Dental Implant Registry

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the 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.

Principal Investigator:

Signed: _____ Date: _____

Name: *Nicolaas Geurs DDS, MS*

Title: Professor and chair

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BoP	Bleeding on Probing
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSI	Clinical Site Investigator
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NC	Node Coordinator
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
OHRQoL	Oral Health-Related Quality of Life
OHSR	Office of Human Subjects Research
PBRN	National Dental Practice Based Research Network
PD	Protocol Deviation
PI	Principal Investigator
PO	Program Official, NIDCR, NIH
PS	Project Scientist, NIDCR, NIH

QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

PROTOCOL SUMMARY

Title: Dental Implant Registry

Précis: Dental rehabilitation of partially and fully edentulous patients with endosseous implants has become a routine treatment modality, and it is estimated that up to 5 million dental implants are placed each year. There is a body of literature to suggest that biological and prosthetic complications occur, which may interfere with the health of the peri-implant tissues and the function and esthetics of the implant restoration. The purpose of this prospective, observational study conducted within the National Dental Practice-Based Research Network (PBRN) is to quantify the incidence of biologic and prosthetic complications and assess risk factors for implant complications.

Approximately 200 practitioners from 6 Regional Network Nodes will be recruited to enroll approximately 1550 patients with approximately 2000 implants for longitudinal observation. Patients will be enrolled at the time of implant prosthetic placement. Baseline patient demographic and characteristics, mucosal and prosthetic characteristic data and radiographic images taken for standard of care purposes will be obtained. Follow-up clinical data and standard of care radiographic images will be collected at 1, 2, and 3 years after prosthetic placement.

Objectives and Outcomes: Primary objective: quantify the incidence of biologic and prosthetic complications amongst patients receiving dental implant therapy in a practice setting.

Primary outcomes: biologic (peri-implant mucositis, peri-implantitis, implant failure), and prosthetic complications that have compromised implant esthetics and/or function.

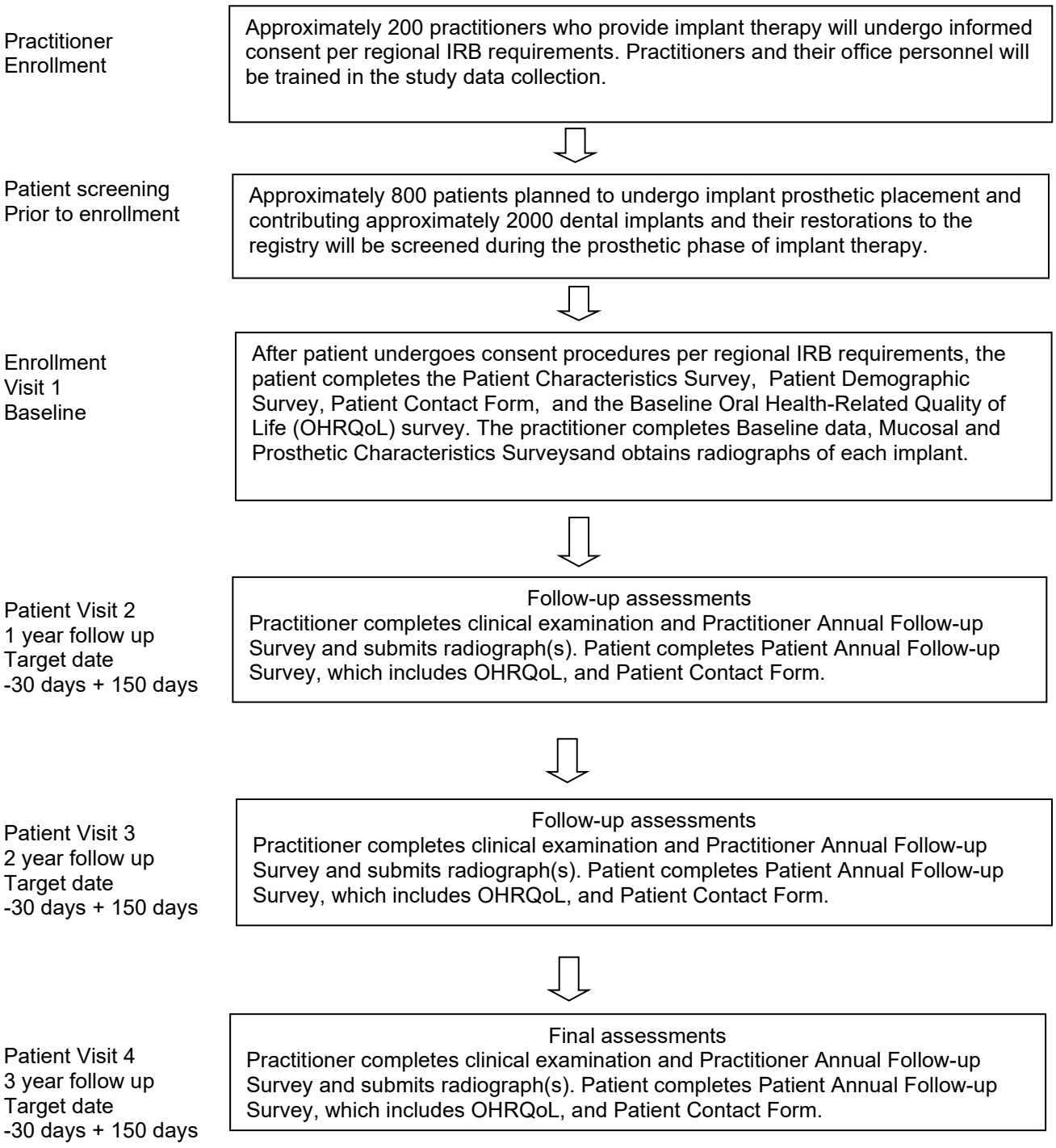
Secondary objectives:

- Determine risk factors for biologic and prosthetic complications amongst patients receiving dental implant therapy in a practice setting.
- Assess patient OHRQoL (Oral Health-Related Quality of Life) and satisfaction with esthetics and function following implant therapy.

	Secondary outcomes: Patient, surgical, prosthetic risk factors; biologic and prosthetic complications, and OHRQoL. Tertiary objectives: - Explore the influence of prosthesis type on the incidence of prosthetic and biologic complications in a private practice setting. - Explore factors predictive of patient OHRQoL (which includes satisfaction with esthetics and function). Tertiary outcomes: Surgical and prosthetic factors; biologic and prosthetic complications, OHRQoL.
Population:	Approximately 200 National Dental PBRN practitioners from all six regional nodes will enroll approximately 1550 patients planned to undergo implant prosthetic placement to contribute approximately 2000 dental implants for longitudinal observation.
Study Duration:	Approximately 5 years
Subject Participation Duration:	Approximately 3 years for patients and approximately 4 years for practitioners
Estimated Time to Complete Enrollment:	Practitioner Enrollment = approximately 12 months Patient Enrollment = approximately 12 months

Schematic of Study Design:

