# The Common Practices of Head and Neck Examinations in U.S. Dental Offices

**NIDCR Protocol Number: 15-062-E**

**NIDCR Funding Mechanism:** U19-DE-22516

**NIDCR Grant Principal Investigator (GPI):**

Gregg Gilbert, DDS, MBA

**Study Principal Investigator (SPI):**

Walter J. Psoter, DDS, PhD.

**Institution:**

University of Rochester, Eastman Institute for Oral Health

**NIDCR Program Officials:**

Dena Fischer, DDS, MSD, MS

**Draft or Version Number: 9.0**

**09 March 2017**

## STATEMENT OF COMPLIANCE

The study will be conducted in accordance with 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 or Clinical Site Investigator:

| | | | |
|---|---|---|---|
| Signed: | | Date: | |
| | Name: Gregg H. Gilbert, DDS, MBA | | |
| | Title: Professor and Chair | | |

Study Principal Investigator:

| | | | |
|---|---|---|---|
| Signed: | | Date: | |
| | Name: Walter J. Psoter DDS, PhD | | |
| | Title: Associate Professor, University of Rochester, Eastman Institute for Oral Health | | |

Co-Investigators:

| | | | |
|---|---|---|---|
| Signed: | | Date: | |
| | Name: Douglas Morse DDS, PhD | | |
| | Title: Associate Professor, NYU College of Dentistry | | |
| Signed: | | Date: | |

| | | | |
|---|---|---|---|
| Signed: | | Date: | |
| | Name: Michael Robinson PhD | | |
| | Title: Professor, University of Florida | | |
| Signed: | | Date: | |

# TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

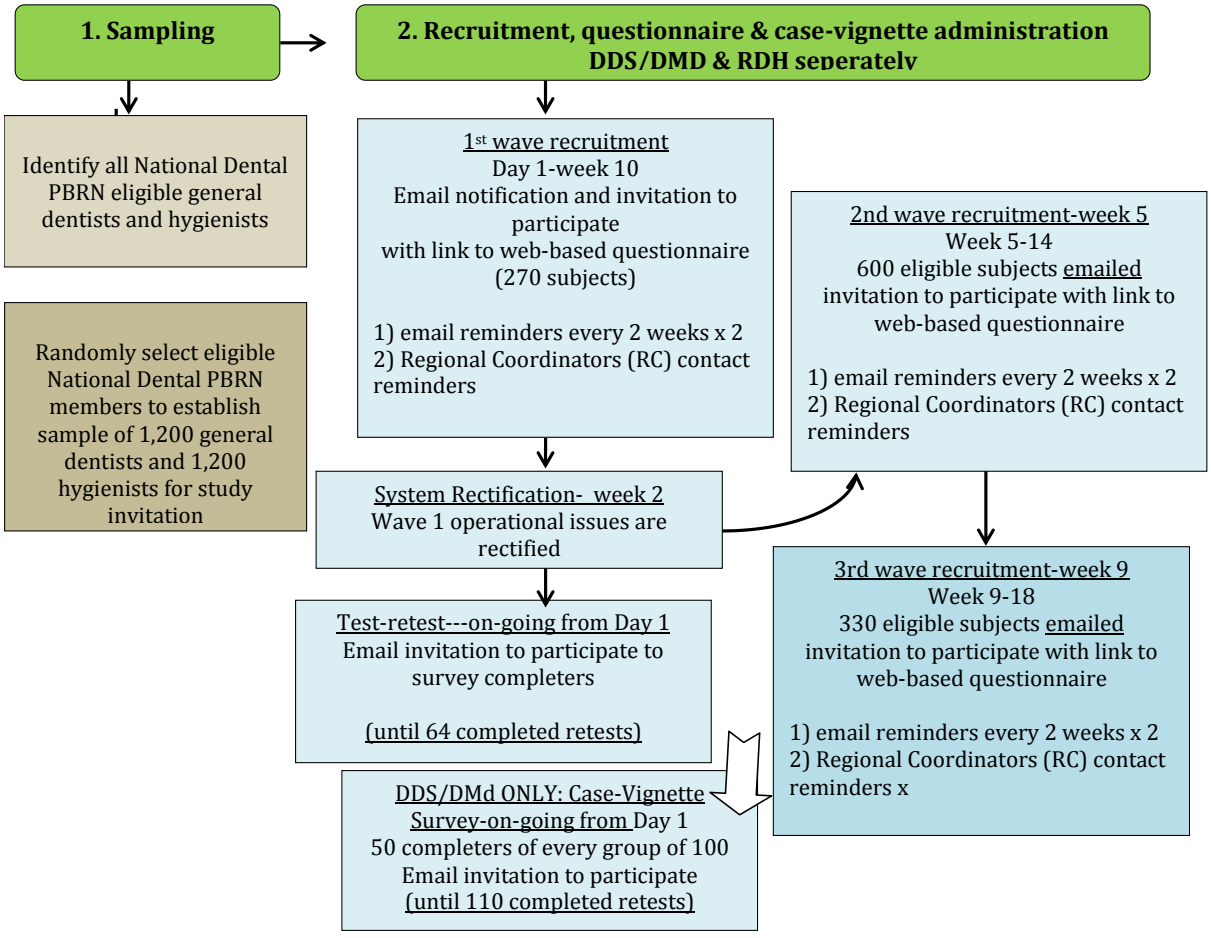
| | |
|---|---|
| CFR | Code of Federal Regulations |
| CC | Coordinating Center |
| DHHS | Department of Health and Human Services |
| DM | Data Manager |
| FFR | Federal Financial Report |
| FWA | Federalwide Assurance |
| GCP | Good Clinical Practice |
| GLM | Generalized Linear Model |
| GPI | Grant Principal Investigator (at CC) |
| HNC | Head and Neck Cancer |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| N (n) | Number (typically refers to participants) |
| ND-PBRN | National Dental Practice-Based Research Network |
| NIDCR | National Institute of Dental and Craniofacial Research, NIH, DHHS |
| NIH | National Institutes of Health |
| OC | Oral Cancer |
| OCE | Oral Cancer Examination |
| OCTOM | Office of Clinical Trials Operations and Management, NIDCR, NIH |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| RC | Regional Coordinator |
| SMS | Study Management System |
| SPI | Study Principal Investigator |
| US | United States |

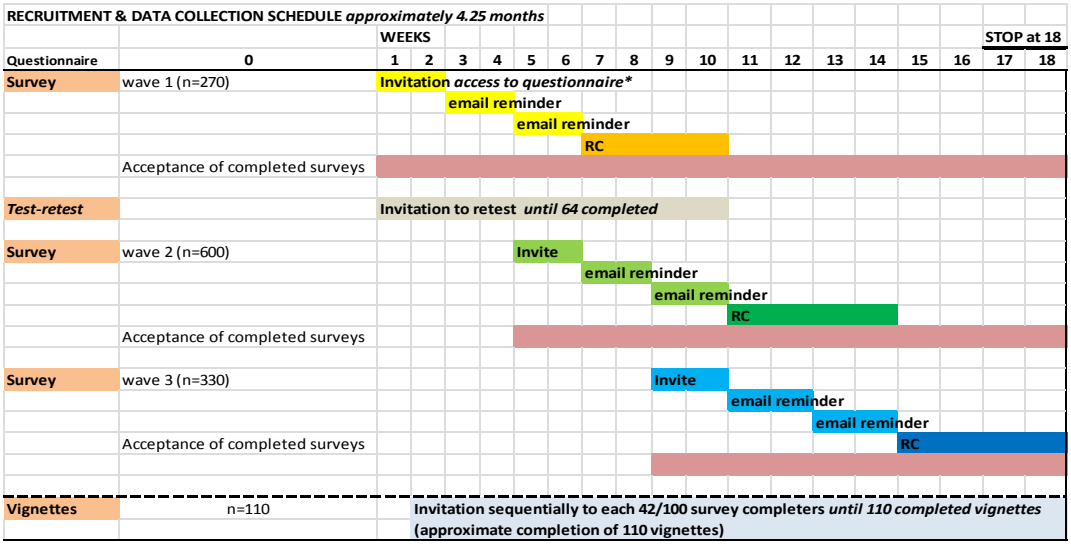
## PROTOCOL SUMMARY

| | |
|---|---|
| **Title:** | The Common Practices of Head and Neck Examinations in U.S. Dental Offices |
| **Précis:** | Worldwide, there were an estimated 274,000 new cases and 127,000 deaths attributed to oral cancer (OC) (ICD-O C00-C06),[1] and over 600,000 new cases of head and neck cancer (HNC) reported in 2008.[2] Over 70% of U.S. dentists self-report performing oral cancer (screening) examination (OCE) on most of their patients *over 40 years* of age, although the completeness, quality, frequency and validity of these examinations are unknown. [3-7] Regardless, 18% of adults (8% of Blacks and 7% of Latinos) aged 40 years and over are reported to have had an OC examination in the last year. [8] Moreover, only 20% to 29% of adults reported ever having had an OCE. [9-11] The <u>overall goal of the project is to ascertain common practices related to oral cancer examinations by U.S. dentists and dental hygienists</u>, by geographic region, demographics and practitioner and practice characteristics.<br><br>This is a National Dental Practice-Based Research Network (National Dental PBRN) survey study that consists of 2 components: 1) a questionnaire survey (33 questions), and 2) sixteen standardized clinical case-vignette presentations with 6 specific process questions. National Dental PBRN <u>general</u> dentists and dental hygienists will be invited to participate in the study to describe the details of the OCE, including who, what, when, where, and why, as well as the details involved with patient disposition of newly discovered "suspicious" for oral pre-malignant or malignant lesions. |
| **Objectives:** | The **<u>primary objective</u>** of this study is to describe the common practices of oral cancer examinations (OCEs) amongst National Dental PBRN practitioners based upon person, place and time.<br><br>The **<u>secondary objectives</u>** of this study are to describe the:<br>a) Communication practices between the practitioner and patient and the practitioner and referral clinician related to the OCE;<br>b) Practitioner and practice characteristics related to frequency and comprehensiveness of oral cancer examination *(predictors of quality & quantity of OCE)*;<br>c) Practice, practitioner, and lesion characteristics related to practitioners' suspicion for pre-malignancy or malignancy, lesion management decisions and preferred referral practitioner;<br>d) Self-reported number of identified lesions suspicious for pre-malignancy or malignancy and number of lesions biopsied or referred; |
| **Population:** | The sampling frame is all National Dental Practice-Based Research Network (National Dental PBRN) general practice dentists and |

| | |
|---|---|
| | hygienists. We will invite approximately 1,200 each of general dentists and hygienists who are active clinicians to participate in the study. The targeted yield will be 900 completed questionnaires for each practitioner type.<br><br>For the case vignettes survey, the sample will consist of 110 dentists who have completed the first questionnaire. |
| **Number of Sites:** | N/A |
| **Study Duration:** | Approximately 24 months. |
| **Subject Participation Duration:** | Approximately 30 minutes each to complete the survey and the clinical case presentations (vignettes). |
| **Estimated Time to Complete Enrollment:** | Approximately six months. |

