Prophylactic Use of Antibiotics in Dental Practice

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the Code of Federal Regulations (CFR) on the Protection of Human Subjects (45 CFR Part 46), and the National Institute of Dental and Craniofacial Research (NIDCR) Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection 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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SIGNATURE PAGE- NETWORK STAFF

A copy of this page is to be signed by all Steering Committee members, Regional Coordinators, and other National Dental Practice-Based Research Network (PBRN) staff members responsible for conducting any portion of the study (if not already designated to sign the protocol above). The signature page should be printed, signed, then scanned into a PDF document and submitted to the Coordinating Center (NDPBRN-helpdesk@westat.com) for storage on the Internal Website.

The signature below constitutes:

1) acknowledgement of having read this protocol version (as indicated in the upper right corner of this page) and the attachments, and

2) an assurance that this individual will conduct all of his or her assigned study tasks 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 guidelines.

3) an assurance that this individual will read and follow all study plans applicable to his/her role on the study (e.g. Regional Coordinators will read and follow the Manual of Procedures (MOP), Practice Training Manual, Clinical Monitoring Plan, and other applicable plans developed in the future).

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Title: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AHA	American Heart Association
AP	Antibiotic Prophylaxis
CC	Coordinating Center
CFR	Code of Federal Regulations
CHS	Carolinas Healthcare System
CISO	Chief Information Security Officer
CMC	Carolinas Medical Center - Main Campus
FFR	Federal Financial Report
GPI	Grant Principal Investigator
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health Act
IE	Infective Endocarditis
IRB	Institutional Review Board
IS	Information Security
ISMP	Information Security Management Program
MOP	Manual of Procedures
N	Number (typically refers to participants)
NND	National Network Director
NIDCR	National Institute of Dental and Craniofacial Research, NIH
NIH	National Institutes of Health
NIST CSF	National Institute of Standard and Technology Cybersecurity Framework
OCTR	Office Clinical and Translational Research
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PCI-DSS	Payment Card Industry Data Security Standards
PJI	Prosthetic Joint Infection
QA	Quality Assurance
QC	Quality Control
RAS	Regional Administrative Site
RC	Regional Coordinator
SAE	Serious Adverse Event/Serious Adverse Experience
SMS	Survey Management System
SPI	Study Principal Investigator
UAB	University of Alabama at Birmingham
UP	Unanticipated Problems

PROTOCOL SUMMARY

Title: Prophylactic Use of Antibiotics in Dental Practice

Précis: Since the advent of antibiotics in the mid-1940s, and in particular with the first formal recommendations for antibiotic prophylaxis (AP) by the American Heart Association (AHA) in 1955, there has been a significant proliferation of the use of secondary AP in dental practice.[1-3] However, there is increasing controversy about the widespread use of antibiotics for some prophylactic, as well as therapeutic dental purposes, primarily due to concerns about antibiotic resistant bacteria and adverse drug reactions, weak evidence to support the practice of AP, and the costs and inconvenience associated with the use of AP. Consequently, this study aims to identify critical conceptual and standardization gaps in the practice and implementation of AP for patient populations felt to be at increased risk to develop infective endocarditis (IE) and/or prosthetic joint infections (PJI) prior to dental procedures. By surveying approximately 2,500 members of the National Dental Practice-Based Research Network, we expect to reveal some of the common tendencies and practices regarding AP by practitioners across the United States.

Objectives:

The primary objective of this study is to explore dentists' beliefs and behaviors related to antibiotic prophylaxis (AP) guidelines and prescribing practices to prevent local or distant site infection after dental treatment.

The secondary objectives of this study are to explore: Factors related to dentists' adherence to AP guidelines for the prevention of IE and PJI and their influence upon AP prescribing practices; dentists' knowledge about risks of bacteremia and the utility of using AP to prevent distant site infection.