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

With the advent of osseointegration, dental rehabilitation of partially and fully edentulous patients with endosseous implants has become a routine treatment modality, and it's estimated that up to 5 million dental implants are placed each year.[1, 2] While in many cases dental implants have been reported to achieve long-term success, they are not immune from complications associated with improper treatment planning, patient-related factors, surgical and prosthetic execution, material failure, and maintenance.[3] The longitudinal survival rates of osseointegrated dental implants range between 90-96.2% after 5 years.[3-5] These numbers represent implants that are present and in function but may not fully capture rates of peri-implant disease and/or health. There is a substantial body of literature to support that biological and prosthetic complications occur which may interfere with the health of the peri-implant tissues and the function and esthetics of the implant restoration[6]. Peri-implant diseases are classified into peri-implant mucositis, inflammation restricted to the peri-implant mucosa, and peri-implantitis, characterized by peri-implant bone loss.[3] There is variability in the reported prevalence of peri-implant diseases. A systematic review of the literature of studies reported rates of peri-implantitis range from 10-47% of all implants in a time period ranging from 1 to 20 years.[7-9] Rates of peri-implant mucositis have been observed in up to 64% of subjects with dental implants.[9]

Peri-implant diseases are initiated by accumulation of bacterial plaque. Exposure to such plaque leads to inflammatory changes in tissues surrounding the implants.[11-13] Risk factors for peri-implantitis as described in a meta-analysis include periodontitis, smoking, pathological microflora, uncontrolled diabetes and lack of maintenance care.[14] While prosthetic complications do not have an underlying microbiological etiology and do not, in most cases, jeopardize the osseointegration of the dental implant, they are nevertheless a clinical problem during the practice of treating implant patients. Cement remnants after restoration of the implant have also been associated with peri-implant inflammation and bone loss.[15] A recent review has identified six categories of technical or prosthetic failures: loosening of screws, screw fracture, fracture of framework, fracture of abutment, chipping/fracture of veneering material, and decementation.[16] As reported in this retrospective analysis, the overall incidence of technical or mechanical complications for all implants in partially edentulous patients was 10.8% for single implant restorations and 16.1% for partial fixed implant supported prostheses over approximately a 5-year period.[16] The most common form of mechanical complication for single implant restorations was screw loosening resulting from a veneering material fracture in partial fixed implant supported prostheses.[16]

Innovations in biomaterials, implant and prosthesis design and the knowledge of wound healing have led to many changes in the practice of implant dentistry over the past decade. The need for more recent studies and better reporting of mechanical

complications with patient-based and prosthesis-based rates of mechanical and technical complications has been recognized.[17]

The limitations of the current body of literature of biologic and prosthetic complications are based on many small studies and in large part conducted in academic and specialty settings. Many of these studies have been retrospective and may not accurately represent the setting of private practice. An example is the retrospective study of the PEARL (Practitioners Engaged in Applied Research and Learning) network of private practitioners, in which the implant failure, defined as excessive bone loss as measured on submitted radiographs, was 18.7% over a mean follow-up period of 4.2 years. Thus, the success rate in this study was lower than historic controls of studies conducted in academic or specialty settings.[17] There is limited data available on the implementation of risk assessments in a practice setting and their impact on the prevention of peri – implant disease. There is an additional paucity of research to address other factors that can influence implant outcomes, such as implant design, implant surface characteristics, implant placement, loading protocols, occlusion and prosthesis design. [19] Many of the previous retrospective studies that have examined implant outcomes have focused on survival data rather than success. There is a lack of studies evaluating the function, tissue health and patient satisfaction of implant systems in maintenance phase in community practices.

In orthopedics, significant improvement in the clinical practice and in the quality of care has been shown from the results of the national total joint replacement registry.[20, 21] We will create an implant registry within the National Dental PBRN that will record the setting and implant therapy provided, the implants used, the prosthetic therapy provided and any complications. The purpose is to quantify the incidence of biologic and prosthetic complications and assess risk factors for and develop a risk assessment for implant complications. Better understanding of the complications and the risk factors associated with implants could lead to the development of clinical strategies and protocols for the prevention of adverse implant therapy outcomes.

2.2 Rationale

Prospective, longitudinal studies are needed to identify significant risk factors for peri-implant diseases. This will allow better information to be shared with practitioners and patients regarding possible complications, which seem to be common occurrences with a significant number of implant restorations.[19] Furthermore, this could give practitioners relevant information to assist in treatment decisions that would improve outcomes.[20] It would also be a relevant addition to the implant literature to have information based on real-world dental care-delivery experiences rather than specialty or academic clinical studies.

The National Dental PBRN offers a great opportunity to gather data in a comprehensive manner on a large, diverse patient population, and therefore, the results may be

generalizable to a wide range of patients in a private practice setting. The registry will create opportunities for subsequent, additional targeted studies on specific complications available from the registry data. We expect that the results from this study could significantly impact the clinical practice of implant dentistry and the quality of care and satisfaction of patients.

2.3 Potential Risks and Benefits

This is an observational study. Research participants will not receive dental care or an intervention as a study procedure but will continue to receive routine clinical care as patients of the participating dentists. Risks of dental procedures provided as part of routine clinical care are not considered to be study-associated.

2.3.1 Potential Risks

As with any study, there is the possibility of breach of confidentiality. Appropriate precautions will be taken and procedures will be followed to maintain confidentiality. These include use of unique study codes for participants, encryption of electronic data for transmission to the coordinating center, and password-protected computers for data storage. Compliance with all IRB regulations concerning data collection, data analysis, data storage, and data destruction will be strictly observed.

2.3.2 Potential Benefits

Participation in the study will provide no direct benefit to participants. Benefits would accrue to society in enhanced understanding of implant complications and the associated risk factors. Thus, study results could enhance care for future patients through evidence-based recommendations for more timely and appropriate interventions and prevention of these complications.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
To quantify the incidence and prevalence of biologic complications amongst patients receiving dental implant therapy in a private practice setting.	Biologic complications will be defined as an implant that presented with measured bone loss on the radiographs and/or bleeding on probing, or failed implant. Biologic complications will be defined as a) Peri-implant mucositis: Bleeding on Probing (BoP) and/or purulent exudate without measured bone loss, or b) Peri-implantitis: measured bone loss on the radiographs, or c) Implant failure: an implant that has been lost or is planned to be removed Incidence estimation will be based on a Poisson model for incidence per implant and year of follow-up.	a) The presence or absence of Bleeding on Probing (BoP) is measured by the practitioners at the annual evaluation visits and recorded in the annual follow-up surveys. b) The radiographic bone changes are measured on the radiographs by calibrated examiners, utilizing the known geometry of the implant to convert to mm of bone change. Bone loss is defined as the negative change of the bone level measurements from the baseline radiographs taken at the time of prosthetic insertion. c) Implant Failure: absence or planned removal of implant	Baseline data are collected at the time of prosthesis insertion and at each of the three annual follow-up visits. The radiographs taken for clinical care purposes at prosthesis insertion and the 1, 2 and 3-year follow-up visits that are approved by the study team to be added to the radiograph repository will be utilized for radiographic assessments.
Objective	**Brief Description/Justification of Outcome Measure**	**Outcome Measured By**	**Time Frame**
To quantify the incidence and prevalence of prosthetic	Prosthetic complications will be defined as any complication that has compromised the esthetics	At baseline, practitioners will record surgical data (implant brand, size	Baseline surgical and specific prosthetics data

complications amongst patients receiving dental implant therapy in a private practice setting.	and/or function of the implant restoration. Incidence estimation will be based on a Poisson model for incidence per implant and year of follow-up.	and diameter, surgical therapy and site development, healing complications) and prosthetic data (type of restorations, abutment, restorative material, and occlusal scheme). At follow-up, practitioners will collect clinical data and record the presence or absence of the following complications on the prosthetics data collection survey: loose or lost screw, screw fracture, structural fracture, resin or porcelain fractures, loss of retention, abutment/ implant misfit.	will be collected at the insertion of the prosthesis. The annual follow-up surveys at years 1-3 will record the presence or absence of prosthetic complications.