## Figure 1: Schematic of Study Design:
## OCE study flow chart: Questionnaire & Case-Vignettes



# 1 KEY ROLES AND CONTACT INFORMATION

| | |
|---|---|
| **Grant Principal Investigator:** | Gregg H. Gilbert, DDS, MBA<br>Professor and Chair<br>University of Alabama at Birmingham<br>1720 Second Ave. South<br>School of Dentistry, SDB 109<br>Birmingham, AL 35924-0007<br>Phone: 205-975-8886<br>Fax: 205-975-0603<br>Email: ghg@uab.edu |
| **Study Principal Investigator:** | Walter J. Psoter, DDS, PhD<br>Associate Professor<br>Eastman Institute for Oral Health<br>625 Elmwood Avenue, Box 683<br>Rochester, NY 14620<br>Email: wp9@nyu.edu |
| **NIDCR Program Officials:** | Dena Fischer, DDS, MSD, MS<br>Phone: 301-594-4876<br>NIH/NIDCR/DER<br>6701 Democracy Boulevard, MSC 4878<br>Bethesda, MD 20892-4878<br>Email: dena.fischer@nih.gov |
| **Coordinating Center:** | Westat<br>1600 Research Boulevard<br>Rockville, MD 20850 |

| | |
|---|---|
| **Institutions:** | **Western Region (region #1)**<br>Administratively based at the Kaiser Permanente Center for Health Research, Portland Oregon<br>Lisa Waiwaiole, Regional Coordinator<br>Kaiser Permanente Center for Health Research<br>3800 N. Interstate Ave.<br>Portland, OR 97227-1110<br>Office: (503) 335-2454<br>Fax: (503) 335-6311<br>Email: Lisa.Ann.Waiwaiole@kpchr.org<br><br>**Midwest Region (region #2)**<br>Administratively based at the HealthPartners Institute for Education and Research in Minneapolis, MN<br>Emily Durand, Regional Coordinator<br>HealthPartners Institute for Education and Research<br>8170 33rd Avenue South<br>MS: 21111R<br>Minneapolis, MN 55445<br>Office: (952) 967-7404<br>Fax: (952) 967-5022<br>Email: Emily.C.Durand@HealthPartners.com<br><br>**Southwest Region (region #3)**<br>Administratively based at the University of Texas Health Science Center at San Antonio in San Antonio, TX<br>Stephanie C. Reyes, Regional Coordinator<br>7703 Floyd Curl Drive, MC 7894<br>San Antonio, TX 78229<br>Office: (210) 562-5654<br>Fax: (210) 562-4136<br>Email: reyess@uthscsa.edu<br><br>**South Central Region (region #4)**<br>Administratively based at the University of Alabama at Birmingham in Birmingham, AL<br>Andrea Mathews, Program Manager<br>Department of Clinical and Community Sciences<br>School of Dentistry, SDB 114<br>1720 2nd Avenue South<br>Birmingham, AL 35294-0007<br>Office: (205) 934-2578<br>Fax: (205) 996-2172<br>Email: ahmathews@uab.edu |

| | |
|---|---|
| | **South Atlantic Region (region #5)**<br>Administratively based at the University of Florida in Gainesville, FL<br>Deborah McEdward, Regional Coordinator<br>University of Florida<br>P.O. Box 100415<br>Gainesville, FL 32610<br>Office: (352) 273-5848<br>Fax: (352) 273-7970<br>Email: dmcedward@dental.ufl.edu<br><br>**Northeast Region (region #6)**<br>Administratively based at the University of Rochester in Rochester, NY<br>Vi Luong, Regional Coordinator<br>Eastman Institute for Oral Health<br>625 Elmwood Avenue, Box 683<br>Rochester, NY 14620<br>Phone: (585) 275-5780<br>Fax: (585) 273-1237<br>Email: vi_luong@urmc.rochester.edu |
| **Other Key Personnel:** | • Alexander R. Kerr, DDS, MSD (Oral Medicine, NYU)<br>• Maria Lucia Aguilar, DDS, MSD, MS-CI (Network Enrolled Dentist)<br>• Cyril Meyerowitz, DDS, MS (General Dentist, University of Rochester)<br>• Bob Harris, PhD (Statistician, (Westat) as study team member)<br>• Vi Luong (Lead Regional Coordinator, University of Rochester) |

# 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 Background Information

There were an estimated 274,000 new cases of, and 127,000 deaths attributed to oral cancer (OC) (ICD-O C00-C08) worldwide in 2002.[12] Moreover, oral and pharyngeal cancer (OPC) accounted for a projected 40,250 new cases and 7,850 deaths in the United States in 2012,[13] with mouth (oral) cancers comprising approximately 65-70% and oral-pharyngeal 30-35% when salivary gland malignancies are excluded (based on SEER site-specific incidence rates, 2012).[14] Intraoral cancers are predominantly squamous cell carcinomas that generally arise from pre-malignant lesions[15,16] although the majority of oral precancerous lesions do not transform to cancer.[16] It is generally agreed that oral precancerous lesions should be biopsied and evaluated histopathologically. [16-19] A histopathologic diagnosis can be used in assessing disease status and in determining when treatment should be initiated, with the intention of preventing disease progression. Lesion excision, risk factor elimination, and close patient follow-up, offer the best currently available options to manage such lesions. [20,21] As with oral precancerous lesions, early-stage oral cancers are more likely to be asymptomatic than late-stage cancers. The importance of an early diagnosis of OPC is that 5-year relative survival rates are notably higher for persons diagnosed with localized (83%), relative to regional (54%) or metastatic (32%) disease. [22-24] In addition, early, relative to late-stage, OC is associated with decreased treatment-associated disfigurement and other severe physical, social, and psychological morbidities. [25,26] An objective of Healthy People 2010 was to increase the percentage of oral [and pharyngeal] cancers detected at the earliest stage (stage I, localized) to 50%, while an objective of Healthy People 2020 is to increase the proportion of adults receiving an OC screening at least annually. However, it is reported that the distribution by staging at the time of OPC diagnosis is: 33% localized; 45% regional; 17% distant; and 6% unstaged [27] demonstrating a clear delay in the diagnosis of OPC and a significant shortfall in meeting the 2010 objective.

Over 70% of U.S. dentists self-report performing oral cancer (screening) examination (OCE) on most of their patients over 40 years of age, although the completeness, quality, frequency and validity of these examinations are unknown. [3-7] Regardless, the Centers for Disease Control documents that 18% of adults (7% of Blacks and 6% of Latinos) aged 40 years and over are reported to have had an OC examination in the last year. The proportion of high school graduates having an OCE was only 13% and for those not completing high school, the proportion having an OCE dropped from 5% in 1998 to 4% in 2008.[8] Moreover, only 20% to 29% of adults reported ever having had an OCE (1998, 2004). [9-11] Focus groups and surveys of dentists have revealed perceived training deficiencies in both OCE technique and the practitioners' thoroughness. [28-30] Our recent studies in Puerto Rico suggest this is generalizable to all graduates of ADA accredited dental schools; we identified a perceived lack of screening knowledge and personal competency; creating a significant barrier to OCE. [31,32]

*The overall goal of the project is to ascertain the common practices related to oral cancer examinations by U.S. Dentists and Dental Hygienists, by geography, demographics and practitioner and practice characteristics.*

## 2.2 Rationale

There is a body of mutually supportive literature regarding dentist OCE practice issues. In

aggregate, reports suggest that dentists: 1) have insecurity about conducting OCE, [29,33-36] 2) have concerns that patients may have a negative reaction, [29,34,37,38] 3) have concerns that the staff may not be able to communicate OC information adequately, [37,38] 4) have a belief that screenings take too much time,[29,34,37,38] 5) may conduct OC examinations during an initial visit rather than periodically, [6,29,33] 6) prefer more dental school training and continuing education, [3,5,33,34,39] 7) frequently conduct visual inspections only, [29] and 8) prefer that education in multiple formats/settings is desirable. [29,33,34,36,37,40,41] A limited number of reports suggest that potentially effective mechanisms to increase OCE are available although not applied systematically at this time, raising real questions regarding all aspects of current OCE practices across the dental profession, which this proposed study seeks to identify.

The U.S. Preventive Services Task Force (USPSTF) states that "dentists and dental care providers (i.e. dental hygienist), by their profession, examine the oral cavity during the clinical encounter". However, as a recent review has found, little has been reported since 1990 regarding hygienists and head and neck examinations. In the earlier period, it was found that hygienists generally conducted head and neck exams more frequently than dentists, although hygiene exams relied more on visual only rather than visual-tactile, and as the reviewers state: "hygienists' patient assessments and examinations are considered a vital link to dentists' evaluation of patients and pivotal to patient's diagnoses, treatment planning and long term preventive dental care. Yet we have no strong data to support anecdotal and outdated information."[42] Thus, in meeting the Healthy People (2010, 2020) objectives, it is important to gain an understanding about the common practices of head and neck examinations amongst National Dental PBRN practitioners, pertaining to who is doing OCE and on which patients (Person: examiner, patient characteristics), what is the completeness and quality of the exam, i.e., what tissues are being examined in what manner (Place: anatomy, technique), and when are quality OCEs being conducted, e.g., only new patients, annually (Time: frequency). Of additional importance in understanding the OCE ecology are the interactions and processes (e.g., the process for patient disposition in cases of the presence of a "suspicious lesion," the patient actions on being referred for biopsy) between the patient and doctor, and the doctor and patient with the referral specialist. The proposed study will explore the representative distribution of these unknown OCE practices across dental professionals. The National Dental PBRN represents an ideal and cost-effective mechanism to address these critically important questions regarding the person, place, and time distribution of OCE amongst National Dental PBRN practitioners and the resulting disposition and follow-up of patients upon suspicious lesion discovery.