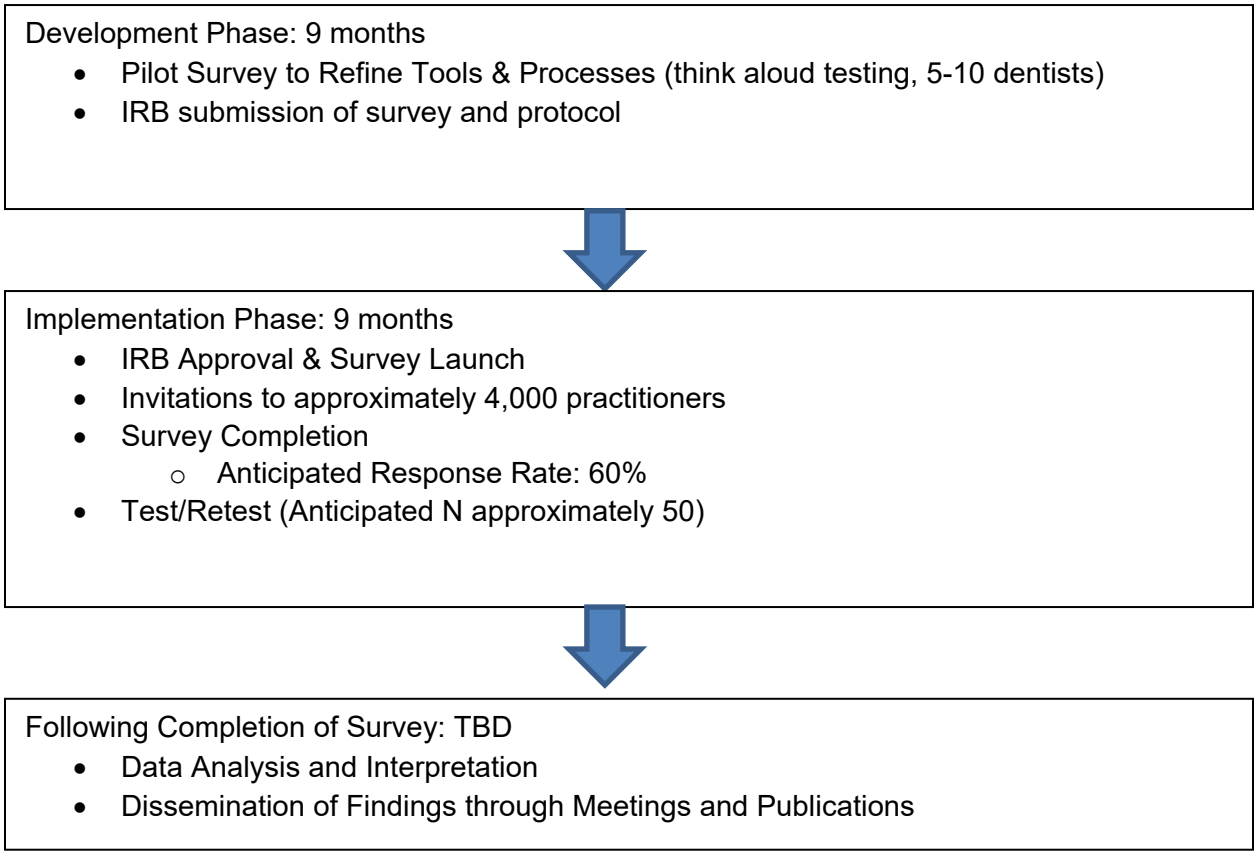
Outcomes: The primary outcome measures are dentists' a) beliefs, and b) behaviors related to AP guidelines and prescribing practices to prevent local or distant site infection.

The secondary outcome measures are: Official resources, professional colleagues, personal preferences, and patient factors related to dentists' adherence to AP guidelines for the prevention of IE and PJI and the influence of these factors upon likelihood to change AP prescribing practices; dentists' knowledge about risks of bacteremia and the utility of AP in preventing distant site infection.

Population: Approximately 4,000 dentist members of the National Dental PBRN with completed Enrollment Questionnaire data (N=4084 based on Completed Enrollment Questionnaires cumulative through January 7, 2017) will be invited to complete the online survey with the goal of obtaining a response rate of approximately 60% (*i.e.*, ~2400 respondents, or

	approximately 2,500 should the response rate be higher). Next, respondents who participated in the large survey will be invited to take the survey a second time for test/retest reliability purposes (Anticipated N = 50).
Number of Sites:	6 NDPBRN regions
Study Duration:	18 months
Practitioner Participation Duration:	One-time completion of survey (approximately 20 minutes). Approximately 50 participants will complete the online survey a second time for the purposes of establishing test-retest reliability.
Estimated Time to Complete Enrollment:	4 months

Schematic of Study Design:



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2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

Scope of the Problem: With the increase in antibiotic resistant bacteria, there is increasing worldwide concern about the widespread use of antibiotics for some prophylactic as well as therapeutic purposes. When antibiotic prophylaxis (AP) is used during an invasive procedure to prevent infection at the site of the procedure (e.g. during placement of a prosthetic joint or prosthetic heart valve), it is referred to as primary prophylaxis. When AP is used to prevent an infection distant to the site of the procedure (e.g., prevention of infective endocarditis from a dental procedure), it is referred to as secondary prophylaxis. The focus of this study is to determine the nature and prevalence of the use of AP for secondary prophylaxis to prevent infections distant from the mouth (Appendix).

For several decades, researchers have studied bacteremia resulting from a variety of dental procedures and these data have contributed to an emphasis on dental procedures as a primary source of transient bacteremia. In comparison, few bacteremia studies have been done for invasive medical procedures (e.g. gastrointestinal, otolaryngology).[1] A review of the literature for 15 of the more common patient populations felt to be at risk of developing an infection distant from the mouth found little or no scientific evidence to support providing secondary prophylaxis for any of these populations, except perhaps for the four cardiac patient populations defined by the American Heart Association (AHA) as “higher risk” (Appendix).[2-4]

The two most longstanding and controversial examples of AP for dental procedures are patients with specific cardiac conditions and those with prosthetic joints. With regard to the American Heart Association guidelines, there has been a gradual movement in the direction towards less antibiotic exposure (e.g., shortened period of coverage), fewer cardiac populations and fewer dental procedures indicated for AP. This culminated in 2007/2008 with significantly modified guidelines for dental procedures in patients with specific cardiac conditions from Guidelines Committees in the United States,[1] Europe,[5] and the United Kingdom (UK).[6] In 2007 the AHA guidelines dropped the “moderate risk” group, which represents about 90%[7] of cardiac patients recommended for AP prior to that time, now recommending it only for the remaining 10%, referred to as “higher risk” populations (Appendix). In 2008, the National Institute for Health and Care Excellence (NICE) in the U.K. revised their guidelines and eliminated the practice of AP for all cardiac patients.[6] The European guidelines were revised as well around this time and they are essentially the same as the AHA guidelines.[5] This significant discrepancy between NICE and the rest of the world has resulted in considerable controversy and concern as to the groups of people who may be at risk from dental procedures,[8] and this concern may be highlighted by a recent paper that points to a significant increase in the incidence of infective endocarditis in England since the NICE guidelines were put in place.[9] There has been a similar controversy with regard to which, if any, patients with prosthetic joints are sufficiently at risk to warrant exposure to antibiotics for any dental procedures.[2,7,10-14] The longstanding practice of using AP for every prosthetic joint patient before dental appointments for the patient’s lifetime changed in 1997 with Recommendations from a Joint Committee of American Dental Association (ADA) and American Association of Orthopaedic Surgeons (AAOS) to prescribe antibiotics for only two years following placement of an implant for healthy patients, and for life for a select group of medically compromised patients.[15] Then, in 2009, the AAOS put out an opinion piece that essentially recommended that the use of AP should return to the pre 1997 era of covering all prosthetic joints, and for the lifetime of the patient. As a result, selected representatives from the ADA and AAOS met again over a 2 year period and published new guidelines in 2012[4] that left clinicians and patients without clear guidance as to a definitive