3.2 Secondary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Determine risk factors for biologic complications amongst patients receiving dental implant therapy in a private practice setting.	Baseline risk factor data collection will include patient specific data, surgical data, and prosthetic data. Follow-up data will collect changes in implant health (biological complications). Biologic complication measurements taken for the Primary Objectives will be used in the model for detection of risk factors. Precision for detection of predictors of complications and	Patient data (patient age, gender, overall health, medications taken, oral health, periodontal disease status etc.), surgical data (described above) and prosthetic data (described above) BoP, gingival health data, and	Data are collected at baseline and at the 1-3-year annual follow-up visits and combined with the BoP and radiographic data.

	correlates of patient satisfaction will be based on effect magnitudes that would be detectable.	radiographs will be collected.	
Determine risk factors for prosthetic complications amongst patients receiving dental implant therapy in a private practice setting.	The risk factors for prosthetic complications can be estimated from a model created with the data collected at the baseline and follow-up data collection timepoints. Baseline data collection will include patient specific data, surgical data, prosthetic data; follow-up data will focus on the prosthetic performance (including prosthetic complications, described in Primary Objective above). Precision for detection of predictors of complications and correlates of patient satisfaction will be based on effect magnitudes that would be detectable.	The practitioners will complete the specific data collection forms for patient data, surgical data and prosthetic data described above.	Data are collected at baseline and at the 1-3-year annual follow-up visit.
Assess patient Oral Health-Related Quality of Life (OHRQoL) and satisfaction with esthetics and function following implant therapy.	Patient centered outcomes are an important aspect of the overall outcomes of treatment. The patients' satisfaction with the esthetics, health and function will be collected by patient surveys. Changes in the overall OHRQoL and patient satisfaction will be reported.	Patients will complete OHRQoL surveys at baseline and follow-up visits. For patient satisfaction, surveys will be administered describing esthetics, function and health prior to the insertion of the implant prosthesis (baseline) and after insertion (follow-up).	The patient survey instruments are completed by the patients prior to insertion of the prosthesis, and at the 1-3-year follow-up visits.

3.3 Tertiary/Exploratory

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Explore the influence of prosthesis type on the incidence of prosthetic and biologic complications in a private practice setting.	The influence of the prosthesis on both prosthetic and biologic complications has been described in the literature. This analysis will explore therapies and strategies associated with dental implant success and that minimize prosthetic or biologic complications.	The incidence of biologic and prosthetic complications will be determined for each type of prosthesis (described above).	Data are collected at baseline and at the 1-3-year annual follow-up visits.
Explore factors predictive of patient OHRQoL (which includes satisfaction with esthetics and function).	The data will be used to construct models to explore the predictive factors for patient success. Data for model inclusion will include baseline patient specific data, surgical data, and prosthetic follow-up data. Peri-implant health and prosthetic performance will also be included.	The OHRQoL will be used to examine the association between patient/implant/therapy factors and the OHRQoL score.	Data are collected at baseline and at the 1-3-year annual follow-up visits.

4 STUDY DESIGN

- This is a prospective, observational 3-year cohort study of patients who undergo dental implant restoration by practitioners of the National Dental PBRN. Practitioners who restore dental implants will recruit and enroll their patients in this cohort study during the prosthetic phase of implant therapy.
- Approximately 200 practitioners from all 6 Network Nodes (approximately 35 practitioners per Node) will participate in the study, with each practitioner contributing approximately 10 patients and a maximum of approximately 50 implants.

- The patient population will comprise patients who plan to receive dental implant restorations provided by practitioners of the National Dental PBRN. Approximately 1550 patients will be enrolled until approximately 2000 implants are available for longitudinal observation. Implants will be clustered within patients and within approximately 200 dental practitioners across network practices. Each enrolled patient can contribute more than one implant if multiple implants will be restored at the baseline visit.

- Practitioner and practice characteristics from the National Dental PBRN Enrollment Questionnaire will be combined with data collected for this observational study.

- The prospective, observational study design will allow an opportunity to inform our knowledge of parameters for implant success and risk factors for biologic and prosthetic complications associated with implant therapy. The study will describe the implant restorative therapy provided by the practitioners, the incidence and prevalence of biologic and prosthetic complications, and will correlate patient-level factors, prosthetic- and implant-level characteristics with the risk for implant complications and the therapies provided for dental implant complications.

- The baseline data collection will occur at the prosthetic placement visit, at which time patient baseline characteristics, their overall health and oral health status will be collected, and peri-implant hard and soft tissue status and prosthesis data will be captured. Patients will undergo annual follow-up visits at 1, 2, and 3 years (with a preferred target window for each visit ranging from a target date of -30 days to +150 days of the visit following prosthetic placement). During or after follow-up visits, patients will report satisfaction with aesthetics and function and oral health quality of life measures. Reminder emails or texts, if the patient opts into text messaging will be sent to patients who do not complete the surveys. Practitioners will record data on the patients' oral health, peri-implant tissue health, and the implant prosthesis(es), with a focus on biologic and prosthetic complications that have occurred since prosthetic placement.

- Consent will be recorded electronically, and data will be collected via electronic means for the entire study. The consent process and enrollment will be completed at the prosthetic placement visit. Practitioners will provide clinical examination and procedural data electronically via tablets, smart-phones, or computers in-office or post visit at baseline and the 1-, 2-, and 3-year annual follow-up visits. Patient-reported data will be collected via tablets, smart-phones, or computers after in-office visits. To assist with in-office data collection, study practitioners may be offered tablets.

- Dental radiographs of each implant obtained for clinical care purposes will be collected at the following 4 time points: 1) baseline at the prosthetic placement visit, 2) 1-year annual follow-up visit, 3) 2-year annual follow-up visit, and 4) 3-year annual follow-up visit. Radiographs will be digitally uploaded via the study portal.

- Practitioners will submit digital radiographs of each study implant, taken at baseline (after implant prosthetic placement) and at annual follow-up visits 1, 2, and 3 years following prosthetic placement. The radiograph should be void of any identifiers. Radiographs will be uploaded to the centralized study database provided by the NCC. The study team completes the final review to determine whether the radiograph is sufficient quality to be included in the radiograph repository. If the radiograph is insufficient quality, the study team will work with the Node Coordinator to provide feedback, if applicable, and determine whether a higher quality radiograph can be found. Radiographs in the radiograph repository will go through the adjudication process, where trained and calibrated evaluators assess the radiograph for quality and will determine peri-implant bone height measurements and prosthetic fit for each implant.
- Depending on the patient's enrollment date and whether future funding is obtained, a patient may not complete all study visits. If that occurs, the NCC, study team, practitioner, and/or Node Coordinator will reach out to the participants to inform them of the study status and future visits.
- If an implant has been removed since the last study visit, the practitioner will note this in the CRFs. The practitioner will complete the CRFs in relation to the situation prior to removal. No additional study visits will occur for the removed implant.
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5 STUDY POPULATION

5.1 Practitioner Inclusion Criteria

In order to be eligible to participate in this study, a practitioner must be deemed study-ready and must meet the following criteria:

- Willing to consent patients to the study following regionally approved procedures
- Performs prosthetic dental implant therapy and implant maintenance care.
- Takes annual radiographs for the evaluation of the health and performance of a dental implant for standard clinical care and is willing to submit these radiographs for research purposes
- Has WIFI in the practice and is able to provide radiographs in electronic format (i.e., jpeg, Digital Imaging and Communications in Medicine [DICOM] or tif)
- Is expected to remain in the practice for the four-year study duration and agrees to collect research participant data during annual follow-up visits or can identify a practitioner who can do subsequent follow-up
- Affirm that the practice can devote sufficient time in patient scheduling to allow focused recording of all data required for the study
- Does not anticipate retiring, selling the practice, or moving during the study
- Be affiliated with the National Dental PBRN