## 2.3 Potential Risks and Benefits

### *2.3.1 Potential Risks*

Risks for the proposed study are minimal. Participants may not feel comfortable answering particular questions on the survey or the clinical case presentations (vignettes). As such, they will have the option to skip questions or to not complete the study.

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. All study documents (e.g. electronic data files) will be kept in a locked file only accessible to research and Coordinating Center (CC) staff members. Identical procedures will be followed by the study PI (SPI) and his designated study team members at their sites. Compliance with all Institutional

Review Board (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.

# 3 OBJECTIVES

## 3.1 Study Objectives

The **primary objective** of this study is to describe the common practices of oral cancer examinations (OCEs) amongst National Dental PBRN practitioners based upon person, place and time.

The **secondary objectives** of this study are to describe the:

a) Communication practices between the practitioner and patient and the practitioner and referral clinician related to the OCE;
b) Practitioner and practice characteristics related to frequency and comprehensiveness of oral cancer examination *(predictors of quality & quantity of OCE)*;
c) Practice, practitioner, and lesion characteristics related to practitioners' suspicion for pre-malignancy or malignancy, lesion management decisions and preferred referral practitioner;
d) Self-reported number of identified lesions suspicious for pre-malignancy or malignancy and number of lesions biopsied or referred;

## 3.2 Study Outcome Measures

The study outcomes will be ascertained through a questionnaire survey and standardized clinical case presentations (vignettes).

*See Figure 2* for partial perceptional model of the three dimensions of selected outcomes to be determined.

*To describe common practices of OCEs amongst National Dental PBRN practitioners*, the following primary outcome measures will be obtained, separately for hygienists and dentists:

a) Person:
   i) Who conducts the OCE (provider characteristics)
   ii) Which patients receive OCEs (patient characteristics/perceived risk factors)
   iii) From whom are patients referred, if anyone (which provider)
   iv) To whom are patients referred, if anyone and why (which provider, for what purpose)
b) Place:
   i) What anatomical sites are examined
   ii) Difference in anatomical sites examined based upon patient characteristics/perceived risk factors
   iii) How are sites examined, including adjunct diagnostic tests/procedures used, utility of adjunct tests/procedures, how are findings integrated into treatment plan
c) Time:
   i) When are patients having an OCE, e.g., new visit only, recall, annual visit
   ii) When are patients with "suspicious" for pre-malignant/malignant lesions referred
   iii) Is a follow-up appointment scheduled with the practitioner when a biopsy is performed

*To describe the communication practices between the practitioner and patient and the practitioner and referral clinician related to the OCE,* communication practices will be obtained:

a) Between the practitioner and patient for:
   i) Lesion discovery
   ii) Referral for lesion
   iii) Positive biopsies that practitioner conducted
b) Between the practitioner and referral clinician:
   i) Whether or not there is a written referral
   ii) What information is included in referral
   iii) Whether or not an appointment for the referral is scheduled by the dental office
   iv) How results are received from referral clinician, e.g., written report, copy of biopsy report, phone call

*The frequency and comprehensiveness of oral cancer examination obtained through the primary outcome measures (person, place and time characteristics), as well as lesion suspicion and management decisions (described below) will be compared by the following practice and practitioner characteristics* (as a minimum) obtained through the National Dental PBRN Enrollment Questionnaire and the Study Survey:

A. Practice characteristics:
   a. Region
   b. State
   c. Practice location, e.g., inner urban/urban/suburban/rural
   d. Practice type, e.g., owner, public health clinic
   e. Number of practitioners in practice
   f. Wait time for appointment
   g. Race/ethnic distribution of patients
   h. Payor class distribution of patients
   i. Using electronic records
   j. Proportion regular attending patients

B. Practitioner characteristics demographic:
   a. Age
   b. Sex
   c. DDS/DMD, RDH
   d. Years since graduating dental school
   e. US/Canadian dental school
   f. Completed residency
   g. Weekly hours practicing
   h. Number of professional organizations a member of
   i. Number of patients treated per week (average)
   j. (RDH) school type, e.g., 2 year, 4 year
   k. (RDH) highest degree
   l. Number hours of continuing education related to oral cancer, OCE, lesion diagnosis
   m. Hands-on OCE training

C. Practitioner characteristics clinical:
   a. Overall confidence in conducting examination procedures
   b. Characteristics of patients receiving OCE
   c. Number of suspicious lesions observed per 6 month period

d. Use of ancillary tests
e. Sufficient time for OCE
f. Sufficient reimbursement for OCE

*To describe the practice, practitioner, and lesion characteristics related to practitioners' suspicion for pre-malignancy or malignancy, lesion management decisions, and preferred referral practitioner*, the following outcomes will be obtained through the questionnaire and vignettes:

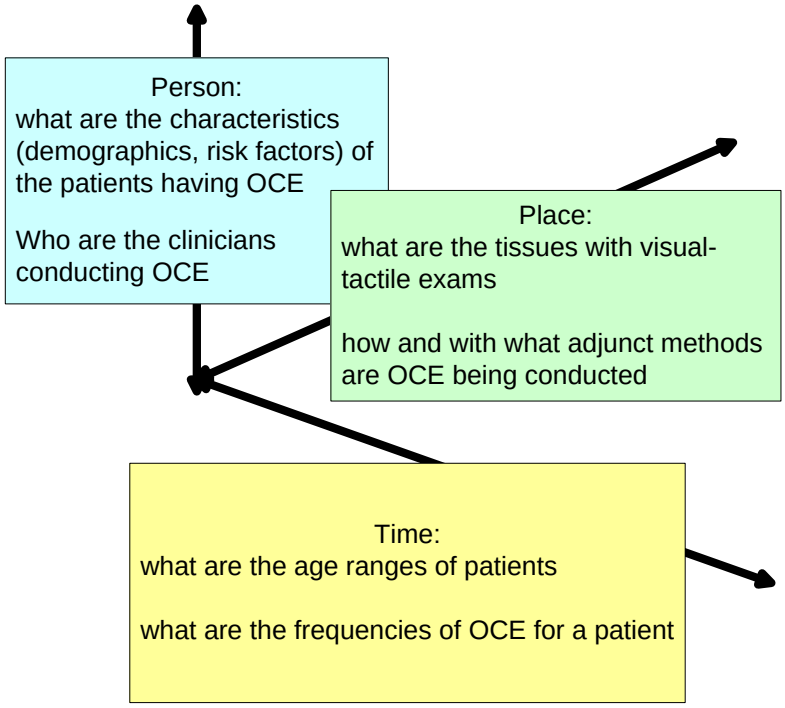
a) Mucosal lesion "parameters of suspicion" for pre-malignancy/malignancy by history, signs & symptoms; and

b) What are the suspicion parameters that define treatment planning decisions, such as watch & wait, perform biopsy, refer for consult/biopsy; what sort of follow-up does the dentist conduct.

*The self-reported number of lesions identified as suspicious for pre-malignancy or malignancy and number of lesions biopsied or referred within the past 6 months* will be ascertained through questionnaire responses:

a) The number of lesions identified as suspicious for pre-malignancy or malignancy
b) The number of biopsies for lesions suspicious for pre-malignancy or malignancy
c) The number of referral consultations for lesions suspicious for pre-malignancy or malignancy
*d)* Practitioner/practice characteristics (described above) predictive of increased biopsies/consults

Figure 2: Perceptional model of dimensions addressed in *Common practices of OCE study*



# 4 STUDY DESIGN

This is a cross-sectional survey study that consists of 2 components 1) a questionnaire survey (33 questions), and 2) sixteen (16) standardized clinical case-vignette presentations with six (6) standard, process questions applied to each vignette. National Dental Practice-Based Research Network clinical general dentists and hygienists will be invited to participate in the study, which aims to describe the common practices of OCEs and the details involved with patient disposition of discovered “suspicious” lesions.

The investigation will consist of 2 cross-sectional surveys. For the first survey, approximately 1200 general dentists and 1200 hygienists will be invited to participate, with a target of 1800 completed questionnaires, 900 for each group. All eligible participants will receive a study invitation email that informs them about the study. The email will also include a link to the electronic version of the survey. There will be 3 waves of email invitations (approximately 4 weeks between Waves 1 and 2, then approximately 3 weeks between Waves 2 and 3). In wave 1, approximately 270 eligible participants will be invited, with response difficulties ascertained and rectified, if present. Beginning with Wave 1, respondents (DDS and RDH) will also be invited to repeat the questionnaire for test-retest reliability (required n=64). For wave 2, approximately 600 remaining eligible participants will be invited to participate. Wave 3 will include the remaining eligible participants (n~330). Following the initial email invitation, there will be a series of prompts within each wave to encourage study participation. For non-responders, an email reminder will be sent at approximately 2 weeks and, if needed, 4 weeks from the invitation email, followed by the Regional Coordinators (RCs) making contacts with the non-responders beginning at approximately 6 weeks post-invitation. Survey completions will be accepted until study data collection is terminated.

Resampling will be conducted in the unlikely event that insufficient participants are recruited from the 2,400 initial invitees. Wave 1 (n=270) test-retest assumes 65% response from electronic only initial invitations and approximately 40% response from request for the retest.

The second survey is a cross-sectional “translational survey” comprised of 16 standardized case presentations-case vignettes. Only general dentists will be eligible to participate in this survey, and a systematic sample of responders of the first survey will be invited to complete the case-vignette questionnaire. In sequential order, approximately 50 of each 100 questionnaire participant groupings, i.e., as each one-hundred completed surveys are accrued, 50 participants will be invited to participate until 110 vignette completions are achieved. This second survey (case-vignettes) target is 110 completions and will take approximately 30 minutes to complete. Resampling will be conducted from the respondents in the very unlikely event that insufficient participants are recruited from the 1,200 initial dentist invitees.

