

A pilot study to evaluate feasibility and acceptance of oral HPV detection in the National Dental Practice-Based Research Network

NIDCR Protocol Number: 14-029-E

NIDCR Funding Mechanism: U19-DE-22516

NIDCR Grant Principal Investigator (GPI):

Gregg H. Gilbert, DDS, MBA

Study Principal Investigator (SPI):

Maura Gillison, MD, PhD

Institutions:

University of Alabama at Birmingham
The Ohio State University Wexner Medical Center

NIDCR Program Officials:

Dena Fischer, DDS, MSD, MS

Draft or Version Number: 3.0

02 September 2016

STATEMENT OF COMPLIANCE

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

SIGNATURE PAGE

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

Grant Principal Investigator/South Central Regional Director:

Signed: _____ Date: _____

Name: Gregg H. Gilbert, DDS, MBA

Title: Professor and Chair

Study Principal Investigator:

Signed: _____ Date: _____

Name: Maura Gillison, MD, PhD

Title: Professor of Medicine, Epidemiology and Otolaryngology
Jeg Coughlin Chair of Cancer Research

Regional Directors:

Signed: _____ Date: _____

Name: Jeffrey Fellows

Title: Regional Director, Western Region

Signed: _____ Date: _____

Name: Brad Rindal

Title: Regional Director, Midwest Region

Signed: _____ Date: _____

Name: Tom Oates

Title: Regional Director, Southwest Region

Signed: _____ Date: _____

Name: Valeria Gordan

Title: Regional Director, South Atlantic Region

Signed: _____ Date: _____

Name: Cyril Meyerowitz

Title: Regional Director, Northeast Region

SIGNATURE PAGE- NETWORK STAFF

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

The signature below constitutes:

- 1) acknowledgement of having read this protocol version (as indicated in the upper right corner of this page) and the attachments,
- 2) an assurance that this individual will conduct all of his or her assigned study tasks according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and guidelines, and
- 3) an assurance that this individual will read and follow all study plans applicable to his/her role on the study (e.g., Regional Coordinators will read and follow the Manual of Procedures (MOP), Practice Training Binder, Clinical Monitoring Plan, and other applicable plans developed in the future).

Signed: _____ Date: _____

Name: _____

Title: _____

TABLE OF CONTENTS

	PAGE
STATEMENT OF COMPLIANCE	2
SIGNATURE PAGE	3
SIGNATURE PAGE- NETWORK STAFF	5
TABLE OF CONTENTS	6
LIST OF ABBREVIATIONS	9
PROTOCOL SUMMARY	11
1 KEY ROLES AND CONTACT INFORMATION	15
2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE	18
2.1 Background Information	18
2.2 Rationale	18
2.3 Potential Risks and Benefits	19
2.3.1 Potential Risks	19
2.3.2 Potential Benefits	21
3 OBJECTIVES	22
3.1 Study Objectives	22
3.2 Study Outcome Measures	22
4 STUDY DESIGN	24
5 STUDY ENROLLMENT AND WITHDRAWAL	26
5.1 Subject Inclusion Criteria	26
5.1.1 Dental Practitioner	26
5.1.2 Head and Neck Specialist (Otolaryngologist or Oral-maxillofacial Surgeon)	26
5.1.3 Patient	27
5.2 Subject Exclusion Criteria	27
5.2.1 Dental Practitioner	27
5.2.2 Head and Neck Specialist	27
5.2.3 Patient	27
5.3 Recruitment and Retention	27
5.3.1 Dental Practitioner	27
5.3.2 Head and Neck Specialist	28
5.3.3 Patient	29
5.4 Subject Withdrawal	30
5.4.1 Reasons for Withdrawal	30
5.4.2 Handling of Subject Withdrawals	31
5.5 Premature Termination or Suspension of Study	31
6 STUDY SCHEDULE	32
6.1 Dental Practitioner and Head and Neck Specialist Preparation and Training	32
6.2 Patient Study Enrollment Schedule	32
6.2.1 Part I, Oral HPV Screening	32
6.2.2 Part II, Oral Cancer Screening (Follow-Up Study)	34

6.3	Practitioner and Staff Survey	36
7	STUDY PROCEDURES/EVALUATIONS	37
7.1	Study Procedures/Evaluations	37
7.1.1	Oral Cancer Screening Examination	37
7.1.2	HPV Results Reporting	37
7.2	Laboratory Procedures/Evaluations	38
7.2.1	Oral Rinse Sample (10mL)	38
7.2.2	Blood Serum Sample (10mL)	38
7.2.3	Specimen Banking	38
7.3	Study Specific Biospecimens	38
7.3.1	Specimen Collection.....	38
7.3.2	Specimen Preparation, Handling and Storage.....	39
7.3.3	Specimen Shipment and Tracking.....	39
7.4	Electronic Questionnaires	40
7.4.1	Administration	40
7.4.2	Technology	41
7.4.3	Training and Troubleshooting.....	41
8	ASSESSMENT OF SAFETY	42
8.1	Specification of Safety Parameters	42
8.1.1	Unanticipated Problems	42
8.1.2	Serious Adverse Events	42
8.2	Reporting Procedures.....	43
9	STUDY OVERSIGHT	44
10	CLINICAL SITE MONITORING	45
11	STATISTICAL CONSIDERATIONS.....	46
11.1	Study Hypotheses.....	46
11.2	Sample Size Considerations.....	46
11.3	Final Analysis Plan	46
12	SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS	48
13	QUALITY CONTROL AND QUALITY ASSURANCE	49
14	ETHICS/PROTECTION OF HUMAN SUBJECTS.....	50
14.1	Ethical Standard	50
14.2	Institutional Review Board	50
14.3	Informed Consent Process	50
14.3.1	General Information.....	50
14.3.2	Oral HPV Screening Consent Process	51
14.3.3	Oral Cancer Screening Follow-up Study Consent Process.....	51
14.4	Exclusion of Women, Minorities, and Children (Special Populations).....	52
14.5	Participant Confidentiality	52
14.6	Future Use of Stored Specimens and Other Identifiable Data	53
15	DATA HANDLING AND RECORD KEEPING	54
15.1	Data Management Responsibilities.....	54
15.2	Data Capture Methods.....	54

15.3	Types of Data	54
15.4	Schedule and Content of Reports	55
15.5	Study Records Retention	56
15.6	Protocol Deviations	56
16	PUBLICATION POLICY	57
17	LITERATURE REFERENCES.....	58
	APPENDICES.....	59

LIST OF ABBREVIATIONS

AE	Adverse Event
CASI	Computer Assisted Self-Interviewing
CC	Coordinating Center
CDC	Centers for Disease Control and Protection
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
Co-I	Co-Investigator
CI	Confidence Interval
CRF	Case Report Form
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FAQ	Frequently Asked Questions
FFR	Federal Financial Report
GPI	Grant Principal Investigator
HIPAA	Health Insurance Portability and Accountability Act
HPV	Human Papillomavirus
IRB	Institutional Review Board
MOP	Manual of Procedures
NHANES	National Health and Nutrition Examination Survey
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
OSU	Ohio State University
PBRN	Practice-Based Research Network
QA	Quality Assurance
QC	Quality Control
SAP	Statistical Analysis Plan
SPI	Study Principal Investigator
RAS	Regional Administrative Site
RC	Regional Coordinator

SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UAB	University of Alabama at Birmingham
UP	Unanticipated Problem
US	United States