5.2 Patient Inclusion Criteria

For patient participants to be eligible to participate in this study, a patient must meet all of the following criteria:

- Provide dated, informed consent
- Willing to comply with all study follow-up visits and be available for the duration of the study
- 19 years of age or older at the time of study enrollment
- Planned for the first implant prosthetic restoration of one or more implants by a participating National Dental PBRN practitioner, with the implants healed and deemed ready to be restored.
- Be able to provide contact information for one other person with a different phone number who will know the patient's whereabouts in the event the patient cannot be reached to complete follow-up visits

5.3 Patient Exclusion Criteria

- Previously enrolled in the study
- Implant prosthesis planned to replace a previously failed implant prosthesis on existing implant

5.4 Strategies for Recruitment and Retention

5.4.1 Practitioner Recruitment and Retention

Node Coordinators from all 6 regions will determine possible interest of dentists by contacting dental practices enrolled in the National Dental PBRN. Practitioner recruitment will be led by the study team in collaboration with Node personnel. Practitioners will be enrolled from all 6 Regional Nodes of the National Dental PBRN. Survey data from the National Dental PBRN showed that 65% of private practitioners reported providing implant therapy within their practices, and 23.7% indicated they routinely provide implant therapy in their practices. The network practitioner database will be used to identify practitioners to recruit for this study.

We will strive to complete patient enrollment within approximately one year. Consequently, it is anticipated that approximately 200 practitioners will be needed to complete patient enrollment during the practitioner-specific enrollment period. Each practitioner may contribute up to approximately 50 implants.

Node Coordinators (NCs) will recruit practitioners from the Network's 6 geographic regions. The recruitment from all Nodes within the Network will capture a cohort of practitioners with a wide geographic distribution. Retention will be an important aspect of the cohort study, and the design of all aspects of the study will take into consideration the burden to the practitioner and the retention of participants. The study team and NCs will maintain efforts to engage practitioners throughout the duration of the study, including addressing practitioner questions and concerns and implementing processes to streamline data collection in dental offices.

For the baseline visit, practitioners will receive $100 remuneration for each implant where the Practitioner has completed the following: Baseline Characteristics, Mucosal Characteristics, Prosthetics Characteristics Surveys and upload of baseline study implant radiographs. For follow up year 1, year 2, and year 3, practitioners will be remunerated $25 per implant for the completion of the Annual Follow-up Survey and submission of radiograph(s) for patients.
For the approximately 2000 implants enrolled we budget for 1X$100 and 3X$25 for the total of $350,000. This is a considerable expense but is justified by the importance of continued longitudinal data collection and retention of the practitioners and patients.

5.4.2 Patient Recruitment and Retention

The target sample size for this observational study is approximately 1550 patients and approximately 2000 implants, clustered within approximately 200 dental practitioners across all 6 Network Nodes. Patients planned for implant prosthetic placement will be recruited by practitioners and/or their office staff over a recruitment period of approximately 12 months. Practitioners will be asked to use a consecutive enrollment strategy. Each practitioner will establish a regular recruitment period (days and/or times) each week that fits the practice and is sufficient to meet enrollment targets. A screening criteria log will be used to record potential patient refusal/non-enrollment and, where allowed, reasons for non-enrollment, during established recruiting periods. Practitioners' recruitment schedules may be adjusted at any time with the consultation of the NC. Each practitioner will be asked to contribute approximately 10 patients, with a maximum of approximately 50 implants per practitioner.

Office staff may provide an information sheet and instruct the patient to discuss the study with the practitioner. All patients presenting at participating Network practices may be considered for eligibility after screening by the practitioners and/or trained office staff. The practitioner or other appropriately trained staff members will ask the patient if the patient wants to enroll in the study, provide the patient with an information sheet if the patient does not already have one, and will obtain the verbal authorization to put their information into the HUB.

Patient retention is important to this study. Patients will be remunerated $25 for the baseline data collection visit and $25 for each of the three annual follow-up visits. Payments will be processed for each completed part of the study.

Study practitioners will be contacted prior to each follow-up data collection interval. The NCC will create reports with practitioner and patient windows that can be accessed by NCs. Node personnel will remind practitioners to follow-up with non-responders prior to the close of each data collection window and may use mail, email, telephone and/or text messages to encourage the scheduling of the follow-up visits.

Opportunities for engagement of the practitioners with the study team may be created throughout the study in the form of webinar based continuing education sessions on topics of interest to the practitioners.

5.5 Participant Withdrawal

5.5.1 Reasons for Participant Withdrawal

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

5.5.2 Handling of Participant Withdrawals

In the case of participant withdrawal from the study, staff will only attempt continued follow-up data collection for participants who are withdrawn due to an unanticipated problem. In those cases, only data related to the completion of reporting requirements for the unanticipated problem will be recorded. Participants withdrawn from the study for any other reason will have the date and reason for withdrawal recorded, but will not have any additional study data recorded. Although participants withdrawn from the study may continue to receive routine clinical care as patients of the participating dentists, additional study data will not be collected from this continuing clinical care (except as noted above).

Replacement of participants who withdraw or discontinue early will be allowed, but only during the enrollment period for each practitioner. The practitioner may attempt to enroll one replacement participant for each participant enrolled who withdraws or discontinues during the practitioner-specific enrollment period. Study team, NCC, ARC, or node personnel may assist practitioners with follow-up of non-responders or withdrawals. If a patient participant expresses a desire to withdraw, first, we will need to know who withdrew and whether they agreed to the original information sheet language only, or to the newly revised language. If they agreed on the newly revised information sheet language, the automated future emails to the participants will be turned off. An email from CHR-NDPBRN-HUB@kpchr.org will be generated to the patient to confirm that automated future questionnaires and emails have been turned off. It will also inform them that their practitioner will continue to collect data on their study implant(s) during future follow-up visits and they must reply back to the email to withdraw consent for their practitioner to collect future data on their study implant(s). If the patient replies back withdrawing consent for their practitioner to collect future data on their study implant(s), no future study data will be collected. Previously, the NCC did not reply back to the email from the participant, and future data on the practitioner's implants was not collected. If a patient who agreed on the original consent language wants to withdraw, we will not be able to ask them to continue to collect their study implant data for use in the study.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. The Principal Investigator is responsible for promptly notifying all parties and providing the reason(s) for the termination or suspension.

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

- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6 STUDY SCHEDULE

Practitioners enrolled in the National Dental PBRN across the six regions who express interest in the study and meet eligibility criteria will be invited to participate. Study information and instructions will be provided to interested practitioners by Node personnel. After practitioners are eligible and enrolled, Practice Training Materials will describe the participant selection procedures, methods for approaching patients and obtaining informed consent, methods for data collection, and other study procedures for the dentist(s) and office staff who will help to execute the study. A summary flow chart will provide an overview of all study visits and study procedures/data collection for each visit. Utilizing a train the trainer model, the NCC will conduct training with the NCs, who will train practices on the EDC. In addition, NCs will conduct in-person or remote protocol and electronic data management system training with practitioners and office 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, the electronic data capture system, and the radiographic upload. 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 region will enroll practitioners into the study to obtain a total of approximately 200 practitioners across all regions. A reasonable balance across regions is preferred but not required;
2) Practitioners will complete activities to be deemed research-ready and study-ready;
3) NCs will train research-ready and study-ready practitioners and their office staff in the appropriate study procedures; and
4) Practices will screen and enroll eligible patients into the study.