prevention strategy.[13] The American Dental Association made an additional effort in 2015 to clarify this issue in the form of a new ADA Statement, essentially recommending against AP for all but a very few of these patients.[14] As a result of this 2015 ADA Statement, the AAOS proposed to the ADA that a new ADA/AAOS group be formed to develop "Appropriate Use Criteria" (AUC) to clarify for practitioners the contradictions between the 2012 guidelines and the subsequent ADA position Statement[15]. The outcome of this AUC was formally accepted by the ADA, but there was continuing concern that this 2017 AUC and the 2015 ADA Statement were imperfectly aligned. As a result, the ADA has created a clarifying Commentary that will be published in February 2017 in JADA.

Relevance to Dental Providers. The risks to individual patients and to society as a whole are significant, for example:

(1) There is increasing concern that the overuse of antibiotics is contributing to or causing major health problems such as antibiotic resistance. Leading public health authorities have stated that "Antibiotic resistance poses a catastrophic threat to medicine"[17] and that "we are at risk of returning to the pre-antibiotic era".[18] These authorities stress the importance of "using antibiotics appropriately and only when necessary",

(2) There is an ongoing concern about adverse drug reactions, to include anaphylaxis and infection with Clostridium difficile, although a more recent publication has contributed data that Amoxicillin is of little concern with regard to risk but that the use of Clindamycin needs to be re-evaluated.[18]

(3) There are widely varying opinions on and compliance with AP guidelines here and in other countries;[3,20,21]

(4) Even if AP was shown to be effective, a very large number of patients may need to receive prophylaxis to prevent one case of distant site infection;[1]

(5) With no randomized trials, the evidence to support the use of AP is controversial. However, a recent paper provides new evidence that could support use of AP;[9] and

(6) There is a significant financial cost and inconvenience associated with the use of AP in the dental office. It has been proposed that the cost for the routine use of AP drugs alone (amoxicillin and clindamycin) for 15 specific patient populations mentioned above would exceed $600,000,000 annually.[2,7] For all these reasons, there is considerable controversy surrounding AP.

2.2. Rationale

Although secondary AP is utilized in dental offices for multiple clinical scenarios, the nature of patient populations, the number of patients involved, and the frequency of use are unclear. In addition, it is not clear what guidelines dental practitioners use when making decisions about the use of AP for these varied patient populations, or the factors that influence their opinions and clinical practice. Consequently, the overall purpose of this study is to gain a better understanding of the opinions, knowledge base and clinical practice related to the use of AP for specific patient populations undergoing dental procedures.

2.3. Potential Risks and Benefits

This study consists of a cross-sectional, single time point self-report assessment of dental providers. The study (survey) will involve National Network dentists only and will not include patient recruitment. National Network member general dentists and specialists who are eligible to participate in Network surveys will be invited to participate without exclusion based on race, ethnicity, gender, or age.

2.3.1 Potential Risks

This study poses minimal risk to subjects. Study participation is completely voluntary and participants may discontinue participation at any time without prejudice. As with any study, there is the potential for loss of confidentiality. Appropriate precautions will be taken to mitigate this risk. These include the use of unique study codes for participants and 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 personnel and will be stored and coded according to guidelines set forth by the overseeing IRB.

2.3.2 Potential Benefits

There is no direct benefit to participating dentists but they have the potential to benefit from their reflection on their own knowledge of risk mitigation strategies in AP prescribing as they respond to items on the survey. As an indirect benefit to participation, knowledge obtained from the survey has the potential to guide content development for an educational intervention targeting risk mitigation strategies for AP prescribing in the dental setting. This survey is intended to collect information regarding existing clinical practices pertinent to the specific patient populations and dental procedures for which AP is prescribed. This data will be collected to explore the necessity of further training, additional research and considerations during the next AHA guideline revisions.

3. OBJECTIVES

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of this study is to explore dentists' beliefs and behaviors related to AP guidelines and prescribing practices to prevent local or distant site infection after dental treatment.

3.1.2. Secondary Objectives

The secondary objectives of this study are to explore:

- Factors related to dentists' adherence to AP guidelines for the prevention of IE and PJI and their influence upon AP prescribing practices.
- Dentists' knowledge about risks for bacteremia and the utility of AP in preventing distant site infection.

3.2. Study Outcome Measures

3.2.1 Primary Outcomes

All data will be collected via an online survey management system. The primary outcome measures are dentists' a) beliefs, and b) behaviors related to AP guidelines and prescribing practices to prevent distant site infection.

Beliefs about AP guidelines will be ascertained with survey questions that address the clarity of AP guidelines: AP regimens, patient populations for whom AP is prescribed, dental procedures for which patients receive AP.