PROTOCOL SUMMARY

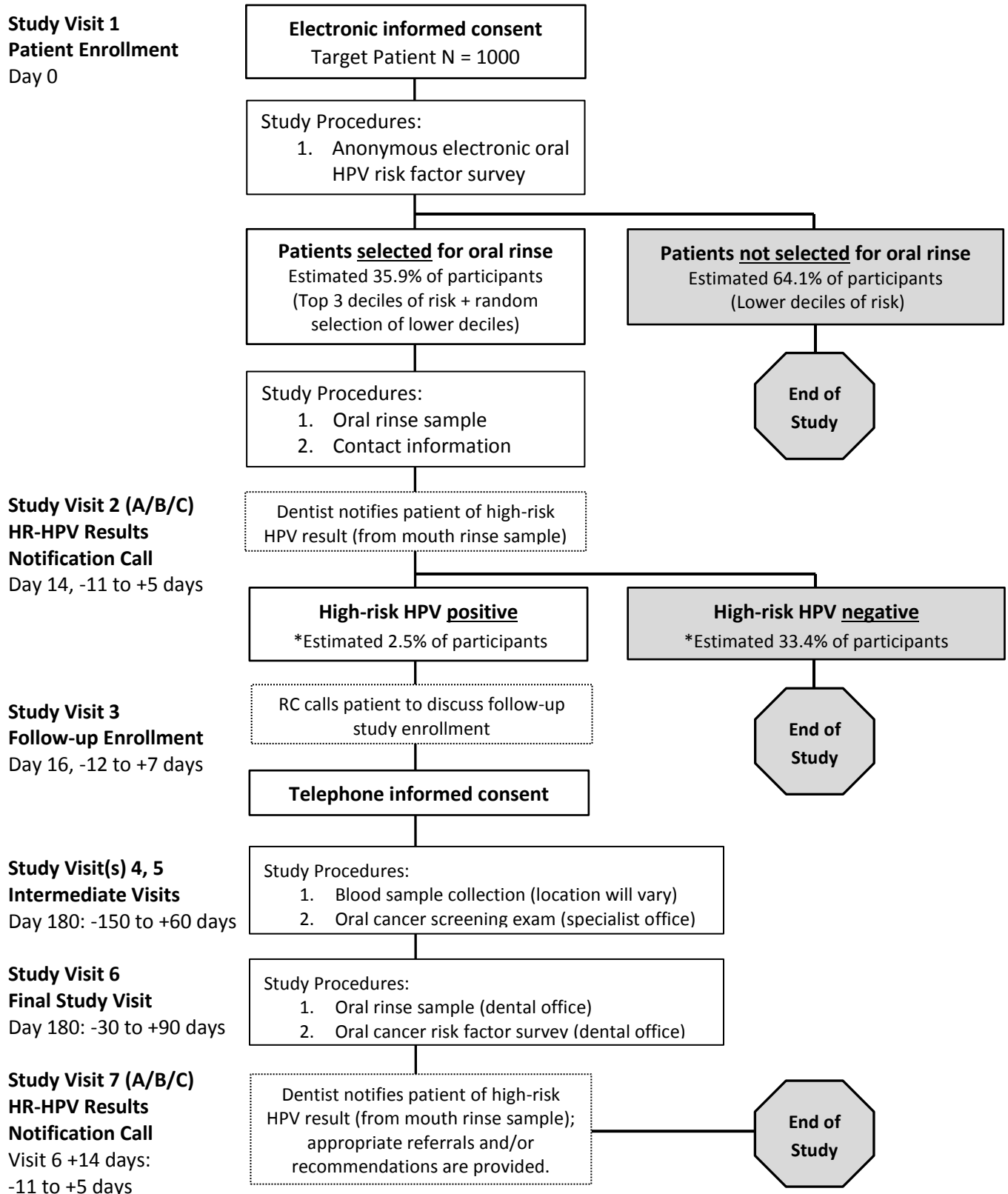
- Title:** A pilot study to evaluate feasibility and acceptance of oral HPV detection in the National Dental Practice-Based Research Network
- Précis:** A target of 1,000 men and women aged 30-69 years will be enrolled over a 6-month period, with up to 1,200 enrollments allowed to avoid cutting off enrollment in the middle of a business day. Approximately thirty practice locations will be recruited from the 6 National Dental PBRN regions (approximately 5 practice locations per region). Approximately 40 practitioners will be recruited among the approximately 30 practice locations. Participating patients will be recruited during routine clinical visits with participating National Dental PBRN practitioners. Each practitioner will recruit approximately 25-50 patients. Patients will be provided a tablet computer on which the study will be explained, electronic consent will be obtained, patient eligibility will be assessed, an oral HPV risk factor survey will be administered, and patient selection for oral rinse collection will be determined. Based on survey responses, the top three deciles of risk (~300) and a random selection of 1 in 12 of those in the lower deciles (~59) will be selected for oral rinse collection (~359 total). An oral rinse sample will be obtained by means of a 30 second rinse and gargle with Scope™ mouthwash (or saline), expectorated into a sterile specimen collection cup, sealed and stored at 4°C. Specimens will be shipped by practice staff approximately weekly or twice a week to a central laboratory for human papillomavirus (HPV) detection. HPV results will be communicated to the dental practitioner through the study's secure web application. Patients with a high-risk oral HPV infection (anticipated to be ~25 individuals) will be offered enrollment into a prospective study inclusive of a blood draw, an oral cancer examination, and a 6-month follow-up dental visit (window: 5-9 months) with a repeat oral rinse and an electronic oral cancer risk factor survey. Patients will be compensated with a gift card for each major study procedure.
- Objectives:** The primary objective of this study is to estimate the proportion of the study population with an oral high-risk HPV infection.
- The secondary objectives of this study are to:
- (1) Evaluate the feasibility and acceptability of baseline study procedures performed by participating patients and staff;
 - (2) Measure the distribution of demographic and behavioral

characteristics associated with oral HPV infection;

- (3) Determine compliance with and feasibility of procedures performed at a 6-month follow-up visit (window: 5-9 months), including blood draw, second oral rinse specimen collection, oral cancer screening examination, and completion of an oral cancer risk factor survey.

Population:	Target of 1,000 men and women age 30-69 years old (up to 1,200 may be allowed).
Number of Practitioners:	Approximately 40 practitioners from approximately 30 practice locations will be recruited from all 6 National Dental PBRN regions (approximately 5 practices per region) to represent the professional population comprising the National Dental PBRN.
Study Duration:	18 months
Patient Participation Duration:	The pilot study is a 6-month longitudinal study (window: 5-9 months). However, the study will be a cross-sectional study with a single visit for the overwhelming majority (approximately 97.5%) of participating patients.
Estimated Time to Complete Enrollment:	3-6 months

Schematic of Study Design:



*The percentages of high-risk HPV positive and high-risk HPV negative shown in this schematic are estimates. These estimates are based upon a risk factor model derived from previous research on 5,500 individuals who are representative of the US population (NHANES).

1 KEY ROLES AND CONTACT INFORMATION

Grant Principal Investigator:	Gregg H. Gilbert, DDS, MBA Professor and Chair University of Alabama at Birmingham 1720 Second Avenue South School of Dentistry, SDB 109 Birmingham, AL 35924-0007 Phone: 205-975-8886 Fax: 205-975-0603 Email: ghg@uab.edu
Study Principal Investigator:	Maura Gillison, MD, PhD Professor of Medicine, Epidemiology and Otolaryngology Jeg Coughlin Chair of Cancer Research The Ohio State University Wexner Medical Center 420 West 12th Avenue Room 690 Columbus, OH 43210 Phone: 614-247-4589 Fax: 614-688-4245 Email: maura.gillison@osumc.edu
NIDCR Program Officials:	Dena Fischer, DDS, MSD, MS Phone: 301-594-4876 Email: dena.fischer@nih.gov NIH/NIDCR/DER 6701 Democracy Boulevard, MSC 4878 Bethesda, MD 20892-4878
Coordinating Center:	Westat 1600 Research Boulevard, WB294 Rockville, MD 20850 Dr. James Korelitz, Director Phone: 301-294-4414 Fax: 240-294-4494 JamesKorelitz@Westat.com

Institutions:

Western Region (region #1)

Administratively based at the Kaiser Permanente Center for Health Research, Portland Oregon
Lisa Waiwaiole, Regional Coordinator
Kaiser Permanente Center for Health Research
3800 N. Interstate Avenue
Portland, OR 97227-1110
Phone: 503-335-2454
Fax: 503-335-6311
Email: Lisa.Ann.Waiwaiole@kpchr.org

Midwest Region (region #2)

Administratively based at the HealthPartners Institute for Education and Research in Minneapolis, MN
Emily Durand, Regional Coordinator
HealthPartners Institute for Education and Research
8170 33rd Avenue South
MS: 21111R
Minneapolis, MN 55445
Phone: 952-967-7404
Fax: 952-967-5022
Email: Emily.C.Durand@HealthPartners.com

Southwest Region (region #3)

Administratively based at the University of Texas Health Science Center at San Antonio in San Antonio, TX
Stephanie C. Reyes, Regional Coordinator
7703 Floyd Curl Drive, MC 7894
San Antonio, TX 78229
Phone: 210-562-5654
Fax: 210-562-4136
Email: reyess@uthscsa.edu

South Central Region (region #4)

Administratively based at the University of Alabama at Birmingham in Birmingham, AL

Andrea Mathews, Program Manager

Department of Clinical and Community Sciences

School of Dentistry, SDB 114

1720 2nd Avenue South

Birmingham, AL 35294-0007

Phone: 205-934-2578

Fax: 205-996-2172

Email: ahmathews@uab.edu

Northeast Region (region #5)

Administratively based at the University of Rochester in Rochester, NY

Vi Luong, Regional Coordinator

Eastman Institute for Oral Health

601 Elmwood Avenue, Box 6863

Rochester, NY 14642

Phone: 585-273-3107

Fax: 585-273-1237

Email: Vi_Luong@URMC.Rochester.edu

South Atlantic Region (region #6)

Administratively based at the University of Florida in Gainesville, FL

Deborah McEdward, Regional Coordinator

University of Florida

PO Box 100415

1395 Center Drive #D10-33

Gainesville, FL 32610

Phone: 352-273-5848

Fax: 352-273-7970

Email: dmcedward@dental.ufl.edu

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Oral human papillomavirus (HPV) infection has been identified as the principal cause of a dramatic rise in oropharyngeal cancer incidence over the last two decades in the United States (US)¹. Oral HPV16 infection is estimated to confer an approximate 50-fold increase in risk for HPV-positive oropharyngeal cancer². And yet, the clinical utility of oral HPV detection for screening for oropharyngeal cancer is unknown.

The recognition that oral HPV infection plays a role in the pathogenesis of oral cancer (inclusive of oral cavity and oropharyngeal cancers) has resulted in a paradigm shift in concepts of risk for oral cancer³. Young individuals without a history of tobacco or alcohol use may nevertheless be at risk for oral cancer⁴. As primary care providers, the dental community is well positioned to play an important role in the development of clinical algorithms for secondary prevention of HPV-associated oral cancers. In the case of another HPV-caused cancer, cervical cancer, screening through detection of cytological alterations induced by HPV infection (the Papanicolaou smear) and, more recently, direct HPV DNA detection, has reduced the incidence of cervical cancer in the US by 80% over the last several decades⁵. Whether analogous screening interventions are possible to stem the rising tide of HPV-positive oral cancer is currently unknown.

2.2 Rationale

The clinical utility of detection of oral HPV infection for identification of individuals for targeted screening for HPV-associated oral cancer is an important question for the dental community to address. Over the last two years, the dental community has been targeted by companies that are marketing commercially available tests for oral HPV detection (e.g., OraRisk HPV Salivary Diagnostics Test, OralDNA Labs, Quest Diagnostics). Unfortunately, no data are available in the medical literature regarding the performance of these assays for oral HPV detection. Furthermore, neither the manufacturer nor the medical literature provides guidance as to the appropriate clinical management of an individual with a positive test. The lack of information regarding appropriate interpretation of the test and clinical management has resulted in a major dilemma for both dental providers and their patients.

