

Treatment of patients on conventional and direct oral anticoagulants in the dental office

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

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

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LIST OF ABBREVIATIONS

ACs	Anticoagulants
CoC	Certificate of Confidentiality
CFR	Code of Federal Regulations
CROMS	Clinical Research Operations and Management Support
DMP	Data Management Plan
DOACs	Direct oral anticoagulants
EDC	Electronic Data Capture
FFR	Federal Financial Report
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IRB	Institutional Review Board
NC	Node Coordinator
NCC	Network Coordinating Center
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PD	Protocol Deviation
PI	Principal Investigator
PID	Practitioner Identification Number
QA	Quality Assurance
QC	Quality Control
UP	Unanticipated Problem
US	United States

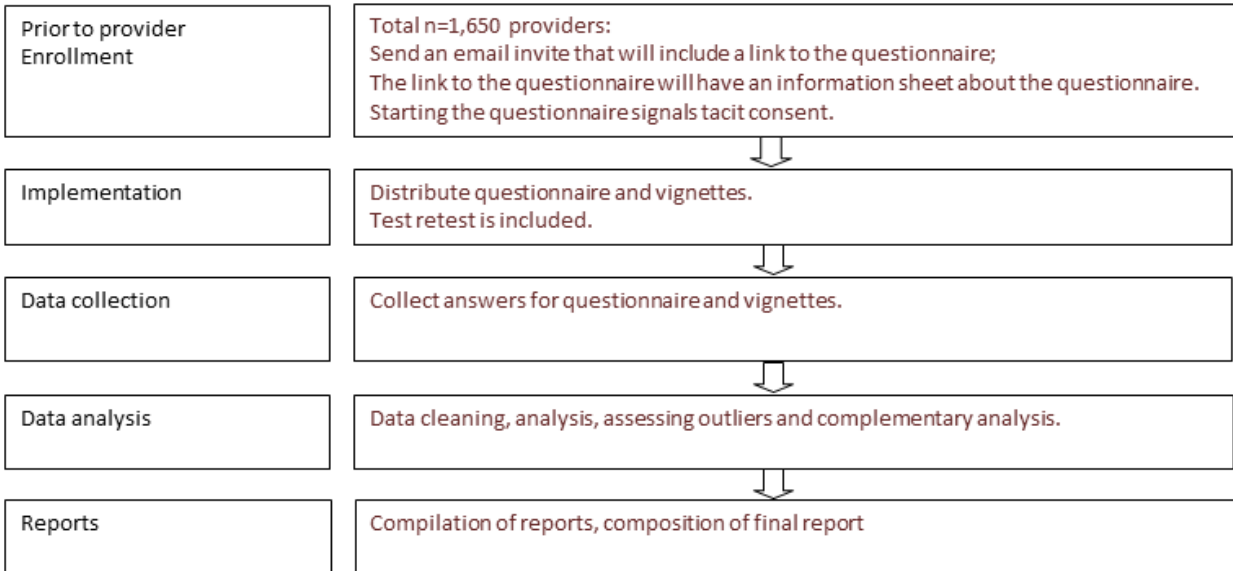
PROTOCOL SUMMARY

- Title:** Treatment of patients on conventional and direct oral anti-coagulants in the dental office
- Précis:** The overall goal of the study is to assess general dentists' approach to the management of patients who currently take anticoagulants and who plan to have a dental procedure that is associated with a bleeding risk, such as scaling and root planing and a simple extraction.
- The information generated from the study will help understand clinical evidence-practice gaps and design future studies regarding dental management of patients taking anti-coagulants (ACs), particularly direct oral anti-coagulants (DOACs).
- This is a cross-sectional National Dental Practice-Based Research Network (PBRN) survey study that comprises 2 components: 1) an electronic questionnaire, and 2) two electronic standardized clinical case-vignette scenarios. Approximately 1,650 National Dental PBRN general dentists will be invited to participate in the study.
- Objectives and Outcome Measures:**
- Primary objective:
- To describe general dentists' approach to managing dental treatment for patients taking conventional ACs and DOACs.
- Secondary objectives:
1. To examine the associations between stopping ACs/DOACS prior to a dental procedure that causes bleeding (and if so, when) and practitioner/practice characteristics.
 2. To describe how general dentists classify the severity of post-operative bleeding.
- Outcome Measures:
- The outcome measures will be: (1) general dentists' current approach to managing patients on conventional ACs and DOACs who have a dental procedure that causes bleeding;