Dentists' prescribing practice behavior will be ascertained with questions that assess:

- The types of patient populations for whom AP is prescribed
- Dentists' adherence to guidelines when prescribing AP
- Whether the dentist consults with the patient's physician/surgeon and/or defers to the physician's/surgeon's decision regarding the need for AP; who provides the AP prescription

3.2.2 Secondary Outcomes

The following secondary outcome measures will be ascertained:

- Official resources, professional colleagues, personal preferences, and patient factors related to dentists' adherence to AP guidelines for the prevention of infective endocarditis (IE) and prosthetic joint infection (PJI)
- The influence of official resources, professional colleagues, personal preferences, and patient factors upon dentists' likelihood to change AP prescribing practices for the prevention of infective endocarditis (IE) and prosthetic joint infection (PJI)
- Dentists' knowledge about risks for bacteremia
- Dentists' knowledge about the utility of AP in preventing infection

The survey data will be merged with coded National Network enrollment data. Data will include basic practice information and practitioner demographics provided in the National Network Enrollment data.

4. STUDY DESIGN

This survey questionnaire is a cross-sectional study that is limited to National Dental PBRN dentists who are currently practicing. Approximately 4,000 dentists will be invited to participate (approximately 2,400 respondents expected for an anticipated 60% average response rate, or approximately 2,500 maximum should the response rate be higher). All Network members, at the limited or full participation level, who are general dentists or specialists (N~992) in Endodontics, Periodontics, Prosthodontics, Orthodontics, Pediatric Dentistry, Dental Public Health, Orthodontics, and Oral/Maxillofacial Surgery will be invited to participate. Oral Pathologists and Oral Radiologists will **not** be invited to participate, as they are rarely involved with issues regarding AP.

Based on previous survey research within the Network, we anticipate an approximately 60% completion rate on average. Westat Coordinating Center will be responsible for randomly selecting dentists from within each Network region. Network regional quotas will help to ensure that each region has adequate representation within the survey.

Participation involves the completion of the practitioner AP Prescribing Practices survey. Dentists will complete the survey online through the REDCap survey management system, or upon special request a paper version can be mailed by a study team member at the Coordinating Center to the individual through standard United States Postal Service (USPS), and returned to sender upon completion via a pre-stamped, “no postage necessary” envelope that will accompany the hard copy. The return envelopes will be pre-addressed to the attention of Peter Lockhart, DDS (SPI), and data entry will be performed by one of the designated study team members at the Coordinating Center. The paper, or hard, copy of the survey will be identical to the web-based survey. Westat Coordinating Center will be responsible for providing the SPI with contact information (including active email addresses) for member dentists randomly selected for participation based on inclusion/exclusion criteria. Dentists will be invited via email. The AP Prescribing Practices survey data will be collected via an online survey instrument housed in the Carolinas Medical Center (CMC) REDCap survey management system (SMS).

Following the launch of the survey, approximately 50 of the initial survey responders will be randomly selected to complete the online survey again (approximately 2 weeks post initial completion) for test-retest reliability purposes.

Development and administration of the survey is detailed in *Section 7*.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

A participant must meet following criteria:

- Is enrolled in the National Dental PBRN as a limited or full network member;
- Is a dentist licensed in the U.S. and is actively engaged in practice.

5.2. Exclusion Criteria

A dentist practitioner meeting the following criteria will be excluded from the study:

- Endorses specialty practice *ONLY* in Oral Radiology or Oral Pathology.

5.3. Strategies for Recruitment and Retention

Eligible dentists will be identified based on the criteria noted from their responses on the Enrollment Questionnaire. To reduce time burden on the Regional Coordinators (RCs), dentists will be recruited in 3 waves, detailed in *Section 6.1*. All eligible dentists will first receive a study invitation email from the SPI explaining the study and inviting them to participate. The invitation will include a unique link to the electronic version of the survey and will clearly state the recommended timeframe for survey completion. Non-responding dentists will be sent reminder emails at approximately 10-14-day intervals after receiving the survey invitation email. The CMC Coordinating Center will send these 2 reminder emails prior to initiation of reminder contact by the designated RCs. Invited participants who have not completed the survey within 7-10 days after the second reminder will receive their third reminder email from the RCs. Invited participants who still have not completed the survey after these 3rd reminder emails will receive reminder contacts (e.g., phone, fax, email, postal mailing, etc.) from their respective RCs to prompt

participation coupled with a reminder of their unique survey link. Invited dentists who have not responded within approximately 10 weeks (from the date the survey was sent to them) will be considered non-responders, and their survey links will be deactivated.

During recruitment, email invitations will be sent in 3 large sample size waves and adjusted by following the response rates live in REDCap. Representative sampling of generalists from the 6 National Dental PBRN regions will thereby be achieved to arrive at approximately 2,500 total surveys for analysis. The size and composition of the first large sample size wave of invitations will be determined based upon pilot data from approximately 40 respondents (preliminary ramp-up launch planned in Timeline). The adjustments will be made using a random generator tool to reduce bias.

To minimize access to survey response data, the SPI will communicate with RCs regarding non-responders through the use of password protected excel spreadsheets that do not contain survey response data. The SPI will deliver updated completion reports to RCs on a regular basis to minimize unnecessary contact with invited participants who have already completed the survey. In addition, the SPI will hold regular Study Team calls to troubleshoot any issues that may arise with study recruitment efforts.

Dentists completing the survey will be remunerated with $50 delivered via email to their active email addresses or other means (e.g., postal mail) if required. This is a cross-sectional survey study; retention strategies are not applicable. However, approximately 50 participating dentists will complete the online survey a second time to establish test-retest reliability. Dentists completing the test/retest will be compensated an additional $50 for their participation.

5.4. Subject Withdrawal

5.4.1. Reasons for Withdrawal

Dentists are free to withdraw from participation in the study at any time upon request.