Based upon the cervical cancer literature, HPV detection does indeed hold promise for identifying individuals at risk for development of oral cancer. Natural history studies of cervical HPV infection have determined that the majority of cervical HPV infections clear within two years⁵. In the case of cervical cancer, persistence of an HPV infection known to be able to cause cancer in humans (referred to as a “high-risk” type) can be used to identify the minority of individuals who are at risk for development of cancer. Persistence of a type-specific “high-risk” oral HPV infection to two years may, by analogy, be used to identify individuals for targeted screening for HPV-associated oral cancer. Unpublished data from the Gillison laboratory

indicate that 50% of individuals with prevalent detection of high-risk HPV infection will have persistent infection at two years (Beachler D et al, submitted).

Although commercial tests for oral HPV detection are not validated, the Gillison laboratory has developed and validated methods for reproducible detection of oral HPV infection and demonstrated the ability to detect type-specific persistence of infection over time⁶⁻¹⁰. These methods were recently used to examine the prevalence of oral HPV infection in the US population in collaboration with the US Centers for Disease Control and Prevention (CDC)¹¹. In this analysis, age, gender, number of sexual partners and current number of cigarettes smoked per day were associated with oral HPV infection. A very brief questionnaire designed to assess these factors can therefore identify the subset of the population most likely to have a prevalent, oral high-risk HPV infection.

A simple 30-second oral rinse and gargle can be used to detect oral HPV infection by any of the HPV types linked to development of cancer. Additionally, blood sera can be evaluated for the presence of antibodies to HPV viral proteins. A recent publication has indicated that the presence of these antibodies may identify individuals with oral HPV infection who are at risk for progression to invasive, HPV-positive oral cancer (Kreimer A. et al JCO 2014).

The US Preventive Services Task Force does not have a recommendation for or against routine screening for oral cancer (inclusive of oral cavity and oropharynx cancers)¹². The standard of care for detection of oral cancer remains opportunistic screening involving physical examination by an experienced clinical practitioner during a routine dental or medical visit. One objective of this pilot proposal is to evaluate feasibility and acceptability of study procedures necessary to accomplish the aims of a future larger study in the National Dental Practice-Based Research Network (PBRN). All of the procedures in this pilot will be identical to those performed as part of the cross-sectional component and one 6-month follow up (window: 5-9 months) of a future larger study. Individuals with oral high-risk HPV infection detected at baseline will also be referred to a head and neck specialist for a standard oral cancer screening examination with visual inspection and palpation. The head and neck specialist performing the examination may be an otolaryngologist or an oral and maxillofacial surgeon trained to perform indirect mirror and flexible fiber optic visualization and palpation of the base of tongue.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

2.3.1.1 Dental Practitioner

There are no risks to dental practitioners as 'subjects' participating in this study other than the unanticipated release of confidential practice information.

2.3.1.2 Head and Neck Specialist (Otolaryngologist or Oral-maxillofacial Surgeon)

There are no risks to Head and Neck Specialists as 'subjects' participating in this study other than the unanticipated release of confidential practice information.

2.3.1.3 Patient

Electronic survey

Potential risks or discomforts of a computer survey may include:

- (1) Embarrassment
- (2) Breach of confidentiality

Oral rinse

Potential risks of the oral rinse may include:

- (1) Burning or stinging sensation in the mouth
- (2) Unpleasant taste

HPV test result

Potential risk of knowledge of positive test for high-risk oral HPV may be:

- (1) Emotional stress

Oral cancer screening examination

Potential risks of a manual oral examination may include:

- (1) Gagging
- (2) Mild discomfort
- (3) Bad taste
- (4) Feeling of pressure
- (5) Sneezing sensation

In those cases where a fiber optic laryngoscopy is required, additional risks may include:

- (6) Nosebleed
- (7) Allergic reaction to numbing medicine
- (8) Infection
- (9) Shortness of breath
- (10) Injury to lining of mouth or throat

Blood draw

Potential risks of a blood draw may include:

- (1) Pain
- (2) Bruising
- (3) Infection

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 Institutional Review Board (IRB) regulations concerning data collection, data analysis, data storage, and data destruction will be strictly observed.

2.3.2 Potential Benefits

2.3.2.1 Dental Practitioner

- (1) Contribution to medical and dental knowledge

2.3.2.2 Head and Neck Specialist (Otolaryngologist or Oral-maxillofacial Surgeon)

- (1) Contribution to medical and dental knowledge

2.3.2.3 Patient

- (1) Notification of high-risk HPV status
- (2) Availability of oral cancer examination for those with high-risk HPV detected in oral rinse sample
- (3) Contribution to medical and dental knowledge

3 OBJECTIVES

3.1 Study Objectives

The primary objective of this study is to estimate the proportion of the study population with an oral high-risk HPV infection.

The secondary objectives of this study are to:

- (1) Evaluate the feasibility and acceptability of baseline study procedures performed by participating patients and staff;
- (2) Measure the distribution of demographic and behavioral characteristics associated with oral HPV infection; and
- (3) Determine compliance with and feasibility of procedures performed at a 6-month follow-up visit (window: 5-9 months), including blood draw, second oral rinse specimen collection, oral cancer screening examination, and completion of an oral cancer risk factor survey (Appendix J).

3.2 Study Outcome Measures

The primary study outcome measure is the proportion of the study population with an oral high-risk HPV infection, which will be assessed through laboratory testing of the oral rinse specimen, recorded on a laboratory testing electronic Case Report Form (eCRF).

Secondary study outcome measures corresponding to the secondary objectives noted above will include:

- (1) The feasibility and acceptability of baseline study procedures performed by participating patient and dental office staff as assessed through:
 - a. Patients:
 - i. Electronic study summary (Appendix A): proportion of patients who agree to learn more about the study; proportion of patients who screen eligible to participate; proportion of patients who agree to the electronic consent.
 - ii. Oral HPV risk factor survey (Appendix C): acceptability of questions about risk factors ascertained in the survey.
 - b. Dental office staff:
 - i. Practitioner acceptability: Practitioners approached to participate in the study, those who agree or decline participation during the consent process, and practitioners who complete study-specific training.
 - ii. Feasibility (protocol education/training; patient recruitment; patient consent; answering questions; collecting, storing, and shipping oral rinses; distributing gift cards; providing test results).

-
- iii. Provider survey (Appendix P): ascertains acceptability (acceptability of extra time required for study procedures; comfort with study procedures; interest in participating in a future study) among practice staff.
- (2) The distribution of demographic and behavioral characteristics associated with oral HPV infection as assessed by the oral HPV risk factor survey (Appendix C) (gender; age; race/ethnicity; marital status; education; cigarette smoking; lifetime number of sexual partners) stratified by oral HPV status (laboratory testing eCRF).
- (3) The compliance with and feasibility of procedures done at the 6-month follow up visit performed by participating patients and dental office staff as assessed through:
- a. Patients:
 - i. eCRFs completed by the Regional Coordinator (RC), and will include a proportion of individuals with oral high-risk infection who: (a) enroll in the prospective study; (b) attend a 6-month follow-up; (c) undergo phlebotomy; (d) undergo ENT exam; and (e) complete the Oral Cancer Risk Factor Survey (Appendix J).
 - ii. Complete Oral Cancer Risk Factor Survey (Appendix J): acceptability of questions about risk factors ascertained in the complete survey.
 - b. Dental Office Staff:
 - i. Feasibility (patient retention; answering questions; collecting, storing, and shipping oral rinses; distributing gift cards; providing test results).
 - ii. Provider survey (Appendix P): ascertains acceptability (acceptability of extra time required for study procedures; comfort with study procedures; interest in participating in a future study) among practice staff.

4 STUDY DESIGN

- This is a cross-sectional study designed to identify the proportion of the study population with an oral high-risk HPV infection that will be offered enrollment into a longitudinal study with a 6-month follow up visit; the study will consist of a single baseline visit for the overwhelming majority (approximately 97.5%) of participating patients.
- The study population will consist of a target of 1,000 men and women age 30-69 years old. In order to avoid a situation where enrollment is cut off in the middle of a business day, up to 1,200 enrollments may be allowed. Enrollment will be halted within approximately 48 hours of reaching the target of 1,000 patients.
- Patients will be recruited during routine clinical visits with participating National Dental PBRN dental practitioners. Approximately, five practice locations will be recruited from each of the six National Dental PBRN regions: Northeast, South Atlantic, South Central, Midwest, Southwest, and Western regions. The approximately 30 total practice locations will be strategically selected to represent diverse dental practice types. Approximately 40 practitioners will be recruited among the approximately 30 practice locations.
- Each participating practitioner will be expected to enroll approximately 25-50 patients, total. For example, at a rate of one patient enrolled per day, enrollment may be complete in approximately five weeks.
- Enrolled patients will participate using a tablet computer, which will explain the study, assess patient eligibility, obtain electronic consent (Appendix A), administer the oral HPV risk factor survey (Appendix C) and determine patient selection for oral rinse collection.
- Based on the oral HPV risk factor survey responses, the top three deciles of risk (about 300 patients) and a random selection of those in the lower deciles will be selected for oral rinse collection. An oral rinse sample will be obtained by means of a 30-second rinse and gargle with Scope™ mouthwash (or saline), expectorated into a sterile specimen collection cup, sealed and stored at 4°C. Specimens will be shipped by practice staff approximately weekly or twice a week to a central laboratory for HPV detection.
- The results of the oral rinse test for high-risk HPV will be communicated to practitioners through the study's secure web application. A 3-tiered approach will be implemented to inform patients of test results:
 - (1) The dentist will be the first to provide the test result;
 - (2) The dentist may refer the patient to a trained RC (one from each region) if the patient has questions that need to be addressed; and
 - (3) If necessary, the RC may refer the patient to the SPI, Dr. Maura Gillison to address additional questions, as needed (pilot study only).