The Study Team, NCC and Node personnel will coordinate the launch of the study. For each of the six regions, participating practitioners will be enrolled over a period of approximately 12 months. Practitioners will begin study recruitment as soon as possible following study training with an NC.

An overview of study procedures to be completed at each study visit can be found in Appendix A.

6.1 Practitioner Enrollment

- Verify practitioner inclusion/exclusion criteria
- Practitioner and eligible staff participate in study training with an NC

6.2 Patient Screening/Enrollment (Day 0)

A potential patient may be told about the study at any dental visit in a participating practitioner's office after it is determined that a patient will undergo (or has undergone) implant therapy that will result in the placement of an implant prosthesis. Practitioners may email the information sheet ahead of time, if desired.

6.3 Patient Baseline Visit Prosthesis insertion (Visit 1, Day 0)

At the prosthetic placement visit if a patient is eligible and interested in the study, the patient will undergo the consenting process pursuant to overseeing IRB requirements. If an eligible patient wishes to decline participation in the study, this occurrence will be noted in the screening log, and the informed consent process will not be completed.

- Verify inclusion/exclusion criteria and complete the Screening Log
- Obtain and document consent according to regional IRB requirements
- After enrollment procedures have been completed, the patient will:
  - Complete the *Baseline Patient Demographics, Patient Contact survey, and Patient Characteristics Survey*
  - Complete the *Baseline Oral Health Quality of Life Survey (OHRQoL) Survey*

The practitioner will:

- Perform an oral examination and complete the *Baseline Data, the Mucosal and Prosthetics Characteristics Surveys*
- Upload radiographs of the study implants that have been obtained for clinical care purposes

6.4 Intermediate Visits

Visit 2, Year 1 post prosthetic insertion, Target Day 365 (range: ~-30 days ~+150 days)

- The patient completes ther:*1-Year Patient Annual Follow-up Survey, which includes the OHRQoL survey and Patient Contact survey*
- Following an oral examination, the practitioner completes the 1-Year *Practitioner Annual Follow-up Survey* to capture the status of the implants and record complications that have occurred since the last visit.
- Practitioner uploads radiographs of each study implant that have been obtained for clinical care purposes

Visit 3, Year 2 post prosthetic insertion, Target Day 730 (range: ~-30 days ~+150 days)

- The patient completes the *2-Year Patient Annual Follow-up Survey*, which includes the Oral Health-Related Quality of Life (*OHRQoL) survey and Patient Contact survey*.

- Following an oral examination, the practitioner completes the *2-Year Practitioner Annual Follow-up Survey* to capture the status of the implants and record complications that have occurred since the last visit.
- Practitioner uploads radiographs of each study implant that have been obtained for clinical care purposes

6.5 Final Study Visit

Visit 4, Year 3 post prosthetic insertion, Target Day, 1095 (range:~ -30 days~ +150 days)

- The patient completes: the *3-Year Patient Annual Follow-up Survey*, which includes the Oral Health Quality of Life (*OHRQoL) survey and Patient Contact survey.*
- Following an oral examination, the practitioner completes the *3-Year Practitioner Annual Follow-up Survey* to capture the status of the implants and record complications that have occurred since the last visit.
- Practitioner uploads radiographs of each study implant that have been obtained for clinical care purposes

6.6 Withdrawal Visit

If a patient 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's withdrawal from the study
- Record other participant information only if consent was not withdrawn. Additional information recorded should only be that which is required for the visit type, as applicable (see above).

7 STUDY PROCEDURES/EVALUATIONS

The intent of this observational study is to observe and record usual clinical care provided by the participating dentists and not to influence or manipulate diagnostic or treatment procedures. We selected our predictive variables based on published research from the dental literature, which generally have focused on patient specific factors, anatomical factors, biological and prosthetic variables.

7.1 Study Procedures/Evaluations and Questionnaire Administration

All baseline and follow-up data will be collected electronically.

Practitioners

Practitioner enrollment/baseline: Practitioners will have completed the *Enrollment Questionnaire* to capture the practice environment, practitioner training, and practitioner experience with dental implant therapy.

Patient baseline: Implant prosthetic placement will occur at the patient baseline visit. Following oral examination and prosthetic placement, practitioners will complete the *Baseline Data Survey and Mucosal and Prosthetics Characteristics Surveys* to record the patient's: 1) oral health and dental status, 2) implant location(s), 3) implant characteristics, 4) surgical procedural details, 5) implant prosthetic restoration procedural details and characteristics, and 6) status of the peri-implant mucosal tissues.

Annual follow-up: Practitioners will complete the *1-, 2-, or 3-Year Practitioner Annual Follow-Up Surveys* based upon clinical examination to record patient information related to: 1) presence/absence of bleeding on probing, 2) probing depth around study implants, 3) presence/absence of purulent exudate, 4) the presence or absence of prosthetic complications

The clinical assessments include:

- Bleeding on Probing (BoP): A plastic dental implant probe is inserted in the peri-implant sulcus or pocket at a depth of 2 mm and gently swept around the implant on the buccal and lingual aspect of the implant. If bleeding occurs at any aspect of the implant, the presence of BoP is recorded. If no bleeding occurs the absence of BoP is recorded.
- Probing depth: Probing is performed with a plastic dental implant probe as parallel as possible to the long axis around each implant. It is anticipated that not all surfaces of the implant restoration will allow for the recording of a probing depth measurement. The deepest probing depth and the location of the measurement per implant is recorded.

- Purulent exudate: If upon the instrumentation of the implant for the assessment of BoP or probing depth purulent exudate (a milky white, yellowish excretion) is observed the presence is recorded for the implant.
- Clinical examination of the prosthesis: Screw fracture, Screw loosening, Loss of screw, Structural fracture, Resin fracture, Porcelain fracture, Loss of retention, Loss of filling covering screw, Abutment/implant misfit, Abutment/prosthesis misfit, Cement remnants present, Wear of the occlusal surfaces.
- Radiographs: Practitioners will submit digital radiographs of each study implant, taken at baseline (after implant prosthetic placement) and at annual follow-up visits 1, 2, and 3 years following prosthetic placement. The radiograph should be void of any identifiers. Radiographs will be uploaded to the centralized study database provided by the NCC. Node Coordinators will review the radiographs and remove identifiers if present. The study team completes the final review to determine whether the radiograph is sufficient quality to be included in the radiograph repository. If the radiograph is insufficient quality, the study team will work with the Node Coordinator to provide feedback, if applicable, and determine whether a higher quality radiograph can be found. Radiographs in the radiograph repository will go through the adjudication process, where trained and calibrated evaluators assess the radiograph for quality and will determine peri-implant bone height measurements and prosthetic fit for each implant.

Patients

Patient questionnaires will ascertain patient satisfaction and OHRQoL thought to be important patient-reported outcomes. Patient satisfaction with function and esthetics will be measured with the OHRQoL.

Baseline: At the implant prosthetic placement visit, patients will complete the *Baseline Patient Demographics, Patient Contact Survey, Patient Characteristics Survey* and *Baseline Oral Health Quality of Life (ORHQoL) Survey*, which will ascertain information related to: 1) demographics, 2) socioeconomic variables, 3) medication use, 4) medical conditions, 5) satisfaction with function and esthetics prior to implant therapy, and 6) oral health quality of life prior to prosthetic implant therapy.