5.4.2. Handling of Practitioner and Patient Withdrawals

Dentists who withdraw from the study will not be replaced. **5.5. Premature Termination or Suspension of Study**

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the SPI will promptly inform the Institutional Review Board (IRB) and will provide the reason(s) for suspension or termination. Circumstances that may warrant termination include, but are not limited to:

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

6. STUDY SCHEDULE

6.1. Stage 1 - Survey Component: Enrollment/Baseline

- Eligible dentists will be identified from responses to National Dental PBRN Enrollment Questionnaire by Westat and will be randomly selected for participation based on inclusion/exclusion criteria; Westat will deliver contact information and selected Enrollment Questionnaire data to the SPI.
- Dentists will be invited to complete an online survey in 3 waves of increasing size to adjust for a balanced regional representation.
- Completion of the survey will indicate that practitioners have read informed consent information and will imply consent. A waiver of signed consent will be sought from the IRB.

6.2. Stage 2 - Retest of the Survey (See Section 7.2)

- Dentists randomly selected from among those participants who have completed the survey within the first two weeks of their survey launch wave will be sent a second online survey request by email approximately two weeks after the receipt of their first completed survey.
- Dentists will be informed that they have approximately one week to respond to the invitation for retest. If a selected retest participant has not completed their retest within this approximate one-week timeframe, the link to the retest survey will be disabled and a new potential retest participant will be selected from those having already completed the survey until a total of approximately 50 retests have been completed.
- Completion of the retest survey will indicate tacit consent.

6.3. Stage - 3 Merging Practitioner Survey with Enrollment Questionnaire

- Survey and Network enrollment data will be linked using participant IDs.
- Contact information will be removed from the final merged dataset and data will be stored/saved using Unique Participant IDs.

7. STUDY PROCEDURES/EVALUATIONS

7.1. Practitioner Survey Development

The initial draft of this survey instrument was developed with feedback from the initial study team (including clinical providers, dental researchers and survey experts) and underwent a cognitive “think aloud” process. We asked several (N=11) dentists to read the questions aloud and verbally express what they thought the question was addressing and how they reasoned through the response options. Additionally, we created two versions of the items - one sorted by hypothesis (i.e., content) and one sorted by cognitive demand and content. The latter form provided us the opportunity to see if we could reduce the cognitive demand of the total survey by arranging the items with respect to the way a respondent needed to think about a question. Historical questions, for example, were grouped together within a content area to ensure that once a respondent began thinking about what happened in the past, the effort to recall these past events could be reused (in effect) instead of immediately discarding the recalled events from working memory. This iterative development process has maximized dental practitioner input in an effort to increase the relevance of the survey and its findings to dentists. The finalized survey instrument was then piloted in its current online format using the REDCap electronic data capture tool for data collection and management.

7.2. Survey Testing-Retesting

The online version of the survey will be administered twice to a subset of approximately 50 dentists to assess the test-retest reliability of the survey. Dentists who complete the online version of the initial survey will be sent a second online survey request by email approximately two weeks after receipt of the first completed survey.

Retest participants will be randomly selected from among those participants who have completed the survey within the first two weeks of their survey launch wave. Dentists completing their initial survey participation will be entered into a randomizer application (randomizer.org). Once randomly ordered, the first listed ~25 dentists will be selected for invitation to the retest. Each dentist will be given approximately one week to complete the retest. If the retest is not completed within the timeframe, the link to the retest survey will be disabled and the next dentist on the randomized list will be contacted. This process will be continued until 50 dentists complete the retest.

7.3. Website and Survey Pilot Testing

The SPI and Study team will perform extensive internal testing of the REDCap survey, including internet browser compatibility. Study team members will also externally test the website prior to administration with study participants.

7.4. Survey Content

Topical areas addressed in the survey are detailed in Section 3. Some information will be collected from Westat and the National Dental PBRN Enrollment Questionnaire (e.g., demographics and practice characteristics) and will be linked to participants' responses to the study survey.

Survey Administration:
An initial study invitation will be sent to eligible dentists via email. The invitation will include information regarding the study and will contain a unique participation link to the survey embedded in REDCap. Dentists will be informed that the survey would ideally be completed in one sitting and that it will take approximately 20 minutes to complete. However, should participants need multiple sittings to complete the survey, they will be able to do this using the "Save & Return Later" feature within the REDCap survey. Should participants decide to "Save & Return Later," they will be able to return to the REDCap survey with their initial login information. Dentists re-access the survey using the unique survey link and will need to enter their login information to verify their identity and gain re-entry to their survey. Should dentists not be able to login, they will need to contact the SPI or their RC to receive new login instructions (possibly restart the survey instead of returning to the saved stage). Dentists will receive three email reminders to complete the survey. Those who do not respond to email invitations will be contacted by the RCs regarding their interest in study participation.

Dentists will be encouraged to visit the secure web site to complete the survey. If no feedback is received or the dentist does not complete the electronic survey after multiple follow up attempts over a period of approximately 10 weeks post-invitation, it will be assumed the dentist is not interested in the study. (See Schematic of Study Design).

8. ASSESSMENT OF SAFETY

8.1. Specification of Safety Parameters

Safety monitoring for this study will focus on unanticipated problems (UP) involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event (SAE).

8.1.2. Unanticipated Problems

The Office for Human Research Protections (OHRP) considers UPs involving risks to patients 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 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 patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2. Reporting Procedures

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. OHRP recommends that investigators include the following information when reporting an adverse event (AE), or any other incident, experience, or outcome as an UP 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 AE, incident, experience, or outcome;
- An explanation of the basis for determining that the AE, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs will be reported to the IRB and to NIDCR within 2 weeks of the SPI becoming aware of the problem.
- All UPs 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 SPI.