The two study components will be delivered sequentially with the vignette recruitment beginning as soon as 50 Wave 1 questionnaire are completed; the questionnaire survey will be completed by a participant, and then he/she will be invited to participate in the case-vignette questionnaire with the case-vignettes delivered to that participant for completion. One follow up email will be made for case-vignette non-responders one week after they receive the initial email and if no response is provided within 3 weeks of the original email they will be closed out of the study.

Development and administration of the questionnaire is detailed in Section 7.1.

# 5 STUDY ENROLLMENT AND WITHDRAWAL

## 5.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, a participant must meet the following criteria:

1. age ≥ 18 years old;
2. is a current limited or full participation member of the National Dental PBRN;
3. is a practicing clinical general dentist or a Registered Dental Hygienist; and
4. is licensed in the U.S. to treat patients, treats patients in the U.S. on a recurring basis and has current contact information on file at which he or she can be contacted.

## 5.2 Strategies for Recruitment and Retention

Recruitment

The sampling frame includes all dentist and hygienist members of the National Dental PBRN. Eligible participants for the first survey will be identified based on criteria noted from their responses to the National Dental PBRN Enrollment Questionnaire. A random sample of 1,200 dentists and 1,200 dental hygienists will comprise the recruitment pool. All eligible participants will receive an email invitation from the CC inviting them to participate in the study. The email invitation will include a link to the electronic version of the questionnaire. Dentists and hygienists will have an opportunity to complete an electronic questionnaire. Based on previous PBRN survey studies, we anticipate a response rate of approximately 75+%. Calls will be held as needed with the Regional Coordinators to review contact information for eligible practitioners discuss recruitment issues and enrollment progress, manage study documentation and procedures, and troubleshoot problems related to enrollment.

Compensation

Participants will be reimbursed $50 for completing the questionnaire. If a participant completes the test-retest of the online questionnaire, or the vignette phase of the study, then an additional $50 will be provided for each study activity.

## 5.3 Subject Withdrawal

Participants may choose not to participate in the study and/or withdraw voluntarily from the study for any reason at any time without penalty.

### *5.3.1 Handling of Subject Withdrawals*

It is anticipated that participants will not be replaced since the invitation numbers are based on prior National Dental PBRN recruitment experience.

## 5.4 Premature Termination or Suspension of Study

The 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 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 futility.

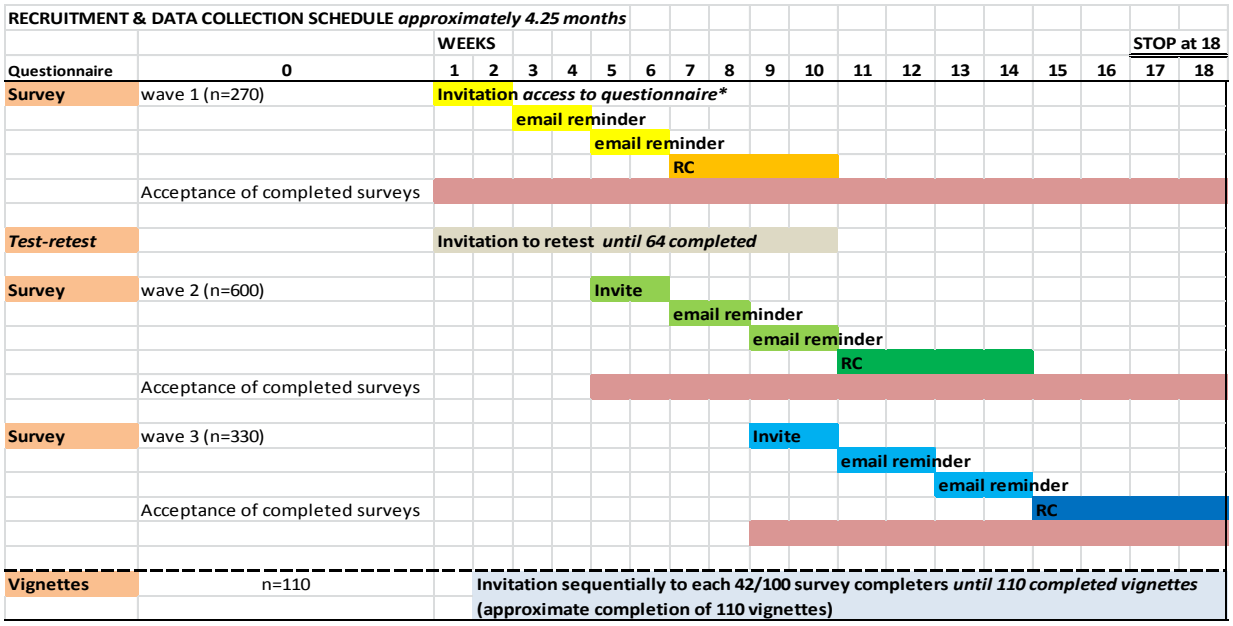
# 6 STUDY SCHEDULE

## 6.1 Enrollment/Baseline – first survey

For this cross-sectional study, eligible practitioners will be identified based upon responses to the National Dental PBRN Enrollment Questionnaire and will be invited to complete an online questionnaire over a period of three to four months.

## 6.2 Enrollment/Baseline – case/vignette (second) survey, parallel with first survey

Online responders who are dentists will be invited to complete an additional case-vignette survey. As described in Section 4, first survey completers will be invited into the second survey until 110 vignette completions are achieved.



# 7 STUDY PROCEDURES/EVALUATIONS

Survey and Vignette Development

This survey was developed by our study team, which had input from oral medicine and pathology specialists, epidemiologists, including cancer epidemiologists, clinicians and questionnaire methodologists. Following the development of the survey, the instrument was reviewed and evaluated by Instrument Design, Evaluation, and Analysis (IDEA) Services at the Coordinating Center, a group with expertise in survey development and implementation. Survey researchers believe that pretesting new surveys can have a substantial positive effect on data quality.

Cognitive Interviewing

A pretest of both the questionnaire and vignette was given to 10 clinical dentists and hygienists recruited from a list provided by the National Dental PBRN in the form of cognitive interviews conducted over the telephone. The interviews were conducted by IDEA Services at Westat. Ten practitioners (dentists and hygienists) were approached and 10 interviews were conducted. During the interviews, respondents reviewed their responses to the completed questionnaire and vignettes, and cognitive interviewers probed to assess possible respondent problems in understanding questions, recalling necessary information, and/or reporting accurately. Participating dentists and hygienists were asked how relevant they thought the items in the draft questionnaire and case presentations were to issues of OCE, and whether any issues relevant to OCE were not addressed in the questionnaire or case presentations. A paper version of the instruments was used during this assessment, because it provided an opportunity to observe if respondents had problems with instructions or any other language in the questionnaire. Results from the pretest resulted in questionnaire and vignette revisions.

Survey Testing-Retesting Format

The online version of the survey will be administered twice to a subset of approximately 64 online respondents to assess the test-retest reliability of the survey. Beginning with Wave 1, survey completers will be invited to retake the survey. Participants will be required to return the retest within 2 weeks of the invitation email. If the test is not completed within the timeframe, the link to the retest survey will be disabled. Each questionnaire will take approximately 30 minutes to complete. Administration of the testing-retesting will continue until 64 completed responses are obtained. The test-retest phase will be completed electronically only.

Website and Survey/Vignette Pilot Testing

The CC's IT team will perform internal testing of the website, including internet browser compatibility. Study team members (e.g., SPI, National Network Director (NND), Regional Directors, Statistician and Regional Coordinators (RC)) will also be given the opportunity to externally test the website prior to administration with study participants.

Survey and Vignette Content

Survey items will include the date and other items used to assess outcome measures specified in subsection 3.2. Some information will be collected from the National Dental PBRN Enrollment Questionnaire (e.g., practitioner and practice characteristics) and linked to participants' responses to the study questionnaire. More specifically:

*The OCE questionnaire survey*

The survey will describe a comprehensive, detailed, multidimensional picture of OCE practices and associated elements, including communication and treatment planning by National Dental PBRN practitioners. The questionnaire will be structured and self-administered on-line and will be designed with skip patterns as appropriate. Participants will have the option to skip questions or not complete the study.

*The case presentations (vignettes)*

The cases presented and their associated questions will provide information regarding the conduct of OCE for patients with different signs and symptoms, and lesion appearance. Specifically, the variable vignette attributes are: lesion color (white, red), location (relatively high-risk/low-risk location), pain, and induration. The case presentations will also explore differences in the disposition of cases as well as patient and consultant communication (when used). The questions will parallel those of the OCE questionnaire survey as applicable for a particular standardized case. The 16 cases are comprised of 4 clinical pictures, each picture with the signs and symptoms having 4 iterations involving, for example, differences in the sign of induration (+/-).

Survey Administration

Eligible participants' i.e., general dentists and hygienists will be identified from their responses to the network's enrollment questionnaire. Although unlikely, responses from participants who do not meet eligibility criteria but who still are asked to complete the survey will be removed prior to statistical analyses.

A waiver of documentation of signed informed consent for participants who complete the electronic survey will be requested. Consistent with regulations outlined by the University of Alabama (UAB) IRB and any regional/local IRBs, information about the study will be provided to all eligible participants in the initial email invitation regarding the upcoming invitation to participate in the study. Completion of the survey will indicate tacit consent.

After the invitation and 2 follow-up email reminders, the CC will provide the RCs with a list of non-responders. The RCs will systematically contact non-responders to encourage survey completion.

If no feedback is received or the participant does not complete the questionnaire after multiple follow up attempts over a period of three months, it is assumed the practitioner is not interested in the study.

Vignette Administration

The 16 cases of each case-vignette survey will be randomized for sequence for each individual subject.

On completion of the case-vignette data collection, all vignette participants will be emailed the 4 case-vignette pictures with the reported histopathologic diagnoses.