and (2) general dentists' classification of the severity of postoperative bleeding

- Population:** The sampling frame is all National Dental Practice-Based Research Network (National Dental PBRN) general dentists. We will invite approximately 1,650 general dentists who are active clinicians to participate in the study. The targeted yield will be 806 completed questionnaires.
- Number of Sites:** N/A
- Study Duration:** Approximately 9 months
- Subject Participation Duration:** Approximately 20 minutes each to complete the questionnaire and the clinical case presentations (vignettes).
- Estimated Time to Complete Enrollment:** Approximately 3 months.

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Dental intervention-related oral bleeding is an important consideration when treating patients on anti-coagulants (ACs). The literature reports extensive bleeding complications in patients on warfarin affecting 1.5-26% of patients.¹⁻²² Major bleeding has been reported in 4.6% of patients treated with warfarin, including during dental procedures.²³ The prevalence of minor bleeding is reported to be 3-9.7%.^{2, 23, 24}

With the emergence of numerous direct oral anti-coagulants (DOACs), the impact of anti-coagulation on procedures causing bleeding is becoming more complex. These DOACs include oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, darexaban, letaxaban) and direct thrombin inhibitor (dabigatran).

DOACs are used for various indications, the most common of which is atrial fibrillation (AF). In addition to prevention of systemic embolism and stroke in AF patients, there are other indications for the use of DOACs. This includes prevention of thromboembolism in patients with mechanical heart valves, and treatment of venous thromboembolic disease, including deep vein thrombosis (DVT) and pulmonary embolism (PE). Another category of patients who are treated for a shorter duration with DOACs to prevent deep vein thrombosis (DVT) are patients undergoing knee or hip replacement surgery. The overall prevalence of AF in the U.S. is 1%. It is estimated that 900,000 people could develop thromboembolic event each year in the U.S. Accordingly, the estimated number of patients treated with DOACs is probably in the hundreds of thousands per year.^{25, 26}

While monitoring risk for bleeding with conventional ACs is routine, at this time there are no validated, reliable and widely offered laboratory tests to assess the anticoagulant effect of DOACs. The lack of tests that correlate with bleeding tendency positions the dentist with no means to identify patients at a high-risk for bleeding.

An important consideration in medical management decisions for dental procedures likely to cause bleeding, when considering stopping anticoagulants, is the risk of bleeding vs the risk of thromboembolism. Large-scale retrospective studies in the dental setting report a bleeding rate of 6-14%.²⁷⁻³¹ Of interest, most of the large studies have been done in oral surgery clinic settings.²⁸⁻³¹ In a large study, "Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)," the risk for major bleeding peri-procedurally was 3.8% and 5.1% for patients treated with two doses of dabigatran, when the dabigatran was withheld 24-48 hours prior to the medical or dental procedure. The risk for minor bleeding peri-procedurally was 8.1% and 9% for dabigatran doses of 110 BID and 150 BID, respectively.²³ Dental procedures represented fewer than 10% of the total number of procedures in this study.

Regarding the risk of thromboembolism, a recent study showed that the risk for thromboembolism after discontinuation of DOACs for major surgery is about 3%.³² However, there is no literature about the risk for thromboembolism in the dental setting, hampering evidence-based clinical decisions for patients taking DOACs.