- Patients with a high-risk oral HPV infection determined from the oral specimen (anticipated to be about 25 patients) will be eligible for a prospective study. Soon after patients are informed of their high-risk oral HPV infection, an RC will contact them about the prospective study which includes a 6-month blood draw (window: 1 to 8 months), 6-month oral cancer screening examination (window: 1 to 8 months), and a 6-month follow-up visit at the dentist office that will consist of a repeat oral rinse and electronic oral cancer risk factor survey (Appendix J; window: 5-9 months). Consent (Appendix I) and enrollment will be conducted by the RC via telephone. RCs will facilitate scheduling of appointments for the prospective study procedures.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

5.1.1 *Dental Practitioner*

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

- (1) Is enrolled in the National Dental PBRN;
- (2) Sees patients on a recurring basis as a part of clinical standard of care (e.g., general dentist, periodontist, orthodontist);
- (3) Able to collect, store and ship oral rinse specimens weekly or twice a week;
- (4) Willing and able to refer patients to a clinical laboratory or phlebotomy service for blood sample collection, storage, and shipping;
- (5) Willing and able to refer participants to a licensed, enrolled Head and Neck Specialist (Otolaryngologist or Oral-maxillofacial surgeon) for an oral cancer screening examination;
- (6) Possesses a biohazard refrigerator and freezer at their dental practice; or is willing to accommodate a study-sourced refrigerator/freezer*; and
- (7) Has an established, secure (as determined by the Ohio State University (OSU) Clinical Data Manager), password-protected wireless internet connection; or is willing to install and support a secure, study-sourced wireless router*.

*Wireless routers and refrigerator/freezers will be provided by the study if either item is the limiting factor for participation. Refer to *Manual of Procedures (MOP): Site Initiation SOP* for details on acquiring these items.

5.1.2 *Head and Neck Specialist (Otolaryngologist or Oral-maxillofacial Surgeon)*

In order to be eligible to participate in this study, a Head and Neck Specialist must meet the following criteria:

- (1) Able to accept research study participants for an oral cancer screening examination; and
- (2) Able to perform an oral cancer screening examination consisting of:
 - a. The palpation of the neck, mouth and base of tongue; and
 - b. Possible indirect examination of the base of tongue by use of mirror or flexible fiber-optic laryngoscope at the discretion of the specialist.

5.1.3 Patient

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

- (1) 30 to 69 years of age;
- (2) Willing to be contacted by the dentist's staff, study staff, and (if eligible) schedulers for follow-up study procedures (blood draw and oral cancer screening examination);
- (3) Willing to provide contact information for one person living at a different address who will know the patient's whereabouts in the event the patient cannot be reached.

5.2 Subject Exclusion Criteria

5.2.1 Dental Practitioner

Not applicable

5.2.2 Head and Neck Specialist

Not applicable

5.2.3 Patient

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

- (1) A history of head and neck cancer, inclusive of cancers of the sinus, oral cavity, pharynx and larynx;
- (2) Received the HPV vaccine;
- (3) Inability to understand study procedures or provide consent in English or Spanish; and
- (4) Intention or expectation to relocate or to change dental provider within six months.

Depending on dental practice policies and institutional review board requirements, participating practices may add, as exclusion criterion (5), 'the absence of medical insurance.'

5.3 Recruitment and Retention

5.3.1 Dental Practitioner

- (1) Approximately 40 practitioners will be recruited from the Northeast, South Atlantic, South Central, Midwest, Southwest, and Western regions of the National Dental PBRN.
- (2) Practitioners at approximately 30 practice locations will be recruited from all 6 regions (approximately 5 practice locations per region).

- (3) Practitioner selection will represent the National Dental PBRN composition estimates detailed in the following publication: J Dent. 2013 Nov;41(11):1051-9. doi: 10.1016/j.jdent.2013.04.002. Epub 2013 Apr 15.

Planned Practitioner Enrollment Table:

Practice Location	Representation in Network	ROCS Enrollment Target
Inner city urban	13.2%	5
Urban (not inner city)	29.6%	12
Suburban	43.2%	17
Rural	13.9%	6
	Total	40
Type of Main Practice	Representation in Network	ROCS Enrollment Target
Owner of private practice, Assoc. or employee of private practice	80.0%	32
HPDG, PDA, and Other managed care org or PPO	7.0%	3
PubH, CHC or pub. funded clinic	4.0%	2
*Fed Gov't facil	1.8%	0
**Academic	7.4%	3
	Total	40

- (4) The RCs will be responsible for recruiting dental practitioners in their region and addressing feasibility issues such as wireless internet and biospecimen storage. The recruitment process will be guided by a Site Initiation Checklist (see MOP), which will help the RC ensure that each enrolled practitioner is equipped with the appropriate tools (refrigerator, freezer and router) and services (referrals for the oral cancer screening examination and phlebotomy) to carry out the study.
- (5) RCs will facilitate a thorough training program for participating dental practitioners and applicable staff (dental hygienists, dental assistants, and administration). This training may be conducted remotely (via webinar) or in person, as regionally determined.
- (6) RCs will provide practitioners and applicable staff (dental hygienists, dental assistants, and administration) with educational materials on the topic of oral HPV infection and its association with oral/oropharyngeal cancers.
- (7) Participating practitioners will be compensated for the time required to complete research activities, receiving \$25 for each baseline visit completed and \$50 for each follow-up visit completed.

5.3.2 Head and Neck Specialist

- (1) Head and Neck Specialists will be recruited based on recommendations from enrolled dental practitioners. Specialists are enrolled in the study so that each participating dental practice location has coverage by a specialist.

- (2) Additionally, participating specialists will be compensated for the time required to complete research activities, receiving \$120.00 for each visit completed.

5.3.3 Patient

5.3.3.1 Recruitment

- (1) A convenience sampling approach will be used to enroll patients, with an emphasis on enrollment of the first 1,000 patients who meet the eligibility criteria from among the approximately 30 practice locations, with an enrollment of approximately 25-50 patients per practitioner. The initial recruitment for screening may be led by other practice staff (e.g., dental hygienists, dental assistants).
- (2) In order to avoid a situation where enrollment is cut off in the middle of a business day, up to 1,200 enrollments may be allowed. Enrollment will be halted within approximately 48 hours of reaching the target of 1,000 patients, total.
- (3) The entire enrollment period is estimated to be approximately 3-6 months.
- (4) Each practitioner is expected to enroll approximately 25-50 patients.
 - a. To meet this recruitment goal, each practitioner should expect to enroll approximately 1-3 patients per day.
 - b. Some practitioners will enroll at a faster rate than others; practitioners are expected to enroll patients according to their patient volume.
- (5) Participant diversity will be assessed in real-time.
- (6) Practices will be expected to participate in enrollment until the recruitment goal (approximately 25-50 patients per practitioner) is met.

Part I, Oral HPV Screening

- (7) All study-related documentation, including consent forms (Appendices B and J) and electronic surveys, will be available in English and Spanish.
- (8) Study procedures, including informed consent (Appendix A), will be conducted by means of a web-based computer application; all surveys will be administered on a touch screen tablet.
- (9) Educational materials with frequently asked questions (FAQ) and resources related to HPV infection and oral cancer will be provided to each participating practice for distribution to patients at the time of enrollment. See Appendix K: *Oral HPV FAQ Documents*.
- (10) Participants who are not selected to provide an oral rinse sample will be paid \$10.
- (11) Participants who provide an oral rinse sample will be paid \$20.

Part II, Oral Cancer Screening Examination/Follow-up Study

- (12) All patients with a positive result for high-risk oral HPV will be offered the opportunity to participate in the follow-up study. See Appendix F: *High-risk Oral HPV Results Notification Script, Positive*.
- (13) Soon after the patient has been notified about the positive High-risk HPV test result, follow-up study consent will be obtained by the RC via telephone with an IRB-approved script (Appendix H).
- (14) All follow-up appointments will be scheduled in concordance with the patients' and practices' schedules. Scheduled follow-up appointments include:
 - a. Blood draw (clinical/local laboratory, community hospital, participating dental practice, mobile nursing service, or Head and Neck Specialist's practice);
 - b. Oral cancer screening examination (participating Head and Neck Specialist's practice); and
 - c. Final study visit consisting of the electronic oral cancer risk factor survey (Appendix J) and repeat oral rinse (participating dental practice).
- (15) Participants will receive \$25 for phlebotomy, \$50 for oral cancer screening and \$50 for follow-up Dental Visit (detailed survey + oral rinse), for a total of \$125.

5.3.3.2 Retention

Retention will apply to a small minority of study participants (anticipated to be approximately 25 patients) enrolled in the 6-month follow-up study.

The CC will work with the Regional Administrative Sites (RAS), study patients and dental providers to coordinate appointments for the follow-up dental visit, blood draw and oral cancer screening examination. The RC may conduct reminder telephone calls for research visits to ensure protocol compliance and patient retention.