# 8 ASSESSMENT OF SAFETY

## 8.1 Specification of Safety Parameters

Safety monitoring for this study will focus on unanticipated problems involving risks to participants.

### *8.1.1 Unanticipated Problems*

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects 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 subject 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 subjects 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

Per National Dental PBRN procedures, unanticipated incidents and events will be reported to the SPI. After the SPI 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 to the IRB and to NIDCR within 2 weeks of the investigator becoming aware of the problem.

- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 1 month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems 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

# 9 STUDY OVERSIGHT

The 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 CC will provide the SPI with current data summaries, and the SPI will review the data for safety concerns and data trends at regular intervals, and will report to the IRB and NIDCR any Unanticipated Problem (UP) or any other significant event that arises during the conduct of the study, per the IRB's reporting time-frame requirements. To ensure data integrity, the SPI, CC, and study team will adhere to quality management processes (see Section 13).

## 10 CLINICAL SITE MONITORING

Clinical site monitoring will not occur for this study. The CC is responsible for launching the study (survey and vignettes) and collecting data received as part of the study. Quality assurance (QA)/Quality Control (QC) activities associated with data collection and processing will be outlined in the Data Management Plan. The CC will ensure that the quality and integrity of study data and data collection are maintained.

# 11 STATISTICAL CONSIDERATIONS

## 11.1 Study Design / Study Hypotheses

This is a cross-sectional survey of the common practices of oral cancer examinations conducted by clinical dentists and dental hygienists. As such, formal hypothesis testing will not be conducted to achieve the study objectives. The study is powered to provide: a) estimates of oral lesions determined by National Dental PBRN practitioners to be suspicious for pre-malignancy/malignancy and biopsied or referred for biopsy, and b) the relative contribution of four cues in decision making about oral lesions suspicious for pre-malignancy/malignancy.

## 11.2 Sample Size Considerations

This investigation encompasses two cross-sectional surveys. The first survey will describe the epidemiology of OCE practices amongst National Dental PBRN practitioners, including key factors associated with OCE and communication practices related to OCE. Additionally, this study will describe practitioner and practice characteristics that predict the level of OCE quality and quantity (frequency).

The second survey involves case-vignettes to examine the decision-making process for identifying suspicious lesions. The sample size estimates for each of these two surveys differ, as described below.

### 11.2.1 OCE survey

For the purpose of sample size estimation, a goal for the OCE survey is to generate point estimates with good precision (narrow confidence intervals) of numbers of oral lesions in the past four months practitioners estimate they:

- Identified as being clinically suspicious for oral cancer/pre-malignancy and biopsied themselves
- Identified as being clinically suspicious for oral cancer/pre-malignancy and referred for consult or biopsy

**Confidence intervals for estimated means:** We require a precise estimate of the mean for the purpose of planning the subsequent follow-on longitudinal study of patients with newly discovered lesions. The table below provides estimates of the sample size required for constructing a two-sided 95% confidence interval (CI) with overall target widths of 4, 6 and 8, with unknown standard deviation, as might be the case when estimating the average percentage of oral lesions that dentists biopsied themselves that were clinically suspicious for pre-malignancy/malignancy. Here the 'Confidence Level' represents the proportion of confidence intervals (constructed in the same manner using the same assumptions and sample size) that would contain the population mean. A sample size of 865 yields a two-sided 95% confidence interval with a distance from the mean to the upper (or lower) limit of the CI that is equal to 2 (1.999) when the estimated standard deviation is 30.0 (highlighted row in table). As the observed standard deviation increases for a fixed target width, the required sample size increases, as it does when the target width narrows for a fixed standard deviation. Given the

stringent demands of the primary question for precision, estimation of all other means will be well powered including those for multiple subgroups.

| Confidence Level | Sample Size (N) | Target distance from mean to CI Limits | Actual distance from mean to CI Limits | Standard deviation(S) |
|---|---|---|---|---|
| 0.95 | 219 | 2.0 | 1.998 | 15.0 |
| 0.95 | 387 | 2.0 | 1.999 | 20.0 |
| 0.95 | 602 | 2.0 | 1.997 | 25.0 |
| **0.95** | **865** | **2.0** | **1.999** | **30.0** |
| 0.95 | 99 | 3.0 | 2.992 | 15.0 |
| 0.95 | 174 | 3.0 | 2.993 | 20.0 |
| 0.95 | 270 | 3.0 | 2.995 | 25.0 |
| 0.95 | 387 | 3.0 | 2.998 | 30.0 |
| 0.95 | 57 | 4.0 | 3.980 | 15.0 |
| 0.95 | 99 | 4.0 | 3.989 | 20.0 |
| 0.95 | 153 | 4.0 | 3.993 | 25.0 |
| 0.95 | 219 | 4.0 | 3.995 | 30.0 |

**Confidence intervals for a proportion:** Below are estimates of the sample size required for constructing a two-sided 95% CI, of pre-specified width, for different assumed levels of the proportion, using a simple asymptotic formula. It is assumed that at least one questionnaire item response will be in the 50% response range, and that it is desired that the estimated study proportion be within ±3.75% of the true population proportion, a confidence range we are targeting. An example question asks: “When conducting an OCE, do you specifically mention to most of your patients that oral cancer is one of the abnormalities you will be checking for?” A sample size of 683 produces a two-sided 95% CI with a total width of 0.075 (7.5%) when the true proportion is equal to 0.50 (highlighted row in table); that is, the estimated proportion is expected to be between 46.3% and 53.7% when the true proportion is 50.0%. Other entries in the above table are interpreted similarly. As the observed proportion increases for a fixed target width, the required sample size would decrease; with an increased target width for the confidence interval, the required sample size would decrease for a fixed proportion.

| Confidence Level | Sample size (N) | Target width | Actual width | Proportion (P) | Lower limit | Upper limit | Width if P = 0.5 |
|---|---|---|---|---|---|---|---|
| 0.950 | 1537 | 0.050 | 0.050 | 0.500 | 0.475 | 0.525 | 0.050 |
| 0.950 | 1291 | 0.050 | 0.050 | 0.700 | 0.675 | 0.725 | 0.055 |
| 0.950 | 984 | 0.050 | 0.050 | 0.800 | 0.775 | 0.825 | 0.062 |
| 0.950 | 554 | 0.050 | 0.050 | 0.900 | 0.875 | 0.925 | 0.083 |
| **0.950** | **683** | **0.075** | **0.075** | **0.500** | **0.463** | **0.537** | **0.075** |
| 0.950 | 574 | 0.075 | 0.075 | 0.700 | 0.663 | 0.737 | 0.082 |
| 0.950 | 438 | 0.075 | 0.075 | 0.800 | 0.763 | 0.837 | 0.094 |
| 0.950 | 246 | 0.075 | 0.075 | 0.900 | 0.863 | 0.937 | 0.125 |
| 0.950 | 385 | 0.100 | 0.100 | 0.500 | 0.450 | 0.550 | 0.100 |
| 0.950 | 323 | 0.100 | 0.100 | 0.700 | 0.650 | 0.750 | 0.109 |
| 0.950 | 246 | 0.100 | 0.100 | 0.800 | 0.750 | 0.850 | 0.125 |
| 0.950 | 139 | 0.100 | 0.100 | 0.900 | 0.850 | 0.950 | 0.166 |

**Overall summary of sample size estimations for OCE questionnaire study:** Even for a highly demanding precision of ±2 cases per year and a "worse case" scenario of a questionnaire item having a mean with a standard deviation of 30, this would require **865** participants completing the questionnaire**.** We will be targeting a sample size of 900 with returned questionnaires; this represents approximately one quarter of the more than 3,600 dentists and 60% of the 1,500 hygienists enrolled. The targeted 900 increase from the sample size estimate of 865 is in order to account for partial completion of questionnaires. To achieve these target goals, 1200 will be invited to participate; this assumes a conservative completion rate of 70% based on prior ND-PBRN participation rates in the 67% to 70% range.

### 11.2.2 LENS case-vignettes presentation effect size estimates

To investigate variability in practitioner approaches to OCE for diagnosis and disposition of lesions, four decision variables will be investigated: lesion color, lesion location, pain and induration. These variables, chosen by experts as most likely utilized by dental professionals in decision making regarding oral lesions suspicious for pre-malignancy/ malignancy, will be explored through idiographic (the level of the individual) and group (nomothetic) analyses.[43-45]

**Idiographic analyses:** To describe the usage of the four "decision cues," a series of 6 vignette questions will be regressed separately on the four cases, each case having four variations of the four signs and symptoms (cues), for a total of 16 distinctive case-vignettes. Each case-vignette serves as the 'subject' in the LENS analysis, for a total sample size of (n=16). The objective is to determine the effect size and statistical significance of the four cue variables. In determining the effect size estimate, we will test each individual cue while controlling for the three other cues, and up to three additional (adjustment) variables.

It is assumed that a model including any three cues should produce a relatively high regression R-square (≥0.5), and that the inclusion of one additional cue will produce a meaningful change in R-square, defined as an absolute change of ≥15% (≥0.15). Although an alpha of 0.1 and power (1-β) of 80% are commonly used for idiographic analyses, the table below shows results based on a sample size of 16 (16 separate vignettes) controlling for six independent variables (3 cue variables plus 3 adjustment variables), under various baseline R-square and alpha scenarios; alphas of 1.0, 0.05 and 0.025 are presented, allowing for the possibility of multiple comparison adjustments, if desired.

| | | | | **Independent Variable Tested (cue variable)** | | **Independent Variables Controlled** | |
|---|---|---|---|---|---|---|---|
| **Power** | **N** | **Alpha** | **Beta** | **Count** | **(Δ $R^2$** | **Count** | **$R^2$** |
| 0.80 | 16 | 0.025 | 0.2 | 1 | 0.14 | 6 | 0.70 |
| 0.80 | 16 | 0.050 | 0.2 | 1 | 0.12 | 6 | 0.70 |
| 0.80 | 16 | 0.100 | 0.2 | 1 | 0.10 | 6 | 0.70 |
| 0.80 | 16 | 0.025 | 0.2 | 1 | 0.18 | 6 | 0.60 |
| 0.80 | 16 | 0.050 | 0.2 | 1 | 0.16 | 6 | 0.60 |
| 0.80 | 16 | 0.100 | 0.2 | 1 | 0.13 | 6 | 0.60 |
| 0.80 | 16 | 0.025 | 0.2 | 1 | 0.23 | 6 | 0.50 |
| 0.80 | 16 | 0.050 | 0.2 | 1 | 0.20 | 6 | 0.50 |
| **0.80** | **16** | **0.100** | **0.2** | **1** | **0.16** | **6** | **0.50** |

The table demonstrates that even at a low baseline R-square of 0.5 (control variables), a meaningful change in variance explained (change of ≥15%) will be detected (highlighted in yellow); with even stricter demands on the alpha parameter, a change of approximately 20% in variance can be detected relative to this baseline R-square.

