibility for reporting of safety events to ensure patient participant safety and reviewing protocol deviations and considering study modifications if needed to ensure data integrity.

Study data will be entered directly onto eCRFs by the practitioner/designated office staff or patient participant via the NCC-managed study-specific electronic data system. The EDC provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation; 3) access to study datasets that can be imported into common statistical packages; and 4) procedures for importing data from external sources.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The PI, study team, and ARC and NCC personnel will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the National Dental PBRN central IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the central IRB before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to patient participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the patient participant. Consent forms will be IRB-approved, and each patient participant is required to read and review the document or have the document read to him or her. The practitioner or designee will explain the research study to the patient participant and answer any questions that may arise. The patient participant will sign the informed consent document prior to any study-related assessments or procedures. Patient participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw at any time throughout the course of the study. A copy of the signed informed consent document will be given to patient participants for their records. The rights and welfare of the patient participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. No further data collection will occur for research purposes; any data collected prior to withdrawal will be used for missing data imputation.

The consent process will be documented in the clinical or research record.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

Any sex, gender, or racial/ethnic group of practitioners and patient participants (proportional to the composition of the participating dentist’s patient population) may participate in this study. However, as per the exclusion criteria, women who are currently pregnant or lactating may not be considered for this study. Children are excluded from this study, as it is atypical for this age group to exhibit stage II-III

periodontitis. Young adults <40 years will be excluded to eliminate rare cases of substantial periodontitis, which may be associated/ related to systemic diseases.

15.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to patient participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the study sponsor.

The study monitors or other authorized representatives of NIDCR may inspect all study documents and records required to be maintained by the PI, including but not limited to, medical records (office, clinic, or hospital) for the study patient participants. The clinical study site will permit access to such records.

Certificate of Confidentiality

To further protect the privacy of study patient participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (*https://humansubjects.nih.gov/coc/index*). As set forth in *45 CFR Part 75.303(a)* and *NIHGPS Chapter 8.3*, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the patient participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research patient participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

NIH Data Sharing Policies

As described in section 17, it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). PIs and funding recipient institutions will ensure that all mechanisms used to share data include proper plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research.

15.6 Future Use of Stored Specimens and Other Identifiable Data

Plaque biospecimens will be stored for the duration of the study in the laboratory of Dr. Kotsakis. Practitioners will be given the option to not collect plaque biospecimens as part of their study activities. Study patient participants will be given the option on the informed consent document to have plaque biospecimens collected and stored for future research. For those patient participants who have consented to future use of collected biospecimens, after quality control assessment, plaque biospecimens will be stored at -80C in the laboratory of Dr. Kotsakis. These samples will be used to build a periodontal plaque biorepository that will include samples from trial patient participants. This biorepository will be curated by the study team for future work on periodontal microbiome studies and personalized microbiome approaches to adjunctive antibiotic use by the authors or other researchers following permission.

The plaque specimens will be shipped by practice staff to the laboratory in pre-labelled envelopes provided to all practitioners. Upon receipt to the lab by local study staff, samples will receive unique identifiers consistent with the patient participant ID of the clinical trial for subsequent matching of clinical and microbiome results. Bacterial DNA will be extracted using previously described protocols (Bamashmous et al. 2021) and stored at -80C. The IDs will be entered in a log that will only contain study ID numbers and no other identifiers. The log will be curated by the PI and his local study team and stored in a password-protected computer with printed copies stored in a lockable cabinet for security. The linked file to the patient participant information for matching with the clinical trial data will only be accessible to the PI after trial completion and unblinding.

These stored samples will be kept long-term in -80C storage and might be distributed or used for future research studies without additional informed consent. The only identifiers associated with the plaque specimens will be age, sex, race, ethnicity, randomization group. Patient participants who do not consent to (e.g., opt out of) future use of plaque biospecimens will not undergo collection of the biospecimens for this study. If subjects wish to withdraw their biospecimens they may contact the NCC team at CHR-NDPBRN-HUB@kpchr.org. NCC team will have the identifiable patient information in their system and can link the participant ID to their names. The study team (PI's team) will not have this information.