5.4 **Subject Withdrawal**

5.4.1 ***Reasons for Withdrawal***

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

An investigator may terminate a study patient's participation in the study if:

- (1) Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient.
- (2) The patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 Handling of Subject Withdrawals

Withdrawn patients will not be replaced. In the case of patient withdrawal from the study, staff will only attempt continued follow-up data collection for patients who are withdrawn due to an unanticipated problem (UP). In those cases, only data related to the completion of reporting requirements for the UP will be recorded. Patients 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 patients withdrawn from the study may continue to receive normal clinical care as patients of the participating dentists, additional study data will not be collected from this continuing clinical care (except as noted above).

5.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Grant Principal Investigator (GPI) 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:

- (1) Determination of unexpected, significant, or unacceptable risk to patients.
- (2) Insufficient adherence to protocol requirements.
- (3) Data that are not sufficiently complete and/or evaluable.

6 STUDY SCHEDULE

6.1 Dental Practitioner and Head and Neck Specialist Preparation and Training

The study will proceed in stages:

- (1) Dental practitioners at approximately 30 practice locations are assessed for interest in the study.
- (2) Head and Neck Specialists are assessed for interest in the study, such that each participating practice location will have coverage by an interested specialist.
- (3) IRB submission, approval and verification of the study protocol and its appendices are completed.
- (4) Dental practitioners and participating Head and Neck Specialists are recruited, receive necessary IRB training, and sign and submit (mail or in-person) the practitioner informed consent form (Appendix N; if required by that region's IRB), Individual Investigator Agreements, University of Alabama at Birmingham (UAB) Master Service Agreement, and similar regulatory documents.
- (5) Practitioners are fully informed of and review the electronic oral HPV and oral cancer risk factor surveys (Appendices C and K) in their entirety.
- (6) Practitioners, dental practice staff, and Head and Neck Specialists are trained on study procedures, including operation of the web-application, administration of questionnaires, and collection of oral rinse specimens. RCs facilitate this training remotely (webinar) or on-site, as regionally determined.
- (7) Practitioners and specialists are trained to answer questions regarding oral HPV and counsel high-risk HPV-positive patients. RCs facilitate this training remotely (webinar) or on-site, as regionally determined.
- (8) Specific roles and responsibilities of the practitioners and their staff are determined according to their site-specific workflow and documented by the RC.
- (9) RCs complete the Site Initiation Checklist (see MOP) prior to study initiation to ensure that practitioners are properly equipped to perform study procedures.
 - a. RC/CC delivers a refrigerator/freezer (if necessary), wireless router (if necessary), tablet computer, specimen collection kits and shipping supplies to appropriate locations.
- (10) Practitioners begin patient enrollment.

6.2 Patient Study Enrollment Schedule

A Study Schedule of Events is provided as Appendix D. The following sections detail the major events that will occur at each visit. There will be some flexibility to complete certain events in the order that is most convenient for staff workflow.

6.2.1 Part I, Oral HPV Screening

Patient Enrollment and Screening (Visit 1, Day 0)

Location: Dental practitioner's office or clinic

1. Verify eligibility via web application;
2. Obtain consent via web application (Appendix A);
3. Administer electronic oral HPV risk factor survey via web application (Appendix C).
 - a. If patient is **not selected** by the web-application for oral rinse sample (approximately 64.1% of patients), a practice staff member will notify the patient that his or her **involvement in the study is complete**.
 - b. If patient is **selected** by the web-application for oral rinse sample (approximately 35.9% of patients); **continue through Visit 1, steps 4-5**.
4. Obtain participant contact information via web application;
5. Obtain oral rinse sample (done by dentist, dental hygienist or dental assistant); oral rinse samples are stored at 4°C, then shipped in batches to study laboratory by practice staff approximately once or twice a week.
6. Once the patient's oral rinse sample is received by the HPV detection laboratory (Polaris Innovation Centre), results will be communicated to dental practitioners within approximately 5 business days via the secure web application.
 - a. If patient has a **negative** high-risk oral HPV test result (anticipated to be approximately 33.4% of patients), proceed to **Visit 2A**; or
 - b. If a patient has an oral rinse sample that is not evaluable, proceed to **Visit 2B**; or
 - c. If patient has a **positive** high-risk oral HPV test result (anticipated to be approximately 2.5% of patients), proceed to **Visit 2C**.

HR-HPV Results Notification – Negative (Visit 2A: Day 14, -11 days to +5 business days)

Location: Telephone

1. Using an approved script (Appendix E), the dentist notifies the patient of their negative high-risk oral HPV test result and explains that their involvement in the study is now complete.

HR-HPV Results Notification – Not Evaluable (Visit 2B: Day 14, -11 days to +5 business days)

Location: Telephone

1. Using an approved script (Appendix G), the dentist notifies the patient that their oral rinse was deemed “not evaluable” by the study laboratory and the high-risk oral HPV test could not be conducted.
2. The caller will then invite the patient to schedule a visit at the dental office to recollect the oral rinse sample that can be sent for evaluation of high-risk HPV.

HR-HPV Results Notification – Positive (Visit 2C: Day 14, -11 days to +5 business days)

Location: Telephone

1. Using an approved script (Appendix F), the dentist notifies the patient that they have a positive high-risk oral HPV test result and explains that a RC will call them with a detailed explanation of the follow-up portion of the study.

6.2.2 Part II, Oral Cancer Screening (Follow-Up Study)

Follow-up Enrollment (Visit 3; Day 16, -12 days to + 7 days)

Location: Telephone

1. Using an IRB-approved script (Appendix H), the RC provides a detailed explanation of the follow-up study to the patient, answers questions and potentially obtains telephone consent.

Intermediate Visit – Blood Draw (Visit 4; Month 6, -5 months to +2 months)

Location: The blood draw location will be determined by the RC and dental practice on a site-by-site basis. Options include clinical laboratory, community hospital, mobile phlebotomy service, participating Head and Neck Specialist's office or a participating dental practice capable of drawing blood.

1. The phlebotomist obtains a blood serum sample, using a CC-provided, pre-labeled blood sample collection kit.
2. The blood serum sample is shipped by the collaborating blood-draw location overnight to the study laboratory at the Ohio State University, using the CC-provided, pre-printed, prepaid shipping materials.

Intermediate Visit – Oral Cancer Screening Examination (Visit 5; Month 6, -5 months to +2 months)

Location: Participating Head and Neck Specialist (Otolaryngologist or Oral-maxillofacial Surgeon) clinic

1. Licensed, participating Head and Neck Specialist conducts a comprehensive head and neck exam.

Final Study Visit (Visit 6; Month 6, -1 month to +3 months)

Location: Dental practitioner's office or clinic

1. Oral cancer risk factor survey administered via web application (Appendix J);
2. Dentist, dental hygienist, or dental assistant obtains repeat oral rinse sample; oral rinse samples are stored at 4°C, then shipped in batches to study laboratory by practice staff once or twice a week;
3. If blood sample is collected at Visit 6, sample collection and shipping procedures will be same as mentioned for the blood draw at the Intermediate Visit (Visit 4).

HR-HPV Results Notification – Negative (Visit 7A: Visit 6 +14 days, -11 days to +5 days)

Location: Telephone

1. Using an approved script (Appendix E), the dentist notifies the patient of their negative high-risk oral HPV test result and explains that their involvement in the study is now complete.

HR-HPV Results Notification – Not Evaluable (Visit 7B: Visit 6 +14 days, -11 days to +5 days)

Location: Telephone

1. Using an approved script (Appendix H), the dentist notifies the patient that their oral rinse was deemed “not evaluable” by the study laboratory and the high-risk oral HPV test could not be conducted.
2. The caller will then invite the patient to schedule a visit at the dental office to recollect the oral rinse sample that can be sent for evaluation of high-risk HPV.

HR-HPV Results Notification – Positive (Visit 7C: Visit 6 +14 days, -11 days to +5 days)

Location: Telephone

1. Using an approved script (Appendix F), the dentist notifies the patient that they have a positive high-risk oral HPV test result and provides appropriate education and counseling.
2. The dentist may ask the patient if they are interested in being contacted regarding participation in a future study that will monitor for persistent HPV infection.
3. The dentist notifies the patient that their involvement in the follow-up study is complete.

6.3 Practitioner and Staff Survey

Once a practice location has completed patient enrollment and all patient follow-up procedures, each practice staff member will be asked to complete the Provider Survey (Appendix P) to collect information on the feasibility and acceptability of study procedures among dental office staff.

7 STUDY PROCEDURES/EVALUATIONS

7.1 Study Procedures/Evaluations

7.1.1 Oral Cancer Screening Examination

- (1) The oral cancer screening examination will be conducted between the baseline and final study visit.
- (2) The RC will facilitate scheduling of this visit with a participating, licensed Head and Neck Specialist.
- (3) The oral cancer screening examination may involve:
 - a. The palpation of the neck, mouth and base of tongue;
 - b. Possible indirect examination of the base of tongue by use of mirror or flexible fiber-optic laryngoscope at the discretion of the specialist; and
 - c. Soft tissue abnormalities, which will be recorded on study-specific case report forms (CRFs).
- (4) Any abnormal findings will be evaluated and treated per the standard of care at the expense of the participant/participant's insurance. This may include a referral to a Head and Neck Specialist in the patient's insurance network.

7.1.2 HPV Results Reporting

- (1) High-risk oral HPV test results from a patient's oral rinse sample will be reported to practitioners via the study's secure, password-protected web-based application within a week of the sample's receipt at the Gillison HPV detection laboratory (located at the Polaris Innovation Center, 2001 Polaris Parkway, Room 1507, Columbus, OH 43240).
- (2) A 3-tiered approach will be implemented to inform patients of test results:
 - a. The dentist will be the first to provide the patient with their high-risk HPV test result via phone (Sections 6.2.1 and 6.2.2);
 - b. If necessary, a trained RC (one from each region) will speak with the patient to address their questions; and
 - c. After the RC has addressed questions, the patient may contact the SPI, Dr. Maura Gillison with additional questions (pilot study only).
- (3) The dentist will offer to send the patient a copy of their high-risk HPV results report (Appendix Q: HPV Results Template) along with a letter of interpretation (see Appendix R and S: Results Reporting Letter for Positive and Negative Results, respectively), so that he or she may take it to his or her physician for follow-up.