**Nomothetic analyses:** All data will be aggregated for group analyses of meaningful cue (signs and symptoms) use for diagnoses, diagnostic supplementation procedures, and treatment planning. This will follow Idiographic analyses in order to identify sub-populations demonstrating counter-trends in cue use that will be apparent in the individual analyses, but may be averaged out with group analyses.

As with the Idiographic analyses, vignette questions will be regressed on the four cue variables and at least three controlling variables, and the change in variance explained by the model (R-square change)and the statistical significance examined with the deletion of each of the four cue variables.

| | | | | **Independent Variable Tested (cue variable)** | | **Independent Variables Controlled** | |
|---|---|---|---|---|---|---|---|
| **Power** | **N** | **Alpha** | **Beta** | **Count** | **$R^2$** | **Count** | **$R^2$** |
| 0.80 | 50 | 0.05 | 0.20 | 1 | 0.07 | 6 | 0.50 |
| 0.80 | 70 | 0.05 | 0.20 | 1 | 0.05 | 6 | 0.50 |
| 0.80 | 100 | 0.05 | 0.20 | 1 | 0.04 | 6 | 0.50 |
| 0.80 | 50 | 0.05 | 0.20 | 1 | 0.08 | 6 | 0.40 |
| 0.80 | 70 | 0.05 | 0.20 | 1 | 0.06 | 6 | 0.40 |
| 0.80 | 100 | 0.05 | 0.20 | 1 | 0.04 | 6 | 0.40 |
| 0.80 | 50 | 0.05 | 0.20 | 1 | 0.10 | 6 | 0.30 |
| 0.80 | 70 | 0.05 | 0.20 | 1 | 0.07 | 6 | 0.30 |
| **0.80** | **100** | **0.05** | **0.20** | **1** | **0.05** | **6** | **0.30** |

A sample size of 100 at 80% power can detect an R-square change of 0.05 attributed to one Independent variable (one cue) using an F-Test with a significance level (alpha) of 0.05 (highlighted in table). The cue tested is adjusted for an additional six independent variables (3 cue variables plus 3 adjustment variables) with a conservatively modeled low R-Square of 0.30.

**Overall summary of sample size estimates for OCE case-vignette study:** The idiographic analysis is well powered to detect clinically meaningful contributions of each of the four cues in decision making about oral lesions suspicious for pre-malignancy/malignancy. For the nomothetic analyses a targeted sample size of approximately 110 dentists (allowing for approximately a 10% sample increase for unforeseen assumptions) will be able to detect small but meaningful changes in the variance explained by expert determined, most meaningful signs and symptoms of an oral mucosal lesion being pre-malignant/malignant, and how those cues are used for diagnoses, diagnostic supplementation procedures, and treatment planning. To achieve this target, 200 dentists will be invited to participate, again assuming a conservative completion rate of 55%.

## 11.3 Analysis Plan

**11.3 NB.** A separate draft Statistical Analysis Standard Operating Procedure details the statistical approaches and investigators' roles and responsibilities related to analyses. It will be finalized in the study developmental period prior to data collection and will reflect reviewers' suggestions.

**11.3.1 Data cleaning:** Simple descriptive statistics (frequencies and data plots) will be used to identify duplicate, out-of-range, inconsistent, and missing data.

**11.3.2 Missing Data:** both unit and item non-response rates will be analyzed.

**11.3.3 Data Analyses** (*the following Data analyses will address each study objective)*

**1) Descriptive and exploratory analyses**: Descriptive and exploratory analyses will serve as the basis for producing adjusted estimates and identifying potentially predictive variables. These distributions and relationships will guide the choice of cut-points, where needed, for creating categorical independent variables and the selection of additional covariates for adjusted modeling. Concurrently with univariate analyses, bivariate analyses will be conducted for all questionnaire variables by study team identified variables from the National Dental PBRN Enrollment questionnaire using parametric/non-parametric t-tests, ANOVA, and Fisher's Exact test.

**2) The primary objective:** *describe the common practices of oral cancer examinations (OCEs) amongst National Dental PBRN practitioners based upon person, place and time*.
Primary analyses:
OCE practice and underlying decision process distributions will be estimated that are related to: person, place and time, separately for dentists and dental hygienists; unadjusted and adjusted for practitioner characteristics.

A) Primary Analyses of Primary Objective:

1. Means (standard errors [SEs]) or proportions (95% confidence intervals [CI]) will be produced for each questionnaire item, nationally and by ND-PBRN region.
2. Statistical differences between National Dental PBRN regions will be tested by each questionnaire item using generalized linear modeling (GLM) to regress the questionnaire responses on the regions (as dummy) variables, and adjusting the p-value for multiple comparisons.
3. Adjusted means (SEs) for continuous variables and frequencies (as percentages)[46] for categorical measures will be produced for each questionnaire item being regressed on previously determined Enrollment covariates utilizing generalized linear modeling (GLM).

B) Secondary analyses of Primary Objective will be conducted of all covariates to be included in the regression modeling that were identified through the bivariate analysis as having a $p \leq 0.1$.

**3) Secondary Objectives**

**3a) Secondary Objective a:** *Communication practices between the practitioner and patient and the practitioner and referral clinician related to the OCE.*

A) Analyses for this objective (3a) will follow those analytic approaches described for the Primary Objective (above; primary and secondary analyses)

**3b) Secondary Objective b*:*** *Practitioner and practice characteristics related to frequency and comprehensiveness of oral cancer examination (predictors of quality & quantity of OCE).*
Determining practitioner/practice characteristics predictive of OCE technique comprehensiveness and quantity (frequency) will be accomplished by creating quality and quantity Indexes.

A) In order to create the quality and quantity indexes, the following processes will be conducted:
   1) Qualitatively define variables as gold standards of practice:
      a. Indication of quality, e.g., palpation of anterior cervical lymphatic nodes
      b. Indication of quantity (frequency), e.g., always for new patients
   2) Conduct GLM with multivariable regression models of the gold standards regressed on all candidate variables to establish variables highly associated with each gold standard (and thus not necessary for index inclusions).
   3) Multidimensional scaling (MDS) will be employed to identify variables with dissimilarities in order to classify associations and produce a "perceptional map" to identify spatially associated variables to the gold standards.

B) Identifying quality predictors: Approach 1 GLM analyses
The approach will regress each index on the previously determined Enrollment covariates Generalized linear modeling with appropriate distribution and link functions will be utilized. Parameter estimates will be produced to establish the magnitude of the associations.

C) Identifying quality predictors: Approach 2 regression TREE (recursive partitioning) analyses:
This objective will be accomplished using regression TREE analyses, with each index as the outcome variable and all selected covariates (described above) as candidate predictors.

**3c) Secondary objective c:** *Practice, practitioner, and lesion characteristics related to practitioners' suspicion for pre-malignancy or malignancy, lesion management decisions and preferred referral practitioner*

A) *Case-Vignettes Data Analyses (3.c.a):*
Two sets of analyses (individual and group) will be conducted, based on the lens model approach [47-57] to evaluate cue (color, location, pain, and induration) use in decisions to assess lesions for pre-malignancy/malignancy.

**Individual (idiographic) analyses:** we will use individual-level analyses to examine each participant's cue use regarding the decision to assess an oral mucosal lesion as suspicious for pre-malignancy or malignancy. **Group (nomothetic) analyses:** In addition to individual (idiographic) analyses, we will conduct group-level analyses. Separate multivariable GLM models, using appropriate distribution and link functions, will be specified similar to the idiographic analyses with four cues (color, location, pain, and induration) as predictors of dentist decisions, unadjusted and adjusted by practitioner characteristics.

B) Analyses for "what are the suspicion parameters that define treatment planning decisions, and referee questions" (3.c.b and 3.c.c), will follow those analytic approaches described for the Primary Objective (above; primary and secondary analyses)

**3d) Secondary objective d:** Self-reported number of identified lesions suspicious for pre-malignancy or malignancy and number of lesions biopsied or referred;

A. Primary analysis: Rates will be generated for the reported numbers of biopsies, referrals and combined biopsies/referrals. The continuous variable means (SEs) for the number of suspicious lesion biopsies performed over the prior six months and referrals for consultations over the prior three and six month periods will be generated and annualized; for dichotomized and categorical variables the frequencies of reported biopsies, referrals and combined biopsies/referrals will be generated. Secondary analyses will be conducted to determine predictors of high and low rates of discovery.

**4) Questionnaire-based statistics:** The test-retest analysis will consist of correlations for continuous variables and kappas for dichotomized variables. For correlations, assuming an $\alpha$ = 0.05 and power =0.80, power analyses (PASS 12) support a sample size of n=64, for testing a coefficient of 0.05 from an idealized 0.95 correlation; for kappas, the required sample size would be 44 for a k=0.7 from an idealized k=0.9.

## 12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source data/documents will be maintained by the CC for this study. The CC will use a survey management system (SMS) to program the electronic survey and vignettes. Participants are sent an email invitation with a direct link to either the electronic survey and/or vignettes. After a participant submits the electronic survey, data will be available in the SMS.

Only study personnel i.e., the SPI, NND, SPI designated study team members, and CC staff will have access to these data elements. All research computers and associated study documents will be password-protected. Data files will be kept in a secure, locked file in the SPI's office and at the CC. A copy will also be stored on a password-protected UAB network computer only accessible to the NND.