Genetic testing will not be performed in this study.

16 DATA HANDLING AND RECORD KEEPING

The PI's local study team and the NCC data management team are responsible for ensuring the accuracy, completeness, and timeliness of the data reported. They will maintain adequate case histories of study patient participants, including accurate CRFs, and source documentation in collaboration with the NCC.

Only study personnel (i.e., PI, Co-I's, NCs, ARC, NCC personnel) will have access to the study data elements in the study database as described in Section 16.3 Types of Data. Study personnel will include those who are on the approved IRB study protocol. All study personnel will have completed the required training elements for human subjects' research certification.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the PI. All source documents must be reviewed by the PI's study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the PI or designee. Data quality will be assessed using measures such as time from study visit to data entry, time to resolution of data queries, number of missing forms, and proportion of all study variables queried.

16.2 Data Capture Methods

Study-specific electronic questionnaires will be developed to include fields for all data elements and will be translated into eCRFs, which will be entered in a secure EDC system. eCRFs will be used to obtain data from participating practitioners and patients at each study visit. Practitioner and patient participant eCRFs and OHIP-5 data will be captured through the NCC's electronic data capture system, as described in the study-specific data management plan developed and maintained by the NCC.

Data on periodontal charting (PD, BoP, GM, CAL) will be captured via each clinic's existing dental software application. The participating practitioner office staff will upload images of the periodontal charting to the EDC system. PI's study staff will review the images for readability and to confirm that PHI is limited to what is required for the study. The PI's local study team will access the images and enter them into a local data base which will be uploaded to the study EDC via REDCap.

The only biospecimen data that may be recorded will be the quantity of extracted DNA if quality control occurred for the sample, which will be kept in the biospecimen log and will be available for merging with the periodontal data using the patient participant unique IDs in cases where microbiome analysis will be performed. Note this data recording will be done at the PI's institution and will not involve the NCC.

16.3 Types of Data

There will be five recorded outcome variables, which will include:

- Periodontal measurements to include PD, BoP, CAL
- OHIP-5 questionnaire responses
- Safety event data

The rest of the variables are calculated from these variables.

16.4 Schedule and Content of Reports

Quality Control Reports: Regular QC reports will be available on the HUB for this study and will be viewable by the Study PI, their designates, NCs, the NCC Data Manager and the Study Managers. These reports are intended to help the NCs review all data issues that may require follow-up with the practitioners or patients. Specific reports for incomplete forms and missing forms as well as reports where data may not have been completed in the correct sequence (e.g., schedule of assessments) will be generated. The NCs will use these reports to work with the practitioners to rectify any erroneous or incomplete data.

Study Remote Quality Management Reports: Standardized Study Remote Monitoring reports will be created and posted to the study module on the HUB. These reports contain summarized data on enrollment, retention, protocol deviations, safety events, etc. These summary reports will be viewable by study team members, network staff, NCC staff and NIDCR.

Schedule and Content of Reports

Ongoing Data Review Meetings	Schedule	Content
Study team meetings	Weekly	Ongoing data review
Study Team PI with NIDCR PO Calls	Monthly	Ongoing data review
Study team biostatistician and analyst meeting with NCC	Monthly	Ongoing data review
Study Team PI and Executive Team	Quarterly	Study update
Medical Monitor reports	Bi-Annually	Study update

16.5 Study Records Retention

Study records will be maintained for at least three years from the date that the last grant federal financial report (FFR) is submitted to the NIH.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or Good Clinical Practice requirements. The noncompliance may be on the part of the patient participant, the investigator, or study staff. Protocol deviations will be assessed for their impact on safety, study operations, and data integrity. Appropriate corrective and preventive actions will be implemented, if warranted.