7.2 Laboratory Procedures/Evaluations

7.2.1 Oral Rinse Sample (10mL)

- (1) Standard operating procedures (SOPs) will be used for specimen processing, DNA purification and HPV detection; See MOP: Laboratory SOPs.
- (2) High-risk types of HPV include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73.
- (3) Samples found to be β -globin negative will be reported “inevaluable.”
- (4) Oral rinse samples may undergo evaluation for additional biomarkers, such as detection of HPV E6 protein.

7.2.2 Blood Serum Sample (10mL)

Samples will be evaluated for HPV 16, 18, 31 and 35. Sera will also be evaluated for the presence of antibodies to HPV viral proteins, specifically E6 and E7 antibodies, through a proprietary test.

7.2.3 Specimen Banking

- (1) Participants may be asked during the consent process if they agree to donate their oral rinse sample(s) and blood samples to be stored for future research.
- (2) If the participant agrees, his/her sample(s) will only be used by the principal investigator for research related to oral cancer risk and may include the evaluation of genes related to the risk of oral/oropharyngeal cancers.

7.3 Study Specific Biospecimens

See *MOP, Section 10: Specimen and Laboratory Management*, for detailed information regarding Oral Rinse and Blood Sample Collection, Labeling, Shipping and Handling Procedures.

7.3.1 Specimen Collection

7.3.1.1 Oral rinse

- (1) An oral rinse is only to be collected from individuals selected by the web application.
- (2) An oral rinse consists of a 30 second swish and gargle with ScopeTM mouthwash.
- (3) An oral rinse sample should be collected by a study-trained dentist, dental hygienist or dental assistant, as determined by the site or practitioner; the staff member collecting the rinse will be guided by an oral rinse collection tool and timer on the web application.
- (4) An oral rinse sample should be collected when the patient arrives in the dental exam room, prior to the patient’s dental exam or cleaning.

7.3.1.2 Blood

- (1) A blood sample is only to be collected from individuals enrolled in the follow-up (longitudinal) component of the study.
- (2) The blood sample may be collected at one of the following locations (determined by the RC and practitioner prior to study initiation):
 - a. Clinical laboratory
 - b. Community hospital
 - c. Mobile phlebotomy service (e.g., HEI)
 - d. Participating dental practice (with an on-site RN or phlebotomist)
 - e. Participating specialist's office
- (3) The blood sample should be collected in a single red-top (blood serum) tube by a clinical or laboratory professional trained in drawing blood, using a CC-provided, pre-labeled blood sample collection kit.
- (4) Participating blood-draw locations will be compensated for the time required to do the research, according to their usual collection for the procedures.

7.3.2 Specimen Preparation, Handling and Storage

7.3.2.1 Oral rinse

- (1) The sample must be stored at 4°C in the practice's designated biohazard refrigerator until shipping.
- (2) If necessary, the sample may be stored or transported in a cooler with ice packs for up to 4 hours until refrigeration is possible.

7.3.2.2 Blood

- (1) The blood sample must be left to coagulate at room temperature for 30 minutes.
- (2) After 30 minutes, the blood sample must be stored at 4°C until it is shipped.
- (3) If necessary, the sample may be stored or transported in a cooler with ice packs for up to 4 hours until refrigeration is possible.

7.3.3 Specimen Shipment and Tracking

7.3.3.1 Oral rinse

- (1) A sample must be shipped from the dental practice to the Gillison HPV detection laboratory (located at the Polaris Innovation Center, 2001 Polaris Parkway, Room 1507, Columbus, OH 43240) within five business days of its collection.
- (2) Multiple samples may be shipped together in batches weekly or twice weekly.
- (3) Shipping instructions, supplies and prepaid air bills will be provided by the CC.

7.3.3.2 Blood

- (1) Blood samples must be shipped to the Ohio State University lab on the day they are drawn.
- (2) Shipping instructions, supplies and prepaid air bills will be provided by the CC.

7.4 **Electronic Questionnaires**

7.4.1 **Administration**

The following questionnaires (surveys) will be administered as described in Section 6.2 (dependent on the part(s) of the study the patient is participating in):

- (1) Electronic oral HPV risk factor survey (Appendix C)*
 - a. Purpose: To determine patient's oral HPV risk profile; based upon questionnaire responses, both high- and low-risk patients may be selected for oral rinse sample.
 - b. Completed by: Patient
 - c. Length: 10-20 questions
 - d. Duration: Lower completion time is 2 minutes, upper completion time is 6 minutes
- (2) Electronic oral cancer risk factor survey (Appendix J)*
 - a. Purpose: To administer a detailed risk factor survey to determine baseline and lifetime measures of factors known to be associated with risk of oral cancer. Many of these factors are also associated with oral HPV infection (e.g., sexual behavior, smoking).
 - b. Completed by: Patient
 - c. Length: 37-147 questions
 - d. Duration: Lower completion time is 5 minutes, upper completion time is 35 minutes
- (3) Provider survey (Appendix P)
 - a. Purpose: To assess feasibility and acceptability of study procedures among dental staff.
 - b. Completed by: Dentist, dental assistant, dental hygienist or other dental administrative staff
 - c. Length: 19 questions
 - d. Duration: Lower completion time is 3 minutes, upper completion time is 6 minutes

Surveys marked with an asterisk (*) in the list above are based on previously validated instruments used in National Health and Nutrition Examination Survey (NHANES) and previous Gillison lab case-control and epidemiological studies.

The oral HPV risk factor survey questions are compiled from questions used in the NHANES 2009-2010 study cycle, which were administered to almost 5,000 NHANES study participants, and were used in the development of the model analyzing sociodemographic and behavioral risk factors associated with oral HPV infection.

The oral cancer risk factor survey was derived from several large-scale population-based surveys, as well as prior Gillison research team study surveys. Questions in the detailed risk factor survey are derived from validated sources such as NHANES (demographic, sexual behavior), the Behavioral Risk Factor Surveillance System (demographic), the Lifetime Tobacco Use Questionnaire (tobacco, and modified for alcohol and marijuana), and Gillison research team surveys (see D'Souza G, et al, NEJM 2007; tobacco, alcohol, marijuana, and sexual behavior). The cancer history section was derived from a questionnaire developed by the James Cancer Center for assessing cancer risk based on personal and familial cancer history. Modified versions of the follow-up detailed risk factor survey using a computer assisted self-interviewing (CASI) format on tablet computers have been administered to over 800 participants in the RTOG1016 study and over 700 participants in a 5-year case-control study currently being conducted by the Gillison research team.

7.4.2 Technology

- (1) Study procedures and electronic questionnaires will be administered within a secure web-based application accessed via tablet computers.
- (2) A secure, password-protected wireless router is required in order for a practitioner to participate in this study; See MOP: *Site Initiation SOP*.
 - a. Practitioners without a wireless internet connection will be provided with a secure, study-sourced wireless router prior to study initiation.
- (3) One to two tablet computers will be provided to each participating practitioner, depending on their enrollment rate and patient volume; See MOP: *Site Initiation SOP*.

7.4.3 Training and Troubleshooting

- (1) RCs will be trained on how to operate the tablet computers and the web application via web seminar with the Ohio State University Clinical Data Manager. See MOP: *Web Application User Guide*.
- (2) Participating practitioners and their staff members will be trained on tablet computer and web application operation by their regional RC. See MOP: *Web Application User Guide*.

8 ASSESSMENT OF SAFETY

8.1 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 (SAE).

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:

- (1) 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;
- (2) 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
- (3) 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.

8.1.2 *Serious Adverse Events*

An SAE is one that meets one or more of the following criteria:

- (1) Results in death
- (2) Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- (3) Results in inpatient hospitalization or prolongation of existing hospitalization
- (4) Results in a persistent or significant disability or incapacity
- (5) Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2 Reporting Procedures

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 AE, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- (1) Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number.
- (2) A detailed description of the AE, incident, experience, or outcome.
- (3) An explanation of the basis for determining that the AE, incident, experience, or outcome represents an unanticipated problem.
- (4) 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:

- (1) Unanticipated problems that are SAEs will be reported to the IRB and to NIDCR within one week of the investigator becoming aware of the event.
- (2) Any other unanticipated problem will be reported to the IRB and to NIDCR within two weeks of the investigator becoming aware of the problem.
- (3) 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's centralized reporting system via Rho Product Safety:

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

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

- (1) US: 1-888-746-7231
- (2) International: 919-595-6486

9 STUDY OVERSIGHT

In addition to the GPI's and Study Principal Investigator's (SPI) responsibility for oversight, study oversight will be under the direction of the PBRN Data and Safety Monitoring Board (DSMB) composed of members with expertise in dentistry, practice-based research, study design and statistics. The DSMB will meet at least annually to assess safety and efficacy data for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the NIDCR.

10 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. The network RAS will be responsible for clinical site monitoring for this study. RCs at each RAS will provide study training to practitioner sites and perform clinical site monitoring activities, to evaluate study processes and documentation based on NIDCR standards and principles of good clinical practice.