All UPs will be reported 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 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

9. STUDY OVERSIGHT

The GPI and SPI will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The SPI will review the survey data for safety concerns and data trends at regular (weekly) intervals, and will promptly report to the IRB and NIDCR any UP, protocol deviation, or any other significant event that arises during the conduct of the study.

10. CLINICAL SITE MONITORING

Clinical site monitoring will not occur for this survey study. The SPI is responsible for launching the survey and collecting data received as part of the survey. The SPI will ensure that the quality and integrity of study data and data collection are maintained. The RCs will be responsible for following up with eligible dentists who are considered non-respondents (see *Section 5.3*) to encourage study participation.

NIDCR reserves the right to conduct independent audits as necessary.

11. STATISTICAL CONSIDERATIONS

11.1. Study Hypotheses

The primary objective of this study is to explore dentists' beliefs and behaviors related to AP guidelines and prescribing practices to prevent distant site infection. The secondary objectives of this study are to explore: Factors related to dentists' adherence to AP guidelines for the prevention of IE and PJI and their influence upon AP prescribing practices; dentists' knowledge about risks for bacteremia and the utility of AP in preventing distant site infection.

11.2. Sample Size Considerations

All objectives of the current study are either descriptive or exploratory - rather than hypothesis testing - in nature. Therefore, standard sample size calculations based on anticipated effect sizes do not apply. However, based on a survey guideline report by Brinkman W-P *et al.**, our proposed sample size will allow us to perform statistical analyses for observed small to medium effect sizes (comparing general dentists to specialists, all categories included) and for medium to large effect sizes (specialist subcategories). Our sample size was selected based on the total number of dentists available as of January 7th 2017 (N=4002 including 3002 general dentists (GDs) and 992 specialists, excluding the category "other", see Table 1 below). Our 3-pronged recruitment approach will ensure comparable representation of both general and specialist dentists from all National Dental PBRN regions and minimize the margin of error to compare generalists with specialists overall or to compare some of the specialist subcategories (e.g. pediatric dentists vs. non-pediatric specialists). Table 1 below presents National Dental PBRN enrollment data for each region from Jan 7, 2017. Table 2 presents the number of invited participants and anticipated number of completing participants, per each dentist or region category with respective survey margins of error (MOE) at 95% confidence level. Proposed sample size allows for a margin of error of 3.15% (+/- 0.34 (SD)) on average per region (generalists and specialists combined),

0.05% for general dentists and 2.55% for specialists (all regions combined), at 95% confidence level. The online tool (https://www.qualityoutcomes.com/samplesize.aspx) was used to determine whether samples size per region or per specialty were appropriate to allow for minimal MOE possible.

* Preliminary version of: Brinkman, W-P (2009). Design of a Questionnaire Instrument, Handbook of Mobile Technology Research Methods, ISBN 978-1-60692-767-0, pp. 31-57, Nova Publisher.

Table 1. National PBRN Enrollment as of Jan 7th 2017

Region	Dentists all PBRN	Total Dentists w/o "Other"	GDs	SPs	Total SPs w/o Other	Specialists subcategories					
						Endo-dontist	Pediatric Dentist	Perio-dontist	Prostho-dontist	Oral/Maxillo-facial Surgeon	Ortho-dontist
1. Western	599	583	415	184	168	22	21	11	6	7	101
2. Midwest	494	481	350	144	131	19	23	17	12	8	52
3. Southwest	797	783	594	203	189	27	36	43	11	19	53
4. South Central	755	744	606	149	138	21	28	27	14	12	36
5. South Atlantic	585	577	446	139	131	20	20	19	18	4	50
6. North East	852	834	599	253	235	24	42	37	20	18	94
Total	4082	4002	3010	1072	992	133	170	154	81	68	386

Table 2. Sample size determinations per region and per specialty category (60%) response rate), 95% confidence level

Region	GDs	Sps	Total Size Region	MOE Region	Specialists subcategories					
					Endo-dontist	Pediatric Dentist	Perio-dontist	Prostho-dontist	Oral/Maxillo-facial Surgeon	Ortho-dontist
1. Western	249	100	**350**	**3.33**	13	13	7	4	4	60
2. Midwest	210	79	**289**	**3.65**	12	14	10	7	5	31
3. Southwest	356	113	**469**	**2.87**	16	21	26	7	11	32
4. South Central	363	83	**446**	**2.94**	13	17	16	8	7	22
5. South Atlantic	268	79	**346**	**3.34**	12	12	11	11	3	30
6. North East	359	141	**500**	**2.78**	14	25	22	12	11	56
Total Size Cat.	**1805**	**595**	**2400**	**1.27**	**80**	**102**	**92**	**49**	**41**	**231**
MOE Cat.	**0.05**	**2.55**	**1.27**	-	**7.00**	**6.20**	**6.59**	**9.00**	**10.00**	**4.10**

Final Analysis Plan

Two forms of missing data will be addressed by our analysis of main outcomes. First, we anticipate some degree (approximately 40%) of *total non-response*: dentists sent a unique survey participation link who do not respond/initiate the survey within the study period for a variety of reasons including refusal, non-contact, illness, death, or some other barrier preventing participation. Data missing due to total non-response will be addressed by the following approach: (1) We will describe characteristics of dentists who did not respond to the survey using data from their National Dental PBRN Enrollment Questionnaire; (2) We will then examine and report potential demographic (age, gender, ethnicity) and practice (specialty, practice location, primary practice setting) characteristic differences between respondents and total non-respondents; (3) If significant demographic differences emerge between respondents and non-respondents, sample-

weighting adjustments will be applied to the data; and (4) Main outcomes will be analyzed using both non-weighted and weighted datasets.