## 13 QUALITY CONTROL AND QUALITY ASSURANCE

For the QA/QC activities associated with data collection and processing, the CC will develop a Data Management Plan in which the specific data QA/QC procedures will be provided. These procedures will include the development of automatic data quality checks in the SMS and the processes related to the data manual review, discrepancy management, delinquent data handling, data updates, data verification and data audits.

# 14 ETHICS/PROTECTION OF HUMAN SUBJECTS

## 14.1 Ethical Standard

The SPI 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.

## 14.2 Institutional Review Board

This protocol will be reviewed by the National Dental PBRN Central Institutional Review Board (IRB). The UAB IRB for Human Use serves as the National Dental PBRN Central IRB.

Once 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 then performs all future continuing protocol reviews and amendment (new protocol version) reviews.

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 or other local institution elects not to use the National Dental PBRN Central IRB, the protocol, consent form (if warranted), recruitment materials and all participant materials will be submitted to the regional or other local institution IRB for review and approval.

Approval (either centrally for those regions who agree to central approval, or regionally/locally 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.

For those study investigators requiring IRB approval by their institutions, the study institution PI will submit for IRB approval and provide the Central IRB with the appropriate approved IRB documents.

## 14.3 Informed Consent Process

A waiver of documentation of signed informed consent for practitioners who complete the electronic questionnaire/vignettes will be requested. Consistent with regulations outlined by the UAB IRB and any regional/local IRBs, information about the study will be provided to eligible practitioners in the initial study invitation as well as in the electronic questionnaire prior to the start of the questionnaire questions. Completion of the questionnaire will provide tacit consent.

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

Minors (< 21 years-old) will not be enrolled in this study. National Dental PBRN dentists and hygienists of any gender, gender identity, or racial/ethnic group may participate if they meet eligibility criteria.

## 14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the 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.

Only study personnel (i.e., NND, SPI, SPI designated study team members (deidentified database), and CC staff) will have access to research study documents. Participants' pre-assigned identification numbers (i.e., practitioner IDs (PID) assigned by the National Dental PBRN) will be used to maintain study records and organize data files. A file linking participants' names with their unique identification number will be kept in a password-protected file by the CC and on the GPI's computer and will be destroyed after the study analysis is completed in accordance with regulations set forth by the IRB.

# 15 DATA HANDLING AND RECORD KEEPING

The study team is responsible for ensuring the accuracy and completeness of the data reported, and following the data collection procedures as outlined in the DMP.

Access to study data will be provided to study team members, including the SPI, study team members designated by the SPI, RCs and CC staff.

## 15.1 Data Management Responsibilities

The SPI will work closely with the CC to ensure that the electronic surveys and vignettes are being collected appropriately and confidentiality is being maintained according to the protocol-specified procedures. Conference calls will be held approximately every month during the data collection phase to monitor progress, manage study documentation and procedures, and troubleshoot any problems that may arise.

Staff at the CC will develop and maintain a SMS based on the study survey/vignettes. The DMP will include details on the SMS and procedures that would be followed to launch and monitor the study. The data reported in the network's Practitioner Database will be used by the CC staff to identify eligible clinical dentists and hygienists for this study.

## 15.2 Data Capture Methods

RedCAP will be the SMS for this study. The CC will conduct preliminary testing and review of data fields in the initial programming and online launching of the survey. Survey study data will be backed up on a regular basis during the data collection period via servers that offer data security.

The SMS will ensure that all required data are collected per protocol requirements, and the data fields in the system are checked for completeness and consistency so that data entered into the web system can be validated and data errors be corrected. Edit checks will be programmed into the web survey to correct data issues in real time. Reports or tools will be developed to help monitor the data activities.

## 15.3 Types of Data

Data consist of participants' responses to the electronic questionnaire/vignettes only. Additionally, the NDPBRN Enrollment Database will be incorporated into the study databases.

## 15.4 Schedule and Content of Reports

Ongoing reports to monitor enrollment will be produced approximately every 2 weeks for study team and NIDCR review. The contents of the reports will include the summary of data collected and can be developed in separate sections by key characteristics or regions.

Final data analysis reports that address objectives of the study will be produced for review by the NIDCR and study team. The content of these reports will be determined by the study team and the CC and defined in the Statistical Analysis Standard Operating Procedure.

The procedure for locking the database prior to final analysis will be detailed in the study Data Management Plan. Briefly, the SMS data will be locked and final SAS, SPSS and Stata datasets will be generated at the end of the study. Prior to locking the database, the CC's Data Manager (DM) or designee will ensure all data is complete and clean as determined by the study team. Then, the DM will obtain approval from the SPI and Project Manager to proceed with the data lock.

No masking or coding is anticipated for this study.

### 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 NIH or longer as dictated by IRB or state laws/regulations.

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way no sooner than three years from the date that the grant federal financial report (FFR) is submitted to the NIH and with the PI and SPI concurrence. The file connecting subjects' names with their unique identification number will be kept in a password-protected file by the CC and on the SPI's computer for a minimum of three years, in accordance with IRB regulations, before being securely erased on agreement by the GPI and the SPI.

## 15.6 Protocol Deviations

A protocol deviation (PD) is any noncompliance with the clinical study protocol or GCP principles. The noncompliance may be on the part of the participant, the investigator, 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 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.

## 17 OVERALL STUDY TIMELINE

| | | Study Month | | | | | | | | | | | | Year 06 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Year 05 (with April start date) | | | | | | | | | | | | | | | | | | | | | | | |
| Study | Tasks | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| Development | Final development (CC) | X | X | X | X | X | X | | | | | | | Data analyses | | | | | | | | | | | |
| | IRB (CC) | | | | X | X | X | | | | | | | Scientific presentations | | | | | | | | | | | |
| | preparation: common background & methods-MS/abst | | X | X | X | X | X | X | X | X | X | X | | Manuscripts | | | | | | | | | | | |
| | preparation of data management and analytic coding | | X | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | |
| | | | | | | | DATA COLLECTION | | | | | | | | | | | | | | | | | | |
| Questionnaire | email recruit 1-test syst (n=270) 2 invites then to R/C | | | | | | | X | | | | | | | | | | | | | | | | | |
| | evaluate recruitment / questionnaire delivery | | | | | | | X | X | | | | | | | | | | | | | | | | |
| | Test-retest invitations to recruit group 1 | | | | | | | X | X | | | | | | | | | | | | | | | | |
| | email recruit 2 (n=600), 2 invites then to R/C | | | | | | | | X | X | | | | | | | | | | | | | | | |
| | email recruit 3 (n=330), 2 invites then to R/C | | | | | | | | | X | X | | | | | | | | | | | | | | |
| | email recruit 4 (n=xx, from resample), 2 invites then to R/C *if necessary* | | | | | | | | | | X | X | | | | | | | | | | | | | |
| | Lesion/biopsy numbers determined (initial 500) | | | | | | | | | X | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| | e-data set cleaned | | | | | | | | | | | X | X | | | | | | | | | | | | |
| | merging of data sets (Westat) | | | | | | | | | | | | X | | | | | | | | | | | | |
| | Lesion/biopsy numbers determined-final | | | | | | | | | | | | | X | | | | | | | | | | | |
| | *if pt-centered study feasable, prepare NDPBRN concept* | | | | | | | | | X | X | X | X | X | X | X | X | X | X | | | | | | |
| | analyses: reliability & representativeness | | | | | | | | | | | | | X | X | | | | | | | | | | |
| | *Presentations/MS "A" if lesion prevalance findingsof interest* | | | | | | | | | | | | | | | X | X | X | X | X | X | | | | |
| | descriptive and exploratory statistics OCE practices (study team) | | | | | | | | | | | | | | X | X | X | X | | | | | | | |
| | presentations and MS "B"- descriptives "Common practices of OCE" | | | | | | | | | | | | | | | | | | X | X | X | X | X | X | X |
| | descriptive and exploratory statistics OCE communications (study team) | | | | | | | | | | | | | | | | | X | X | X | X | | | | |
| | presentations and MS "C"- descriptives "OCE communications practices: patient and practitioners" | | | | | | | | | | | | | | | | | | | X | X | X | X | | |
| | sub-group analyses (study team) | | | | | | | | | | | | | | | | X | X | X | X | X | | | | |
| | presentations and MS "D"-sub-group or "OCE lesion management decisions" | | | | | | | | | | | | | | | | | | | | X | X | X | X | X |
| | predicting quality & quantity of OCE analyses or lesion management | | | | | | | | | | | | | | | | | | | | X | X | X | X | |
| | | | | | | | DATA COLLECTION | | | | | | | | | | | | | | | | | | |
| Vignettes | email recruit 1 (50% every 100 e-mail respondents) | | | | | | | X | X | X | | | | | | | | | | | | | | | |
| | data management & cleaning | | | | | | | | | | X | | | | | | | | | | | | | | |
| | merging of data sets (Westat) | | | | | | | | | | | X | | | | | | | | | | | | | |
| | Descriptive and exploratory statistics (UF-Robinson) | | | | | | | | | | | | X | X | | | | | | | | | | | |
| | idiographic analysis (UF-Robinson) | | | | | | | | | | | | | | X | X | X | X | | | | | | | |
| | nomothetic analysis-LENS study case data (UF-Robinson) | | | | | | | | | | | | | | | | | | X | X | X | X | | | |
| | presentations and MS "E"-"Cues used by general dentists in the assessment of oral lesions" | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X |