All details about clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by Westat, under the direction of the National Dental PBRN, in collaboration with the NIDCR Office of Clinical Trials Operations and Management (OCTOM) and the NIDCR Program Official. The CMP will specify practitioner training activities, the type and frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of patient data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at each practitioner site. The RCs will provide reports of the findings from monitoring and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the practitioner, GPI, SPI, OCTOM, and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

11 STATISTICAL CONSIDERATIONS

Statistical considerations, including sample size and power calculations, are further detailed in the Statistical Analysis Plan (SAP).

11.1 Study Hypotheses

This pilot study is designed to test the following hypotheses:

- (1) The proportion of the high-risk HPV infection among individuals selected for oral rinse collection will be similar to the proportion predicted by the risk factor model;
- (2) Baseline study procedures will be feasible and acceptable to dental practice staff and patients;
- (3) The distribution of demographic and behavioral risk factors in the study population will be similar to the US population; and
- (4) Participants will be compliant with follow-up study procedures, including the blood draw, oral cancer screening examination, second oral rinse specimen collection and detailed oral cancer risk factor survey (Appendix J); and
- (5) Arranging and conducting the procedures will be feasible for RC and dental practice staff.

The study will determine whether or not oral HPV detection can be used to identify individuals in a dental practice who are at high-risk for HPV-associated oral cancer and who should be targeted for referral and screening for oral cancer.

11.2 Sample Size Considerations

The sample size for this pilot study is based upon a dichotomous outcome in which participating patients are categorized as low-risk versus high-risk for oral high-risk HPV infection. Based upon our risk model derived from 5,500 individuals who are representative of the US population (NHANES), we expect 30% of the study population to be categorized as high-risk. A two-sided test of proportions with a type 1 error of 0.05 indicates that a pilot study with 1,000 individuals will have 90% power to detect a 5% or greater difference in the proportion of the study population that is categorized as high-risk. The ability to enroll a sample size of 1,000 will also provide assurance that a study with a large sample size is feasible in the National Dental PBRN.

11.3 Final Analysis Plan

To accomplish the primary objective, our outcomes of interest will be the number of individuals determined to be in the top three deciles of risk based on our model (i.e., those selected for oral sample collection based on risk) as well as the proportion of those individuals with an oral high-risk HPV infection. Based upon our model in NHANES, we would expect that 30% of the participating population would be selected for specimen collection and that the resulting population would have an oral high-risk prevalence of 8.43% (95%CI 6.68% to 10.14%). The number of individuals selected as high-risk will be informative with regard to the distribution of

risk factors in the study population, and the proportion positive will be informative with regard to the β -estimates for our risk model.

Shown in the table below are the upper and lower bounds of the 95% CI for the proportion positive for oral high-risk HPV infection, assuming a range of 10-50% of the study population is categorized as high-risk based on our model. A proportion of the study population with oral high-risk infection that falls within the confidence bounds in the table below, given the sample size, will indicate that the β -estimates in our NHANES model are reasonable estimates of risk to the study population.

Sample size	Proportion	95% Confidence Interval	
		Lower Bound	Upper Bound
100	8.43%	2.98%	13.88%
200	8.43%	4.58%	12.28%
300	8.43%	5.29%	11.57%
400	8.43%	5.71%	11.15%
500	8.43%	5.99%	10.87%

To accomplish secondary objectives (1) and (3) a brief Provider Survey (Appendix P) will be administered via tablet computer/web-application to providers at each participating practice to assess acceptability of each procedure and willingness to participate in a future larger study. Results will be reported as summary statistics.

Descriptive statistics for secondary objective (3) include the proportion of individuals with high-risk oral HPV infection who:

- (1) Enroll in the follow-up study;
- (2) Attend a 6-month follow-up;
- (3) Provide blood serum sample; and
- (4) Provide second oral rinse.

To accomplish secondary objective (2) the distribution of the demographic and behavioral variables in the study population will be compared to the weighted distribution of the same factors in the US population per NHANES. In this analysis, the distribution of the populations into deciles of risk will be represented in an $n \times k$ table where n represents the two populations and k the deciles of risk. The distribution will be compared by chi square test with nine degrees of freedom. The distribution of each variable in the two populations will also be compared in univariate analysis. Successful completion of this pilot will therefore: (1) assess patient acceptability of the procedures; (2) provide training to study personnel and assess the feasibility of incorporating the study procedures into clinical practice; and (3) inform the point estimates and models used for sample size determination for a future larger study to ensure that the estimate of 60,000 screened individuals is appropriate.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating practitioner will maintain appropriate medical and research records for this study, using the principles of good clinical practice and complying with regulatory and institutional requirements for the protection of confidentiality of patients. Each practitioner 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 (QA) reviews, audits, and evaluation of the study safety, progress and data validity.

The following clinical records will be considered source documents where they are used to complete CRFs: clinical and office charts, memoranda, and recorded data from automated instruments.

The following eCRFs or portions of eCRFs will be considered source documents, as it is not expected that all patients' clinical charts would contain the exact information collected on these eCRFs: Eligibility Screening, Consent Comprehension, Contact Information, the electronic oral HPV risk factor survey (Appendix C), oral rinse sample collection, the electronic oral cancer risk factor survey (Appendix J), and the provider survey (Appendix P).

All study source documents must be maintained in a secure manner, and practice personnel and network personnel will have access to source documents. Study source documents may include clinical records and as such are subject to HIPAA regulations. These records will be subject to examination and copying as stated elsewhere in this section.

13 QUALITY CONTROL AND QUALITY ASSURANCE

A high-level Quality Management Plan is detailed in Appendix L. In brief, QA and quality control (QC) activities will be implemented for each key study activity, including practitioner recruitment, training, and enrollment; patient screening and enrollment; patient follow-up; data collection; biospecimen collection, storage, shipping, tracking, and processing; and data analysis and interpretation. The study's MOP will provide further detail to operationalize study QA/QC procedures.

For the QA/QC activities associated with data collection and processing, OSU will develop a Data Management Plan (DMP) (outline provided in Appendix M) in collaboration with Westat and/or NIDCR in which the specific data QA/QC procedures will be provided. The procedures will include the development of automatic data quality checks in the web-based application and the processes related to the data manual review, discrepancy management, delinquent data handling, data updates, data verification and approval, and database audit. A work instruction will be provided to the RCs at the RAS with the specified tasks, timelines of completing the tasks, roles and responsibilities. The OSU Clinical Data Manager will work with the RCs to ensure that all procedures are followed and that the data are checked according to the validation requirements specified in the DMP. The OSU Clinical Data Manager will verify the completion of data entry and clarifications by running monitoring reports. Once confirmed that the data entry are complete and the data are verified and approved for accuracy, the database will be locked for final analysis. During the study period, when interim data analysis is needed, the OSU Clinical Data Manager will coordinate the activities with the RCs and the Statistician. The interim datasets will be provided with the data collected as of the specified date. The data in those datasets will be cleaned if possible but may contain pending issues that will be provided to the Statistician if requested. The datasets will be provided to the Statistician via secure data transfer method.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator 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

It is recognized that this protocol must receive the approval of many unique IRBs, and each may have different criteria for patient informed consent. Therefore, different regions may have slightly varied informed consent procedures and documents. For the purposes of this minimal risk, non-intervention study, the following will be considered acceptable by the study investigators, at the discretion of the responsible IRB: electronic consent for the initial (screening) phase of the study, followed by telephone (verbal) consent for the final (follow-up) phase of the study.

The protocol, informed consent documents, appendices and recruitment materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent documents must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

14.3.1 General Information

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Protocols for the informed consent process will vary across practitioners, practices and regions, and will be determined by individual IRBs.

In general, an extensive description of risks and possible benefits of study participation will be provided to patients electronically (initial study visit) or over the phone (follow-up study). All study participants will receive a copy of the Oral HPV FAQ documents (Appendix K) and a hard copy of the informed consent form at the time of enrollment. Due to the variability of informed consent templates and IRB requirements across collaborating practices and regions, the electronic and hard copy consents will not be identical. The language in the electronic consent is universal and administered to every study participant via the study web-application; the patient will read this electronic form and indicate consent electronically. Afterward, region-specific consent procedures will be followed and may include additional verbal and/or written consent procedures. Some IRBs may require study participants to sign a paper informed consent document along with their electronic agreement. For all regions, a region-specific

paper consent document will be provided to each participant for their records after consent procedures have been completed.

All consent forms and scripts will be IRB-approved. The participant is required to read and review the document or have the document read to him or her, and the investigator or designee will answer any questions that may arise. The participant will indicate agreement to participate in the study prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the research record. Study procedures, including patient informed consent will be tracked by means of a web-based computer application. Practitioners will be consented by RCs according to regional IRB requirements. Criteria for consent and results of consent process will be tracked administratively.

14.3.2 Oral HPV Screening Consent Process

The oral HPV screening phase of this study has been determined to be low-risk and therefore electronic consent, administered on a tablet computer/web-application, is appropriate for the first consent process. Appropriate waivers of consent documentation should be obtained by the practitioner's governing IRB, if required.

1. The web application will verify patient eligibility.
2. The consenting individual will inform eligible patients that they may ask questions before, during and after the electronic consent process.
3. The web application will show an IRB-approved Electronic Study Summary. This page will explain the study rationale, procedures, risks and benefits to the patient; See Appendix A: *Electronic Study Summary, Part I (Oral HPV Screening)*.
4. The web application will administer a three-question survey to assess the patient's comprehension of the study.
5. After reviewing the study summary and completing the comprehension survey, the patient may indicate their agreement to participate electronically.
6. A hard copy, IRB-approved Informed Consent Form will be provided to a patient at the time of enrollment. See Appendix B: *Informed Consent Form, Part I (Oral HPV Screening)*.