Second, we anticipate missing data due to *item non-response*: dentists participating in the survey who fail to provide acceptable responses to one or more of the survey items. Item non-response may occur as a result of a participant refusing to answer a specific item on grounds that it is too sensitive, he/she does not know the answer to the item, or he/she overlooks the item by accident. Items skipped due to planned skip-logic will not be coded as missing data. In instances where the non-response rate for an item is low (<5% of respondent sample missing for given item), pairwise deletion will be applied given that the amount of potential bias in univariate and bivariate analyses for that item will be small.[38] Also, in instances where the non-response rate for an item is non-negligible but the missing data is deemed missing completely at random (MCAR), pairwise deletion will be applied. However, in instances of non-negligible item non-response where the MCAR assumption is not valid and data are missing at random (MAR), multiple imputation procedures will be considered.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA / DOCUMENTS

Only study personnel (i.e., NND, SPI, Co-I's, RCs, CC personnel) will have access to the study data elements in the study databases (as described below). Source data for the study consist of the following: (1) Practitioner data from the Enrollment Questionnaire; and (2) Practitioner responses to the electronic AP Prescribing Practices survey.

Enrollment Questionnaire Data. Enrollment Questionnaire data will be provided to the SPI by the Westat Coordinating Center. Enrollment questionnaire data will be provided in a separate file from identifying/contact information. The contact information file and the Enrollment Questionnaire data file will be linked by the use of unique participant IDs. A file linking participant IDs with identifying information will be stored electronically in a password protected file on the CMC secure server network. The contact information file will be used as the basis for communication of study completion status between the SPI and the RCs. Password protected recruitment logs will be shared with RCs via the secure CMC file sharing service on a regular (approximately weekly) basis.

REDCap Practitioner Survey. Dentist participants will directly enter all practitioner survey data into the REDCap SMS. REDCap survey data will be stored in a coded dataset through the use of unique participant IDs.

Survey Closeout. Following close of survey enrollment, a cleaned and completed survey dataset will be merged with participants' selected Enrollment Questionnaire data provided by Westat at the outset of study implementation. A final, merged, cleaned, and coded dataset will be delivered to Westat for archival following the closeout of the study. In addition, the SPI will deliver a Study Participation report to Westat documenting the completion status of participants (e.g., complete, incomplete, refused, ineligible).

13. QUALITY CONTROL AND QUALITY ASSURANCE

For the QA/QC activities associated with data collection and processing, the SPI will specify which data QA/QC procedures will be provided. The procedures will include the development of automatic data quality checks in the SMS for the survey and the processes related to the data manual review, discrepancy management, data verification and approval, and database audit. The REDCap survey will be programmed with edit checks and response limiters to reduce data response errors.

The SPI will ensure that the electronic surveys are being collected appropriately and confidentially and will ensure completeness of data collected. Conference calls with the Study Team (and relevant RCs) will be held at least monthly during the practitioner questionnaire data collection phase to monitor recruitment progress and data completeness and troubleshoot any problems that may arise.

14. ETHICS / PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The GPI, SPI, and Co-Investigators will ensure that this study is conducted in full compliance 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.

14.2. Institutional Review Board

The UAB IRB for Human Use serves as the National Dental PBRN Central IRB and will review this protocol. If the local institution has decided to use the National Dental PBRN Central IRB review, the National Dental PBRN Central IRB is the IRB responsible for the review of the protocol. The National Dental PBRN Central IRB would then perform all future continuing protocol reviews and amendment (new protocol version) reviews. The Central IRB would also review unanticipated problems distributed by the Administrative Unit to local institution PIs.

Local institutions have the prerogative to use the National Dental PBRN Central IRB review or conduct their own local review. If a Regional Administrative Site (RAS) or other local institution elects not to use the National Dental PBRN Central IRB, the protocol, consent form(s) or waiver if warranted, recruitment materials and all participant materials will be submitted to the RAS or other local institution IRB (e.g. CMC) for review and approval. Approval (either centrally for those regions who agree to central approval, or regionally for those who do not) of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3. Informed Consent Process

A waiver of documentation of signed informed consent for practitioners who complete the electronic survey questionnaire will be requested. Consistent with regulations outlined by the National Dental PBRN Central IRB and CMC IRB, information about the study will be provided to eligible practitioners in an initial study invitation email as well as in the electronic questionnaire

prior to the start of the survey questions. Completion of the survey will provide a record of tacit consent.

14.4. Exclusion of Women, Minorities, and Children (Special Populations)

Racial and ethnic minorities are invited to participate in the study at least proportional to the composition in National Network dental practitioner membership. Individuals of any gender or racial/ethnic group may participate.

14.5. Participant Confidentiality

Practitioner confidentiality is strictly held in trust by the study investigators, study staff, and the sponsor(s) and their agents. 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 sponsor. Westat, who will be responsible for ensuring dental professionals completing the survey are remunerated $50, will be provided limited, but necessary survey data to fulfill the responsibility of appropriately directing practitioner payments to their desired address.

Participants will be assigned a unique identification number, which will be used to maintain study records and organize data transcripts. The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the study site.

15. DATA HANDLING AND RECORD KEEPING

The study team is responsible for ensuring the accuracy and completeness of the data collected. Only study personnel (i.e., GPI, SPI, Co-I's, RCs, CC personnel) will have access to the study data elements in the study database as described in *Section 15.3 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.