Consistent with investigator and sponsor obligations in ICH E6, study staff will document in study patient participant source documents and explain any deviation from the IRB-approved protocol. The PI will ensure reporting to the sIRB, according to their requirements, any deviations or changes made to eliminate immediate hazards to patient participants and any changes that increase risk to patient participants and/or significantly affect the conduct of the study.

At the time of each Medical Monitor review, all previously unreported PDs must be reported to the Medical Monitor independent of when they are reported to IRBs.

17 PUBLICATION/DATA SHARING

This study will comply with all applicable NIH Data Sharing Policies. See *https://grants.nih.gov/policy/sharing.htm* for policies and resources.

NIH Public Access Policy

The NIH *Public Access Policy* requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to *PubMed Central* immediately upon acceptance for publication. This ensures that the public has access to the published results of NIH funded research.

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

The study is a clinical trial and will comply with the NIH policy that establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results of these trials are submitted to ClinicalTrials.gov.

The Network's "National Dental PBRN Publications, and Presentations Policy" document is available at the network's public web site at *https://www.nationaldentalpbrn.org/publications/* .

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SUPPLEMENTAL MATERIALS

- Site Roster
- Manual of Procedures
- Calibration protocol (if applicable)
- Repository Instructions (if applicable)
- Case report forms
- Quality Management Plan
- Data Management Plan
- Clinical Monitoring Plan
- Statistical Analysis Plan
- DSMB or Oversight Committee Charter

APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

PAAS Schedule of Events

Procedures	**Screening/ Enrollment** (day 0)	**Baseline/ Visit 1a** (day 1)	**Opt. Visit 1b** (day 2-10)	**Medication Check (SMS text)** (day 10)	**Re-evaluation Visit** (6 weeks + 3 weeks)	**Final Study Visit** (12 months, -2,+3 months)	**Unscheduled Visit**	**Early Withdrawal**
Signed Consent Form	X							
Contact Information	X							
ASA Classification	X	(X)						
Periodontal Measurements	X	(X)			X	X		
Assessment of Eligibility Criteria	X	X						
Review of Medical/Dental History		X						
Review of Substance History & concomitant medications		X						
Randomization		X						
Study Intervention (Medication/Placebo Admin.)		X						
SRP Procedure		X	(X)					
Plaque Sample Collection (optional)		X			X			
Assessment of Adverse Events		X	X	X	X	X	X	X
OHIP-5 Self-report Survey		X			X	X		
Oral Hygiene Instruction (OHI)		X	(X)		X	X		
Capsule count				X	X			
Compliance with OSC visits						X		
Record Withdrawal reason								X

APPENDIX B: PACKAGE INSERTS FOR AMOXICILLIN AND METRONIDAZOLE

NDA 50-760/S-011
NDA 50-761/S-011
NDA 50-754/S-012
NDA 50-542/S-025
Page 3

AM:L30
PRESCRIBING INFORMATION

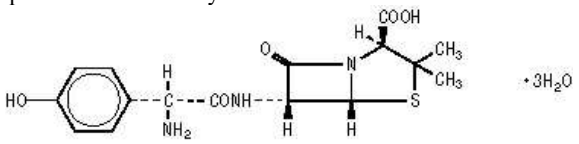
AMOXIL®

(amoxicillin capsules, tablets, chewable tablets, and powder for oral suspension)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AMOXIL (amoxicillin) and other antibacterial drugs, AMOXIL should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Formulations of AMOXIL contain amoxicillin, a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically, it is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. It may be represented structurally as:



The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \bullet 3H_2O$, and the molecular weight is 419.45.

Capsules, tablets, and powder for oral suspension of AMOXIL are intended for oral administration.

Capsules: Each capsule of AMOXIL, with royal blue opaque cap and pink opaque body, contains 500 mg amoxicillin as the trihydrate. The cap and body of the 500-mg capsule are imprinted with AMOXIL and 500. Inactive ingredients: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, and titanium dioxide.