Guidelines or recommendations regarding conventional anticoagulants are available, but these are inconsistent. The American Dental Association (ADA) states that there is no need to discontinue warfarin (also known as Coumadin) prior to dental intervention, and that the International Normalized Ratio (INR) must be evaluated before invasive dental procedures are performed.³³ This approach was supported by the 4th World Workshop of Oral Medicine (WWOM IV) that recommended not modifying or discontinuing warfarin for simple dental extractions when the INR is <3.5. For major invasive procedures, the recommendation is to refer to the physician to consider dose adjustment.³⁴ Nevertheless, the WWOM IV stated that the clinician's judgment, experience, training, and access to appropriate bleeding management strategies are all important components in any treatment decision. The American College of Chest Physicians (ACCP) has released its recommendation for minor (extractions and endodontic) and major dental procedures.³⁵ For minor dental procedures, two options were presented: 1) continue warfarin with co-administration of an oral pro-hemostatic agent; or 2) stop warfarin 2 to 3 days (partial interruption) before the procedure. For a major dental procedure, if warfarin interruption is required, consider bridging with heparin. The American Heart Association/American College of Cardiology (AHA/ACC) published similar guidelines.³⁶ Based on these consensus papers, it seems that for patients taking warfarin, INR drives the decision about modification of warfarin dose/timing. Warfarin should be continued before minor dental procedures if the INR <3.5, and use of local hemostatics is required for bleeding control.

For DOACs, the picture regarding recommendations is more uncertain. The ADA website provides a narrative review of DOACs; however, it is based on evidence from European studies, which do not necessarily apply to the U.S. Furthermore most of the literature available about bleeding risk comes from tertiary hospital settings. The community-based dental practice setting may differ from a hospital-based dental office in its dynamics, scope of practice, and supporting institutional services, such as blood bank or availability of an operating room. Therefore, bleeding risk in community-based dental practice might be viewed differently by community dental practitioners.

In summary, for conventional ACs, despite recommendations and guidelines, little is known about whether community based dentists follow these or what their approach is to the medical management of patients taking ACs requiring dental procedures that may cause bleeding. This is true for patients taking DOACs as well. Furthermore, with DOACs' increased popularity and limited U.S. clinical studies about patient safety related to DOAC use in the dental setting, there is an apparent gap in the literature about the preferred approach to manage these patients.

2.2 Rationale

Our long term goal is to determine the procedure risk of bleeding in patients in dental community practices who are taking conventional ACs and DOACs. There is a high likelihood for dental practitioners in community settings to encounter and treat patients taking conventional ACs and DOACs, with sparse literature on the medical management of these patients' risk of bleeding from procedures; most of the literature comes from studies conducted in hospital or institutional settings in Europe or Asia. Given that the majority of dental practitioners in the U.S. are in community settings, it is therefore important to assess how dental practitioners approach medical management of patients taking conventional ACs and DOACs, prior to and while performing dental treatment with risk for bleeding. Of particular note is the emergence of DOACs, for which we have no laboratory means to determine the level of risk for bleeding, and limited information related to the safety of procedures in community dental practices.

This study will enhance our understanding of the collective dental community's approach to treating patients at risk for bleeding. In particular, it will help us understand dentists' decisions about stopping or continuing anticoagulants, and their pre-, during, and post-procedure patterns of practice. This information may be of value in identifying modes of safe dental practice for patients taking anticoagulants, and, coupled with practitioners' definition of bleeding based on its severity, may help in the design of future studies about management of patients taking ACs in community dental settings.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

This study poses no more than minimal risk to study participants. There are no anticipated physical, psychological, social, legal, economic, or any other anticipated risks to study participants. Study participation is completely voluntary, and participants may discontinue participation at any time without penalty or negative consequences. Participants may not feel comfortable answering particular questions on the questionnaire or on the clinical case presentations (vignettes). As such, they will have the option to skip questions or to not complete the study.