Annual follow-up: Patients will complete the *1-, 2-, or 3-Year Patient Annual Follow-Up Survey, which includes the OHRQoL survey and Patient Contact survey,* to ascertain patient information related to: 1) Contact information changes 2) Changes in health history, medications and smoking habits, 2) OHRQoL following prosthetic implant therapy.

7.2 Development of data collection instruments

Survey development has included refinement of data collection instruments with an emphasis on reducing overall burden and improving acceptability. Surveys have been developed from validated instruments, when possible, that have been modified and/or combined with other instruments.

Practitioner and patient questionnaires to be utilized in this study have undergone an informal cognitive interviewing process with the National Dental PBRN Practitioner Executive Committee members. Guided by a qualitative researcher, PEC members provided feedback on their understanding of the survey content in general, appropriateness of content for the setting, and length of time necessary for completion for practitioner and patient surveys.

7.3 Radiographic Assessment

One trained and calibrated periodontist will first assess diagnostic quality of submitted images. High quality radiographic images should include the following:

- The radiograph should capture the complete length of the implant
- The radiograph should show the most coronal aspect of the crestal bone adjacent to the implant
- The buccal and lingual cusp of the posterior teeth should be aligned and overlap each other
- The contact points between the teeth must not overlap each other
- The image must be sharp and of good contrast

The quality of the radiograph will be assessed by the study team. If the radiograph is of acceptable projection geometry as outlined above the radiograph will be used for analysis. For radiographs that do not meet the above criteria feedback will be provided to the Node Coordinator to pass along to the practitioner to correct the acquisition of future radiographs.

Only Radiographs that are determined to be of sufficient quality will go into the radiograph repository. Every radiograph in the radiograph repository will go through the adjudication process, where two trained and calibrated evaluators assess the radiograph for quality. Two initial evaluators will measure the peri-implant bone height, emergence angle, and prosthetic fit, as described in the following sections. The NCC's adjudication system will compare these measurements and notify a third evaluator if the measurements taken by the initial evaluators vary too much from each other. If the measurements taken by the third evaluator vary too much from both initial evaluators, a panel review consisting of the three evaluators will take place. With the exception of the panel review, the evaluators are blinded to each other's measurements. Each evaluator will upload a marked radiograph into the NCC's adjudication system.

Peri-implant bone height

Bone height will be measured utilizing the known geometry of the implant to convert to mm of bone change. The evaluations will be used to provide confirmation of bone loss, which is defined as the negative change of the bone level measurements from the baseline radiographs taken at the time of prosthetic insertion. Alveolar bone levels will be measured at mesial and distal sites of study implants on all images as the distance between platform of the implant and alveolar bone crest. All measurements will be made in pixels. The unit pixel is merely a digital measurement unit and varies with the resolution with which the image was saved or scanned. For conversion back to millimeters, a known dimension needs to be represented on an image. The implant length or diameter will serve as known entity on the radiographs, and each implant will be measured. The custom conversion for each image utilizing the measured implant length in pixels by the known implant length or spacing between the threads in millimeters. This method allows for the comparison between images taken with different systems and makes the changes clinically relevant as they are expressed in millimeters. Image processing software will be used to capture measurements from the radiographic images.

Measurement of the emergence angle

The mesial and distal emergence angle of the prosthesis will be measured using the implant platform as the vertex, with one ray following the long axis of the implant and the other aligned with the gingival contour of the implant abutment.

Prosthetic fit

The presence of a gap between the abutment and the implant and/or the abutment and the prosthesis will be recorded.

8 ASSESSMENT OF SAFETY

8.1 Definitions of Safety Parameters

8.1.1 Serious Adverse Event

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

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Results in inpatient 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 participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

8.1.2 Unanticipated Problems

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

8.2 Specification of Safety Parameters

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

8.3 Reporting Procedures

8.3.1 Unanticipated Problem Reporting

Per National Dental PBRN procedures, unanticipated incidents and events will be reported to the PI. After the PI is made aware of the incident/event, the following procedures will be followed.

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 10 working days 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 the Clinical Research Operations and Management Support (CROMS) contractor.

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

9 STUDY OVERSIGHT

The PI will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The NCC will provide the PI with current data summaries, and the PI will review the data for safety concerns and data trends at regular intervals, and will promptly submit reportable events to the IRB and NIDCR that arise during the conduct of the study, per the IRB's reporting time-frame requirements. To ensure data integrity, the PI, NCC, and study team will adhere to data quality management processes (please see Section 13).

10 CLINICAL SITE MONITORING

10.1 Site Monitoring

For Network studies, Quality Management procedures and clinical site monitoring (if needed) are conducted to ensure that the study is implemented in accordance with the protocol and other operating procedures, the quality and integrity of study data and data collection methods are maintained, and the safety of human subjects is ensured.

10.2 Site Monitoring Determination

Site monitoring may be needed if there are issues at a practitioner location or office that cannot be addressed via Network quality management processes and office staff re-training. Examples include determining the root cause of an unresolved issue, problematic data found via other quality management processes (e.g., study monitoring reports), and/or problems with informed consent. Efforts will be made to work with the practitioner to resolve site issues before considering a remote or in-person site monitoring visit. In addition, for-cause visits at practices or Central or Node Administrative Sites can be mandated by the NIDCR Office of Clinical Trials Operations & Management (OCTOM), its designees, or can be requested by the NCC, regional staff, or practices.

10.3 Scope of Monitoring Activities

Should there be a need, for-cause study monitoring will be detailed in a Clinical Monitoring Plan developed by NIDCR's CROMS contractor in conjunction with NIDCR. NIDCR will determine where a monitoring visit may occur (e.g., practice, regional Node, central administrative site), whether a for-cause monitoring visit will be performed through the CROMS contractor, and the extent to which network personnel may provide support towards obtaining the documentation needed for the monitoring visit. OCTOM will also determine whether a monitoring visit will be conducted in-person or remotely. The intent of the visit is to address any problems or issues encountered that may require additional training, remediation, or in-person assistance. The scope of the visit will be determined by the issue(s) identified.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Hypothesis 1: The 3-year cumulative incidence of at least one biologic complication of dental implants is 50% amongst patients receiving dental implant therapy in a private practice setting.

Hypothesis 2: The 3-year cumulative incidence of at least one prosthetic complication of dental implants is 50% amongst patients receiving dental implant therapy in a private practice setting.

Hypothesis 3: Incidence of biological complications varies by prosthesis type: screw retained prosthesis have a lower incidence of biologic complications

Hypothesis 4: Incidence of prosthetic complications varies by prosthesis type: cemented restorations have a lower incidence of prosthetic complications

11.2 Sample Size Considerations

The primary objective of the study is descriptive (i.e., to determine the incidence of various outcomes among patients receiving dental implants). As such, a power analysis is based on the precision with which we can estimate the proportion of the occurrence of the primary outcomes (Peri-implant mucositis, Peri-implantitis) among all eligible patients. The study plan is to recruit approximately N=1550 patients with a total of approximately 2000 dental implants. In a published meta-analysis, the prevalence of Peri-implant mucositis was estimated to be 50% and the prevalence of Peri-implantitis was estimated to be around 20% within the three year follow-up period[7,9,32]. To a good approximation, if W is the width of the 95% confidence interval (i.e., the confidence interval is of the form P ± W/2) for an estimated proportion P based on N observations, then the number of participants (N) needed to achieve that width is given by

$$N = 16*P*(1-P) / (W^2) ,$$

where P and W are expressed on a fractional basis. For a given value of W, the formula above is symmetric about P=0.5 and W is largest for P=0.5. Table 1 and figure 1 show the different precision (i.e., width) of our estimated 95% confidence intervals as the underlying cumulative incidence of complications varies.
Table 1.

		width of the 95% confidence interval (W)	
expected 3-year prevalence and cumulative incidence of participant-level complications	N = 1400	N=800	N=500

20%	0.043	0.057	0.072
25%	0.046	0.061	0.078
30%	0.049	0.065	0.082
35%	0.051	0.067	0.086
40%	0.052	0.069	0.088
45%	0.053	0.070	0.089
50%	0.053	0.071	0.090

The secondary objective is to assess association between risk factors and the biologic and prosthetic outcomes. The primary outcomes are Peri-implant mucositis and Peri-implantitis. Based on the assumptions of equal category size, a cluster size of 1.4, and a prevalence of 50% for Peri-implant mucositis and 20% for Peri-implantitis in the reference group, table 2 presents the outcome prevalence values we can detect with varying degree of intracluster correlation coefficient (ICC).