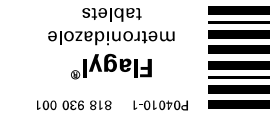
Tablets: Each tablet contains 500 mg or 875 mg amoxicillin as the trihydrate. Each film-coated, capsule-shaped, pink tablet is debossed with AMOXIL centered over 500 or 875, respectively. The 875-mg tablet is scored on the reverse side. Inactive ingredients: Colloidal silicon dioxide, crospovidone, FD&C Red No. 30 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

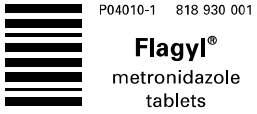
Chewable Tablets: Each cherry-banana-peppermint-flavored tablet contains 200 mg or 400 mg amoxicillin as the trihydrate.

Each 200-mg chewable tablet contains 0.0005 mEq (0.0107 mg) of sodium; the 400-mg chewable tablet contains 0.0009 mEq (0.0215 mg) of sodium. The 200-mg and 400-mg pale pink round tablets are imprinted with the product name AMOXIL and 200 or 400 along the edge of 1 side. Inactive ingredients: Aspartame*, crospovidone NF, FD&C Red No. 40 aluminum lake, flavorings, magnesium stearate, and mannitol.

*See PRECAUTIONS.

Powder for Oral Suspension: Each 5 mL of reconstituted suspension contains 200 mg, 250 mg, or 400 mg amoxicillin as the trihydrate. Each 5 mL of the 250-mg reconstituted suspension contains 0.15 mEq (3.36 mg) of sodium. Each 5 mL of the 200-mg reconstituted suspension contains 0.15 mEq (3.39 mg) of sodium; each 5 mL of the 400-mg reconstituted suspension contains 0.19 mEq (4.33 mg) of sodium.





Flagyl®

metronidazole tablets

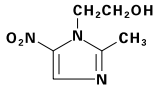
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Flagyl and other antibacterial drugs, Flagyl should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats. (See PRECAUTIONS.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications and Usage* section below.

DESCRIPTION

Flagyl (metronidazole) is an oral synthetic antiprotozoal and antibacterial agent, 1- (β - hydroxyethyl) - 2 -methyl - 5 - nitroimidazole, which has the following structural formula:



Flagyl tablets contain 250 mg or 500 mg of metronidazole. Inactive ingredients include cellulose, FD&C Blue No. 2 Lake, hydroxypropyl cellulose, hypromellose, polyethylene glycol, stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms, with an average elimination half-life in healthy humans of eight hours.

The major route of elimination of metronidazole and its metabolites is via the urine (60 to 80% of the dose), with fecal excretion accounting for 6 to 15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1- (β - hydroxyethyl) - 2 - hydroxymethyl - 5 - nitroimidazole and 2 - methyl - 5 - nitroimidazole - 1- yl - acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m^2.

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess *in vitro* bactericidal activity against most strains of anaerobic bacteria and *in vitro* trichomonacidal activity.

Metronidazole appears in cerebrospinal fluid, saliva, and human milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Following oral administration, metronidazole is well absorbed, with peak plasma concentrations occurring between one and two hours after administration. Plasma concentrations of metronidazole are proportional to the administered dose. Oral administration of 250 mg, 500 mg, or 2,000 mg produced peak plasma concentrations of 6 mcg/mL, 12 mcg/mL, and 40 mcg/mL, respectively. Studies reveal no significant bioavailability differences between males and females; however, because of weight differences, the resulting plasma levels in males are generally lower.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

Microbiology:

Trichomonas vaginalis, Entamoeba histolytica. Flagyl (metronidazole) possesses direct trichomonacidal and amebacidal activity against *T. vaginalis* and *E. histolytica*. The *in vitro* minimal inhibitory concentration (MIC) for most strains of these organisms is 1 mcg/mL or less.

Anaerobic Bacteria. Metronidazole is active *in vitro* against most obligate anaerobes but does not appear to possess any clinically relevant activity against facultative anaerobes or obligate aerobes.