14.3.3 Oral Cancer Screening Follow-up Study Consent Process

Consent for the follow-up portion of this study for those with positive high-risk HPV results must be carried out via telephone by the RC. Appropriate waivers of consent documentation and approval of the telephone consent script should be obtained by the practitioner's governing IRB, if required. See Appendix H: *Telephone Consent Script, Part II (Oral Cancer*

Screening Follow-up Study) and Appendix I: *Informed Consent Form, Part II (Oral Cancer Screening Follow-up Study)*.

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

All men and women between the ages of 30-69 years will be eligible to enroll in this study. Individuals under the age of 30 years are excluded from participation because data from the US population indicate this age group is at extremely low risk for high-risk oral HPV infection and oral cancer.

14.5 Participant Confidentiality

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

For a majority of participating patients, the data will be collected without patient reporting of identifiers (e.g., will be anonymous).

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.

Patients will be assigned a unique identification number, which will be used to maintain study records and organize data transcripts. A file linking patients' names with their unique identification number will be kept in a password-protected file on the CC's computer, separate from all other research records.

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

The tablet computer and web-application are password-protected and all data are encrypted. Questionnaire response data will not be available to local care providers. Study data will be stored on secure servers at OSU and Westat. To protect the confidentiality of the data, a Certificate of Confidentiality will be obtained by the US Federal Government to protect data from release to any party, except with the expressed consent of the study patient. Certificates of Confidentiality were designed to protect patients who participate in studies in which collection of sensitive, stigmatized or illegal behavioral data is necessary. Although administered on a tablet computer to enhance confidentiality of survey administration for the study participant, the software will be a web-based application accessible on any computer. The consent form will include language compliant with HIPAA regulations.

14.6 Future Use of Stored Specimens and Other Identifiable Data

Participants in this study will be asked for authorization to have their oral rinse and blood samples stored in a freezer and potentially used for future research. The samples will be stored at OSU for 10 years, and will only be used by the investigator of this study for research on HPV and how mouth and throat cancers develop. Testing may include analysis of genes that may affect risk of HPV infection, inflammation or cancer. The data from genetic testing will be stored electronically in a secure data repository and will be made available for secondary research.

15 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate CRFs, and source documentation. The Data Management Plan Outline is detailed in Appendix M.

Only study personnel (i.e., GPI, SPI, Co-I's, RCs, and CC personnel) and clinical site monitors will have access to the study data elements in the study database as described in Section 15.3 Types of Data. Study personnel will include those who are on the approved IRB study protocol. All study personnel will have completed the required training elements for human subjects research certification.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents must be reviewed by the study team and data entry staff that will ensure that they are accurate and complete. Unanticipated problems must be reviewed by the investigator or designee.

For eCRFs that are to be used as source documents (see Section 12), the RAS staff will ensure the e-signature is complete. The RAS staff will ensure the data are entered and the discrepancies generated by the system are resolved in a timely fashion based on study requirements. The RAS staff will work with practitioners to clarify any data issues and maintain a tracking log for the data changes. To aid the data collection and data entry activities, OSU will provide electronic data entry guidelines.

The OSU Clinical Data Manager will be responsible for contributing to survey and instrument design, and testing, training, and implementation of data collection and monitoring systems (software).

15.2 Data Capture Methods

A web-based data collection system will ensure that all required data are collected in the study database. As most fields will require a categorical response and some fields will ask for a numeric response, the data field in the database will be programmed to allow only certain values and ranges so that data entered from the web system can be validated and data errors be corrected. Reports and tools will be developed to help monitor the visit and data activities. The reports with the summary of the data completion at enrollment and follow-up by the practitioners will be made available on the network web site.

15.3 Types of Data

Data for the present study consist of the following:

- Questionnaire responses;
- Oral rinse and blood laboratory analysis data; and
- Unanticipated problems data.

The web-based computer application will store questionnaire and oral rinse data. Blood laboratory analysis data will be stored in a separate laboratory database. Safety data related to unanticipated problems reported by patients or staff will also be stored in a separate database.

15.4 Schedule and Content of Reports

During the recruitment period for Enrollment Visit 1, the OSU Clinical Data Manager will provide weekly reports to the CC, which will summarize practitioner-specific and overall enrollment. The CC will distribute these weekly reports to the Network Director and NIDCR. These reports will contain sections for: a) Practitioner accrual by practice location and type specified in Section 5.3.1, and b) patient information in aggregate. These reports will also contain separate sections for each region, with information regarding participant accrual by practitioner.

Reports to assess study retention will be produced weekly during the follow-up study period. The CC will distribute these weekly reports to the Network Director and NIDCR. These reports will provide ongoing monitoring of participant retention. Retention data will be closely monitored. In addition, a report will be produced for each individual practice that includes the practice's attrition rate and a comparison to the overall attrition rate for the study. These reports will be made available to the practitioners.

Reports to the DSMB will be produced at least annually, and may be produced more frequently at the request of the DSMB. As noted in Section 9 Study Oversight, most data elements for inclusion in the DSMB reports will be clearly defined at the organizational meeting of the DSMB.

As portions of the study objectives can be addressed through analyses of baseline data only, it is anticipated that some full analysis can begin after baseline data collection is complete. Interim analysis reports that address objectives requiring all study data to be collected will be produced at the discretion of the Statistician, in consultation with the SPI, and other study team members. The content of these reports will be determined by the Statistician, in consultation with the SPI, and other study team members.

The procedure for locking the database prior to final analysis will be detailed in the study DMP. Briefly, the data will be locked and the final SAS datasets will be generated at the end of the study. Prior to locking the database, the OSU Clinical Data Manager or designee will ensure all data is complete and clean. Then, the CDM will obtain approval to proceed with the data lock. The OSU Clinical Data Manager will then direct the Database Development Manager to lock the database. The date and time of database lock will be documented. All team members will receive written notification from the OSU Clinical Data Manager or designee when the database lock is complete.

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 local IRB or state laws/regulations.

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way after three years from the conclusion of the study (e.g., and files will be securely deleted from computers).

The file connecting patients' names with their unique identification number will be kept in a password-protected file by the CC and on the GPI's computer for a minimum of three years after conclusion of the study, in accordance with IRB regulations, before being securely erased.

15.6 Protocol Deviations

A protocol deviation (PD) is any noncompliance with the clinical study protocol or good clinical practice principles. The noncompliance may be on the part of the subject, the investigator, or study staff. In the event of deviations, corrective actions are to be developed by the study staff and implemented promptly. All deviations from the protocol must be addressed in study subject source documents and promptly 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. At the time of each DSMB review, all previously unreported PDs must be reported to the DSMB independent of when they are reported to IRBs.

16 PUBLICATION 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 National Institutes of Health (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://nationaldentapbrn.org/publication.php>.

17 LITERATURE REFERENCES

1. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J. Clin. Oncol.* 2011;29(32):4294-4301.
2. Gillison M, D'souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus 16-negative head and neck cancers. *J. Natl. Cancer Inst.* 2008;100 (6):407-420.
3. Gillison ML, Alemany L, Snijders PJ, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. *Vaccine.* 2012;30 Suppl 5:F34-54.
4. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N. Engl. J. Med.* 2007;356(19):1944-1956.
5. Bosch FX, Broder TR, Forman D, et al. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine.* 2013;31 Suppl 7:H1-31.
6. Beachler DC, D'Souza G, Sugar EA, Xiao W, Gillison ML. Natural history of anal vs oral HPV infection in HIV-infected men and women. *J. Infect. Dis.* 2013;208(2):330-339.
7. Broutian T, He X, Gillison M. Automated high throughput DNA isolation for detection of human papillomavirus in oral rinse samples. *J. Clin. Virol.* 2011;50:270-275.
8. Fakhry C, Sugar E, Pevtsova C, D'souza G, Gillison M. Two-week versus six-month sampling interval in a short-term natural history study of oral HPV infection in an HIV-positive cohort. *PLoS One.* 2010;5(7):e11918.
9. D'Souza G, Fakhry C, Sugar EA, et al. Six-month natural history of oral versus cervical human papillomavirus infection. *Int. J. Cancer.* 2007;121(1):143-150.
10. D'Souza G, Sugar E, Ruby W, Gravitt P, Gillison M. Analysis of the effect of DNA purification method on the detection of human papillomavirus in oral rinses by PCR. *J. Clin. Microbiol.* 2005;43(11).
11. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. *JAMA.* 2012;307(7):693-703.
12. Olson CM, Burda BU, Beil T, Whitlock EP. *Screening for Oral Cancer: A Targeted Evidence Update for the U.S. Preventive Services Task Force.* Rockville (MD)2013.

APPENDICES

Appendix A: Electronic Study Summary, Part I (Oral HPV Screening)

Appendix B: Informed Consent Form, Part I (Oral HPV Screening)

Appendix C: Oral HPV Risk Factor Survey

Appendix D: Study Schedule of Events

Appendix E: High-Risk Oral HPV Results Notification Script, Negative

Appendix F: High-Risk Oral HPV Results Notification Script, Positive

Appendix G: High-Risk Oral HPV Results Notification Script, Not Evaluable

Appendix H: Telephone Consent Script, Follow-Up Study Procedures

Appendix I: Informed Consent Form, Part II (Oral Cancer Screening/Follow-Up Study)

Appendix J: Oral Cancer Risk Factor Survey

Appendix K: Oral HPV FAQ

Appendix L: Quality Management Plan

Appendix M: Data Management Plan Outline

Appendix N: Practitioner Informed Consent Form

Appendix O: Dental Practitioner Interest Sheet

Appendix P: Provider Survey

Appendix Q: HPV Results Template

Appendix R: Result Reporting Letter – Positive, High Risk

Appendix S: Result Reposting Letter – Negative, High Risk