Table 2.

	Detectable outcome prevalence values	
ICC	Reference group outcome prevalence values = 50%	Reference group outcome prevalence values = 20%
0.1	56.43%	25.40%
0.2	56.55%	25.50%
0.3	56.67%	25.61%
0.4	56.78%	25.71%
0.5	56.90%	25.81%

11.3 Final Analysis Plan

Data quality. Before we carry out any statistical analyses, we will audit the data for quality and completeness. We will examine variable distributions for outliers and ensure that the data distributions meet the assumptions of the planned analysis. We will present the baseline characteristics as means and standard deviations for continuous variables and as counts and percentages for categorical variables. All inferential tests will be carried out at a two-tailed alpha level of .05.

Missing data. We will examine rates and patterns of missingness. If the missing at random (MAR) assumption is met, a common occurrence, we will perform multiple imputation (MI) analysis to impute missing outcome values when the rate of missingness is between 10% and 50%. Results will be reported for both the imputed data sets and a data set including only those who had complete data (“completers only”) for comparison purposes.

Primary Objectives. To quantify the incidence and prevalence of biologic complications and prosthetic complications among patients receiving dental implant therapy in a private practice setting.
For biologic complications, three binary outcomes will be examined: Peri-implant mucositis, Peri-implantitis and implant failure. For prosthetic complications, six binary outcomes will be examined including loosening of screws, screw fracture, structural fracture, resin or porcelain fractures, loss of retention, and abutment/ implant misfit. For the primary analysis, all outcomes will be defined at the person level and will be binary (Y/N) regardless of the number of complications experienced per participant. The 3-year cumulative incidence will be calculated as a ratio, where the numerator will be the total number of persons with one or more new (not existing at baseline) complications by the end of the follow-up period, and the denominator will be the total number of persons at risk for that complication at baseline. The prevalence will be calculated using the total number of persons with a complication (both new and existing) divided by the total number of persons at risk during each time interval (baseline, year 1, 2, and 3). In addition, the incidence and prevalence will be computed separately by age group, DM, smoking status, medication use, Osteoporosis, Radiation therapy, Periodontitis diagnosis, and Gingivitis diagnosis. We will calculate incidence and prevalence for all complications except implant failure (incidence only). If data permits, we'll also examine the number and rates of repeated prosthetic complications and the disease progression in biologic complications (mm bone loss over time) for exploratory analysis.

Secondary Objectives. To examine risk factors for biologic and prosthetic complications among patients receiving dental implant therapy in a private practice setting.
The unit of analysis for the secondary objectives are at the implant level for the biologic complications and the prosthesis level for the prosthetic complications. All the outcomes are binary outcomes (Y/N), and for primary analysis only the first occurrence will be considered. Multiple implants/ prostheses are clustered within the same patient, and multiple patients clustered within practitioners. To account for these correlations, General Estimating Equations (GEE) will be used to identify practitioner, patient and implant variables that are associated with the complications. A binomial model with a logit link function will be used for these binary outcomes. Separate analyses will be conducted for each complication. The variables in table 3 will be considered as potential risk factors.

Secondary analysis will evaluate the association between patient/implant/prosthetic risk factors and the rates of repeated prosthetic complications and the disease progression in biologic complications. For the rates of prosthetic complications, the outcome will be the number (count) of prosthetic complications during the 3-year follow-up period. The unit of analysis will be at the person level, and Poisson models will be used to identify practitioner, patient and prosthesis risk factors that are associated with a higher rate of prosthetic complications. For disease progression in biologic complications, the outcome will be mm bone loss (continuous) over time. Mixed effects model will be used to

account for the longitudinal nature of the data and to identify the practitioner, patient and implant risk factors that are associated with a higher amount of bone loss.

Table 3.

Practitioner level factors	
Number of implants restored per month	biologic and prosthetic complications
Years in practice	biologic and prosthetic complications
Post graduate education	biologic and prosthetic complications
Specialty training	biologic and prosthetic complications
Patient level risk factor	outcome
Age at baseline	biologic and prosthetic complications
Diabetes Mellitus	biologic complications
Smoking status	biologic complications
Medication use SSRI Bone sparing drugs Corticosteroid use	biologic complications
Osteoporosis	biologic complications
Radiation therapy	biologic complications
Periodontitis diagnosis	biologic complications
Gingivitis diagnosis	biologic complications
Parafunctional habits	prosthetic complications
Implant/ Prosthesis level risk factor	
Bone Grafting at time of implant placement	biologic complications
Immediate loading	biologic complications
Reason for tooth loss: Periodontitis	biologic complications
Reason for tooth loss: Endodontic failure	biologic complications
Reason for tooth loss: Caries	biologic complications
Reason for tooth loss: Trauma	biologic complications
Congenitally missing	biologic complications
Removable prosthesis	biologic complications
Poor prosthetic fit	biologic complications
Emergence angle	biologic complications
Cement remnants present	biologic complications
Open contacts present	biologic complications
Single tooth restoration	biologic and prosthetic complications
Multiple unit restoration splinted	biologic and prosthetic complications

Cemented restoration	biologic and prosthetic complications
Custom abutment	biologic and prosthetic complications
Stock abutment	biologic and prosthetic complications
Removable prosthesis full arch	prosthetic complications
Removable prosthesis: poor retention	prosthetic complications
Screw retained prosthesis	prosthetic complications
Opposing dentition: Natural	prosthetic complications
Opposing dentition: Complete denture	prosthetic complications
Opposing dentition: Partial denture	prosthetic complications
Occlusion: Mutually protected	prosthetic complications
Occlusion: Group function	prosthetic complications
Prosthesis material: Porcelain	prosthetic complications
Prosthesis material: Zirconia	prosthetic complications
Prosthesis material: Plastic	prosthetic complications
Prosthesis material: Zirconia with Porcelain veneer	prosthetic complications

Tertiary (exploratory) Objectives. To explore the OHRQoL (Oral Health-Related Quality of Life) following implant therapy, and to explore patient/implant/therapy level factors associated with patient satisfaction and OHRQoL.

The data from the OHRQoL will be used to quantify overall satisfaction with implant therapy and quality of life post-implant therapy, and will be presented at each time point to explore any potential time trend. In addition to baseline demographics and clinical factors, the type and location of prosthesis as well as the different types of complications will be included in correlation analysis with the OHRQoL survey data (Table 2). Because the OHRQoL score is a continuous variable, mixed effects model will be used to examine the association between these patient/implant/therapy factors and the OHRQoL score to account for the longitudinal nature of the data.