15.1. Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff. Dentist participants will directly respond to the electronic survey through the REDCap SMS, or return completed paper survey to sender. CMC will serve as the Data Coordinating Center (DCC) and will provide data management services for this study. The Carolinas Healthcare System Information Security Management Program (ISMP) is a multi-layered security program designed to provide in-depth defense that models that of the National Institute of Standards and Technology Cybersecurity Framework (NIST CSF). The NIST CSF was designed as a scalable cybersecurity framework based upon existing standards and best practices.

Carolinas Healthcare System (CHS) ISMP is designed to meet the regulatory requirements of the Health Insurance Portability and Accountability Act (HIPAA), the Health Information Technology for Economic and Clinical Health (HITECH) Act, the Payment Card Industry Data Security Standards (PCI-DSS), and the North Carolina Identity Theft Protection Act. A Chief Information Security Officer (CISO) oversees the ISMP. CHS also has a dedicated team of Information Security (IS) professionals to manage day-to-day operations of the program. CHS IS Team is responsible for ensuring that all computer systems containing confidential data pertaining to this project have the level and scope of security that meets, or exceeds, that established by the HIPAA Security Rules and the Office of Clinical and Translational Research (OCTR) at CHS.

The CMC data center in which the REDCap servers are housed has strict access control; rejecting and banning IP addresses of any user that is suspicious. Thresholds of use are set by administrators such that, should they be met, the user will be immediately and permanently banned from the application/server. All transactions are securely delivered to the application using SSL (SHA-1 with RSA Encryption; 2048-bits). It is then transmitted internally (behind the firewall) to the database server. All transactions are logged at the server layer, application layer, and the database layer. Access to the data is managed by institutionally sponsored login IDs. All passwords for registered users are salted and are unrecoverable once created. REDCap administrators are also automatically alerted if normal user activity is potentially destructive to collected data within individual data repositories so that it may be prevented and the user directly notified.

While REDCap provides the capacity to program response limiters (to prevent impossible responses, reduce typos), study personnel will review data weekly to identify impossible values, outliers, and missing data. Following close of survey enrollment, a cleaned and completed survey dataset will be merged with dental participants' selected Enrollment Questionnaire data provided by the CC at the outset of study implementation.

15.2. Data Capture Methods

The SMS will ensure that all required data are collected per protocol requirements, and edit checks will be programmed into the web survey to correct data issues in real time. The study team will ensure that data fields in the system are checked for completeness and accuracy so that data entered into the web system can be validated and data errors be corrected. Reports or tools will be developed to help monitor the data activities. The reports with the summary of the data completeness and accuracy will be made available to the GPI, study team, and NIDCR as requested.

15.3. Types of Data

Data for the study consist of the following:

- Practitioner data from the enrollment survey
- Practitioner responses to the electronic practitioner survey
- Practitioner responses to the post survey, test/re-test

15.4. Schedule and Content of Reports

Reports to monitor enrollment will be produced by the SPI bi-monthly and upon request and will be provided to study team, GPI, RCs, and NIDCR for review. The contents of the report will include a summary of respondents and non-respondents to date by region. Regular monitoring of responses and tracking of response patterns by region will also be communicated to RCs to assist with their communication efforts.

15.5. Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the National Institutes of Health (NIH) or longer as dictated by local IRB or state laws/regulations.

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way after three years from the date the grant FFR is submitted to the NIH. The file connecting subjects' names with their unique identification number will be kept in a password-protected file by the SPI for a minimum of three years, in accordance with IRB regulations, before being securely erased.

15.6. Protocol Deviations

A protocol deviation (PD) is any noncompliance with the clinical study protocol or good clinical practice principles. The noncompliance may be on the part of the patient, the practitioner, or study staff. As a result of deviations, corrective actions may be developed by the study staff and should be implemented promptly. All deviations from the protocol must be addressed in study patient source documents and reported to NIDCR and the local IRB, according to their requirements.

Any PD that is reportable to an IRB must also be reported to NIDCR. NIDCR defers to the IRB for reporting time-frame requirements. Once a PD has been reported to an IRB, action must be taken to report the deviation to NIDCR. If the IRB overseeing the study protocol requires annual reporting of PDs to their IRB, that reporting frequency is acceptable to NIDCR.

16. PUBLICATION/DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. All study personnel are required to read in its entirety and agree to abide by the network's "Data Analysis, Publications, and Presentations Policies" document. The current version of this policy is always kept at the network's public web site at http://nationaldentalpbrn.org/publication.php.

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APPENDIX

Use of Antibiotics in Dental Offices for Secondary Prophylaxis

Cardiac:

- High Risk - As defined by the AHA
    - Specific congenital defects
    - Previous infective endocarditis
    - Heart transplants (with valvular defects)
    - Prosthetic heart valves
- Native heart valve disease
- Cardiac pacemakers and defibrillators
- Cardiac stent
- Misc. (e.g., valvular damage from systemic lupus erythematosus)

Non-Cardiac

- Prosthetic Joints
- Shunts
    - Cerebral spinal
    - Renal dialysis
- Vascular grafts
- Transplants
    - Solid organ (e.g., kidney, liver)
    - Hematopoietic stem cell
    - Bone marrow
- Immunosuppresion
    - Drugs (e.g., systemic steroids, cancer chemotherapy)
    - Disease (e.g. AIDS)
- Type 1 Diabetes Mellitus
- Asplenism
- Implants - non-dental
    - Deep brain stimulator

    - Breast
    - Penile
    - Others
- Post Maxillofacial Radiotherapy (e.g., head and neck cancer)
- Vascular catheters
- Debilitated patients
- Autoimmune disease
- Hereditary hemorrhagic telangiectasia