## 18 LITERATURE REFERENCES

1. Jemal A BF CM, Ferlay J, Ward E, Forman D,. Global Cancer Statistics. CA Cancer J Clin 2011;61:69-90.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 (Internet). International Agency for Research on Cancer 2010;Lyon, France:Available from: http://globocan.iarc.fr.
3. Clovis JB, Horowitz AM, Poel DH. Oral and pharyngeal cancer: knowledge and opinions of dentists in British Columbia and Nova Scotia. . J Can Dent Assoc 2002;68:415-20.
4. Horowitz AM, Drury TF, Goodman HS, Yellowitz JA. Oral pharyngeal cancer prevention and early detection: dentists' opinions and practices. . J Am Dent Assoc 2000;131:453–62.
5. Lehew CW, Kaste LM. Oral cancer prevention and early detection knowledge and practices of Illinois dentists--a brief communication. J Public Health Dent 2007;67:89-93.
6. Alonge O, Narendran S. Opinions about oral cancer prevention and early detection among dentists practising along the Texas-Mexico border. Oral Diseases 2003;9:41-5.
7. Applebaum E, Ruhlen TN, Kronenberg FR, Hayes C, Peters ES. Oral cancer knowledge, attitudes and practices: a survey of dentists and primary care physicians in Massachusetts. J Am Dent Assoc 2009;140::461-7.
8. Center of Disease Control. DATA2010 Healthy People Database Obj 21-7. http://wondercdcgov/scripts/brokerexe 2011.
9. Patton LL, Agans R, Elter JR, Southerland JH, Strauss RP, Kalsbeek WD. Oral cancer knowledge and examination experiences among North Carolina adults. J Public Health Dent 2004;64:173-80.
10. Macek MD, Reid BC, Yellowitz JA. Oral cancer examinations among adults at high risk: findings from the 1998 National Health Interview Survey. J Public Health Dent 2003;63:119-25.
11. Horowitz AM, Moon H, HS. G, Yeflowitz JA. Maryland Adults' Knowledge of Oral Cancer and
Having Oral Cancer Examinations. J Public Health Dent 1998;58:281-7.
12. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
13. American Cancer Society. Cancer Facts and Figures 2012. http://wwwcancerorg/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941pdf 2012;Last accessed: Dec 28,2012.
14. National Cancer Institute. 2000-2012 (SEER 18). 2015;http://seer.cancer.gov/faststats/selections.php?#Output:: (acessed 1/7/'16).
15. Mayne ST, Morse DE, Winn DM. Cancers of the Oral Cavity and Pharynx In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. 3rd ed. Oxford: Oxford University Press; 2006:676.
16. Melrose RJ. Premalignant oral mucosal diseases. J Calif Dent Assoc 2001;29:593-600.
17. Lee JJ, Hung HC, Cheng SJ, et al. Carcinoma and dysplasia in oral leukoplakias in Taiwan: prevalence and risk factors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:472-80.
18. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002;52:195-215.
19. Sciubba JJ. Oral cancer and its detection. History-taking and the diagnostic phase of management. J Am Dent Assoc 2001;132 Suppl:12S-8S.

20. Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A. Interventions for treating oral leukoplakia. Cochrane Database Syst Rev 2004:CD001829.
21. Schoelch ML, Sekandari N, Regezi JA, Silverman S, Jr. Laser management of oral leukoplakias: a follow-up study of 70 patients. Laryngoscope 1999;109:949-53.
22. NCI. SEER Fast Stats Oral Cavity and Pharynx Cancer. NIH-NCI 2008;http://seer.cancer.gov/faststats/sites.php?site=Oral+Cavity+and+Pharynx+Cancer&stat=Survival: Accessed: 1/26/08.
23. Morse DE, Kerr AR. Disparities in oral and pharyngeal cancer incidence, mortality and survival among black and white Americans. JADA 2006;137:203-12.
24. SEER Cancer Statistics Review, 1975-2006. National Cancer Institute. Bethesda, MD, 2009. (Accessed Dec 12, 2009 http://seer.cancer.gov/csr/1975_2006/,, at http://seer.cancer.gov/csr/1975_2003.)
25. Chandu A, Smith ACH, Rogers SN. Health-related quality of life in oral cancer: a review. J Oral Maxillofac Surg 2006;64:495-502.
26. Ord RA, Blanchaert RH, Jr. Current management of oral cancer. A multidisciplinary approach. J Am Dent Assoc 2001;132 Suppl:19S-23S.
27. Howlader N NA, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA,. SEER Cancer Statistics Review, 1975-2009 National Cancer Institute 2012.
28. Yellowitz JA, Horowitz AM, Drury TF, Goodman HS. Survey of U.S. dentist's knowledge and opinions about oral pharyngeal cancer. J Am Dent Assoc 2000;131:653-61.
29. Horowitz AM, Siriphant P, Sheikh A, Child WL. Perspectives of Maryland dentists on oral cancer. J Am Dent Assoc 2001;132:65-72.
30. Lehew CW, Epstein JB, Kaste LM, Choi YK. Assessing oral cancer early detection: clarifying dentists' practices. J Public Health Dent 2009;Epub ahead of print.
31. Velez-Vega CM, Morse DE, Sanchez-Ayendez M. A Qualitative Inquirey into the Knowledge, Attitudes/Beliefs and Practices of Health Practitioners in Puerto Rico as They Relate to Oral Cancer Awareness, Prevention, Detection and Care. . In: American Public Health Association (APHA) Annual Meeting. Philadelphia, PA; 2009.
32. Velez-Vega CM, Sanchez-Allendez M, Morse DE. Patient Knowledge, Attitudes/Beliefs and experiences with Oral Health Services in Puerto Rico as They Relate to Oral Cancer Risk Awareness, Prevention, Detection and Care. In: American Public Health Association (APHA) Annual Meeting,. hiladelphia, PA; 2009.
33. Choi Y, Dodd V, Watson J, Tomar SL, Logan HL, Edwards H. Perspectives of African Americans and dentists concerning dentist-patient communication on oral cancer screening. Patient Educ Couns 2008;71:41-51.
34. Macpherson LM, McCann MF, Gibson J, Binnie VI, Stephen KW. The role of primary healthcare professionals in oral cancer prevention and detection. Br Dent J 2003;195:277-81; discussion 63.
35. Cruz GD, Shulman LC, Kumar JV, Salazar CR. The cultural and social context of oral and pharyngeal cancer risk and control among Hispanics in New York. J Health Care Poor Underserved 2007;18:833-46.
36. McCann MF, Macpherson LM, Binnie VI, Stephen KW. A survey of Scottish primary care dental practitioners' oral cancer-related practices and training requirements. Community Dent Health 2000;17:24-30.
37. Laronde DM, Bottorff JL, Hislop TG, et al. Voices from the community--experiences from the dental office: initiating oral cancer screening. J Can Dent Assoc 2008;74:239-41.

38. Choi Y, Dodd V, Watson J, Tomar SL, Logan HL, Edwards H. Perspectives of African Americans and dentists concerning dentist-patient communication on oral cancer screening. Patient Educ Couns 2008;71:41-51.
39. Carter LM, Ogden GR. Oral cancer awareness of general medical and general dental practitioners. Br Dent J 2007;203:E10; discussion 248-9.
40. Gajendra S, Cruz G, Kumar JV. Oral Cancer Prevention and Early Detection: Knowledge, Practices, and Opinions of Oral Health Care Providers in New York State. J Cancer Educ 2006;21:157–62.
41. Bigelow C, Patton LL, Strauss RP, Wilder RS. North Carolina dental hygienists' view on oral cancer control. J Dent Hyg 2007;81:83.
42. Gibson-Howell JC HM. Dental Hygienists' Role in Patient Assessments and Clinical Examinations in U.S. Dental Practices: A Review of the Literature. J Allied Health 2010;39:e1-e6.
43. Wandner LD HA, Torres CA, Lok BC, Scipio CD, Heft MW, Robinson ME,. Using virtual human technology to capture dentists' decision policies about pain. . J Dent Res 2013;92:301-5.
44. Hirsh AT, Callander, S.B. & Robinson, M.E,. Patient demographic characteristics and facial expressions influence nurses' assessment of mood in the context of pain: A Virtual Human and lens model investigation. Int J Nurs Stud 2011;13:220-7.
45. Wandner LD GS, Lok BC, Torres CA, Chuah JH, Robinson ME,. Pain assessment and treatment decisions for virtual human patients. Cyberpsychol Behav Soc Netw 2013;16:904-9.
46. Holford TR. Multivariate methods in epidemiology. NY, NY: Oxford University Press; 2002.
47. Hirsh AT, Alqudah AF, Stutts LA, Robinson ME. Virtual human technology: Capturing sex, race, and age influences in individual pain decision policies. Pain 2008;140:231-8.
48. Hirsh AT, Callander SB, Robinson ME. Patient demographic characteristics and facial expressions influence nurses' assessment of mood in the context of pain: A virtual human and lens model investigation. International Journal of Nursing Studies 2011;48:1330-8.
49. Hirsh AT, George SZ, Robinson ME. Pain assessment and treatment disparities: A virtual human technology investigation. Pain 2009;143:106-13.
50. Hirsh AT, Hollingshead NA, Bair MJ, Matthias MS, Wu J, Kroenke K. The influence of patient sex, race, and depression on clinician pain treatment decisions. Eurpoean Journal of Pain in press.
51. Hirsh AT, Jensen MP, Robinson ME. Evaluation of nurses' self-insight into their pain assessment and treatment decisions. Journal of Pain 2010;11:454-61.
52. Stutts LA, Hirsh AT, George SZ, Robinson ME. Investigating patient characteristics on pain assesment using virtual human technology. European Journal of Pain 2010;14:1040-5.
53. Torres CA, Bartley EJ, Wandner LD, Alqudah AF, Hirsh AT, Robinson ME. The influence of sex, race, and age on pain assessment and treatment decisions using virtual human technology: A cross-national comparison. Journal of Pain Research in press.
54. Wandner LD, George SZ, Lok BC, Torres CA, Hao Chuah J, Robinson ME. Pain assessment and treatment decisions for virtual human patients. Cyberpsychology, Behavior, and Social Networking in press.
55. Wandner LD, Hirsh AT, Torres CA, et al. Using virtual human technology to capture dentists' decision policies about pain. Journal of Dental Research 2013;92:301-5.
56. Wandner LD, Scipio CD, Hirsh AT, Torres CA, Robinson ME. The perception of pain in others: How gender, race, and age influence pain expectations. The Journal of Pain 2012;13:220-7.

57. Wandner LD, Stutts LA, Alqudah AF, et al. Virtual human technology: Patient demographics and healthcare training factors in pain observation and treatment recommendations. Journal of Pain Research 2010;3:241-7.