Table 4.

Patient level factors
Age at baseline
Diabetes Mellitus
Smoking status
Peri-implant mucositis
Peri-implantitis
Implant failures
Periodontitis diagnosis
Gingivitis diagnosis
Parafunctional habits

Implant/ Prosthesis level factors
Removable partial prosthesis
Poor prosthetic fit
Fixed prosthesis
Open contacts present
Single tooth restoration
Multiple unit restoration splinted
Cemented restoration
Screw retained prosthesis
Custom abutment
Stock abutment
Removable prosthesis full arch
Fixed full arch prosthesis
Prosthesis material: Porcelain
Prosthesis material: Zirconia
Prosthesis material: Plastic
Prosthesis material: Zirconia with Porcelain veneer

Practitioner level factors
Number of implants restored per month
Years in practice
Post graduate education
Specialty training

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating practice and the NCC will maintain appropriate research records for this study, using the principles of and complying with regulatory and institutional requirements for the protection of confidentiality of subjects. Each practice and the NCC 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.

The following will be considered source documents for this study and will be maintained by the NCC via an EDC:

- Screening Log
- Baseline Patient Demographics Survey (completed by patient)
- Baseline Patient Characteristics Survey (completed by patient)
- Patient Contact Survey (completed by patient)
- Baseline Oral Health Quality of Life Survey (OHRQoL; completed by patient)
- Mucosal Characteristics Survey (completed by practitioner)
- Baseline Data Survey (completed by practitioner)
- Prosthetic Characteristics Survey (completed by practitioner)
- Radiographs of the study implants, collected at baseline and the 1-, 2-, and 3-year annual follow-up visits
- 1-, 2-, and 3-Year Patient Contact and Annual Follow-up Surveys
- 1-, 2-, and 3-Year Practitioner Annual Follow-up Surveys

All study source documents must be maintained in a secure manner, and authorized practice, ARC, or NCC personnel will have access to the source documents stated above.

13 QUALITY CONTROL AND QUALITY ASSURANCE

For quality management activities associated with data collection and processing, standard procedures for National Dental PBRN studies include automatic data quality checks in the EDC for each electronic CRF and the processes related to the manual review of data, discrepancy management, delinquent data handling, data updates, data verification and approval, and database audit. The EDC will be programmed with edit checks and response limiters to reduce data response errors. If out of range values are entered by the patient or provider, the individual will be alerted and asked to provide a value that is in range.

Reports will be created from the EDC system for the study team to address data accuracy and completeness. NCs will work directly with practices to address data discrepancies and/or missing data/CRFs. The PI will work closely with the NCC to ensure that the electronic CRFs are collected appropriately, and that confidentiality is being maintained according to protocol-specified procedures. Conference calls will be held approximately every month during the data collection phase with the study team and ARC and NCC personnel including NCs to monitor progress, manage study documentation and procedures, and troubleshoot any problems.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 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.

14.2 Institutional Review Board

The protocol and written information sheet will be submitted to the Central IRB for review and approval. Recruitment materials and all participant materials will undergo local context review by ceding IRBs. 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.

14.3 Informed Consent Process

Patients: Participating practices will designate who will execute consent procedures for the study. In most cases this will be the participating dentist. Any personnel who will be assigned to obtain consent will be defined as study personnel and must complete required IRB training. Consent procedures will be administered prior to performing any study-related assessments or procedures.

The patient's consenting process will be initiated via a conversation with the practitioner, pursuant to the overseeing IRB requirements. The practitioner or designee will explain the research study to the patient, answer any questions that may arise, and discuss risks and possible benefits of study participation, if applicable. If required by the responsible IRB, an electronic or paper consent form describing in detail the study procedures and risks will be given to the patient to read and review the document or have the document read to him or her. The participant will e-sign the consent document or give verbal approval of the consent process (depending upon central or regional IRB requirements), and a copy of the consent document will be emailed or given to the patient for his/her records if applicable. The consent process will be documented in the research record. Patients may withdraw consent at any time throughout the course of the study.

14.4 Exclusion of Women, Minorities, and Specific Age Groups

Children, defined as younger than 19 years, are excluded from this study because they have fewer permanent teeth, low treatment need for implants, have not undergone

reliability testing for measures, and are rarely seen in dental clinics for evaluation of implants. Racial and ethnic minorities will be included in this study at least proportional to the composition of the dentist's patient population. Individuals of any gender group may participate as well.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the study 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 study sponsor.

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

Certificate of Confidentiality

To further protect the privacy of study 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 participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

Confidentiality of Data Sharing

As described in section 16, 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.

14.6 Future Use of Stored Specimens and Other Identifiable Data

This observational study will not store any samples for future use.

The radiographic images are stored without any Personal Health Information attached to or associated with the images. These images could be used for future analysis for other purposes.

15 DATA HANDLING AND RECORD KEEPING

Study staff will maintain appropriate 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 subjects. Study staff 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.

15.1 Data Management Responsibilities

The PIs in collaboration with the NCC will review reports of data completeness and accuracy as well as protocol compliance on an ongoing basis throughout the study. A statement reflecting the results of the review will be sent to the NIDCR in the annual report. 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. The process and timeline for review will be detailed in the study-specific Data Quality Management Plan.

15.2 Data Capture Methods

Study-specific electronic questionnaires will be developed to include fields for all data elements and will be translated into electronic CRFs, which will be entered in a secure EDC system. Electronic CRFs will be used to obtain data from participating practitioners and patients at each study visit. The EDC system will also allow for digital radiograph upload. The NCC will conduct preliminary testing and review of data fields in the initial programming and online launch of the EDC. The NCC will ensure that all required data are collected per protocol requirements and edit checks will be programmed in the electronic CRFs to correct data issues in real time. The study team and NC's will respond to data queries generated by the EDC system to ensure correction of data errors. Reports or tools will be developed to help monitor the data capture activities, including checking data fields for completeness and accuracy. Summary reports of data completeness and accuracy will be made available to the study team and NIDCR as requested.

15.3 Schedule and Content of Reports

Quality Control (QC) 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 Manager. 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 Monitoring 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, etc. These summary reports will be viewable by study team members, network staff, NCC staff and NIDCR.

15.4 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 NIH.

15.5 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study procedures described in the IRB-approved clinical study protocol. The deviation may be on the part of the participant, the investigator, or study staff.

Consistent with the investigator obligations in the ICH E6 Guideline for Good Clinical Practice, ARC or NCC personnel will document in study source documents and explain any deviation from the IRB-approved protocol. The PI will report to the IRB any deviations or changes made to eliminate immediate hazards to participants and any changes that increase risk to participants and/or significantly affect the conduct of the study.

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.

16 PUBLICATION/DATA SHARING POLICY

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.

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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APPENDICES

APPENDIX A: Schedule of Events

Patient Procedures	**Study Visit 1 and Screening (Baseline) (Day 0)**	**Study Visit 2 (Day 365; range -30 days +150 days)**	**Study Visit 3 (Day 730; range -30 days +150 days)**	**Study Visit 4 (Day 1095; range -30 days +150 days)**
Assessment of Eligibility Criteria (Screening Log)	X			
Oral examination	X	X	X	X
Baseline Patient Characteristics Survey	X			
Baseline Oral Health Quality of Life Survey	X			
Mucosal Characteristics Survey	X			
Baseline Data Survey	X			
Prosthetic Characteristics Survey	X			
Patient Annual Follow-up Survey		X	X	X
Practitioner Annual Follow-up Survey		X	X	X
Radiographs uploaded	X	X	X	X