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

2.3.2 Potential Benefits

There will be no direct benefit to participants. Participating practitioners may become more aware of new medications that pose a bleeding risk for patients.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
<p>To describe general dentists' approaches to managing dental treatment for patients taking conventional ACs and DOACs.</p>	<p>There are recommendations, and in some cases guidelines, primarily for conventional ACs and less so for DOACs, but these are inconsistent across professional associations. Little is known about community-based dentists' approaches to the medical management of patients taking conventional ACs and DOACs.</p>	<p>The questionnaire assesses general dentists' current approach by addressing these specific aspects of management:</p> <ol style="list-style-type: none"> 1. Whether ACs/DOACs were stopped prior to a dental procedure that causes bleeding. 2. Among those who stop ACs/DOACs, how long prior to dental procedures that cause bleeding the dentist/physician stopped the ACs/DOACs. 3. Whether the dentist makes his/her own decision, suggests to the patient's physician how to act, or defers to the physician's recommendation when treating patients taking ACs/DOACs. 4. The extent to which dentists use laboratory tests to guide their approach when treating patients taking ACs/DOACs. 5. What post-procedure practices are in use when the dentist provides treatment for patients taking ACs/DOACs. 6. Whether the dentists prefer to refer patients taking ACs/DOACs to another dental office. 7. Whether the dentists feel comfortable treating AC/DOAC patients. 	<p>One-time administration of an electronic questionnaire and clinical case vignettes will be used to gather information to measure this outcome.</p>

3.2 Secondary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
<p>1.To examine the associations between stopping ACs/DOACS prior to a dental procedure that causes bleeding (and, if so, when), and practitioner/practice characteristics.</p>	<p>Understanding the association between selected practitioner/practice characteristics and the decision regarding stopping ACs/DOACs may help understand the basis for the management decision.</p>	<p>Associations between stopping ACs/DOACS prior to a dental procedure that causes bleeding (and, if so, when) and these practitioner/practice characteristics will be measured:</p> <ol style="list-style-type: none"> 1. Practice’s region (6 National Dental PBRN regions) 2. Practice’s location (urban or suburban vs rural) 3. Duration since graduating dental school 4. Completion of a general dentistry residency (AEGD or GPR or not). 5. Experience with treating patients on ACs/DOCs 	<p>One-time administration of an electronic questionnaire and clinical case vignettes and use of the National Dental PBRN enrollment questionnaire data will be used to measure this outcome.</p>
<p>2. To describe how general dentists classify the severity of post-operative bleeding.</p>	<p>Conducting studies on postoperative bleeding in the dental community setting is hampered by a lack of classification system for its severity. This outcome measure may help define consensus about its definition for use in future clinical research.</p>	<p>The questionnaire will query the frequency of referring to selected bleeding scenarios as minor, moderate or major.</p>	<p>One-time administration of clinical case vignettes will be used to measure this outcome.</p>

4 STUDY DESIGN

This study is a cross-sectional questionnaire of National Dental Practice-Based Research Network clinical general dentists. Approximately 1650 general dentists will be invited to participate, with a target of obtaining 806 respondents who complete the questionnaire.

Eligible participants will be sent a study invitation email to participate in the study with a link to the electronic version of the questionnaire. The survey will be administered using the Electronic Data Capture System on the Network HUB website, housed at the Network Coordinating Center (NCC). Additional details on the development and administration of the questionnaire are detailed in Section 7.

Following the launch of the questionnaire, approximately 30 of the initial survey responders will be selected to complete the electronic questionnaire again (approximately 2 weeks post initial questionnaire completion) to establish test-retest reliability.

Resampling will be conducted in the unlikely event that we do not reach our target participant enrollment from the approximately 1,650 initial invitees.

5 STUDY POPULATION

5.1 Participant Inclusion Criteria

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

1. Is a current limited or full participation member of the National Dental PBRN (Enrollment Questionnaire [EQ] Qx 7: response category 2 or 3),
2. Has indicated he/she is a General Dentist practicing within the U.S. based on response to questions on the network's Enrollment Questionnaire (EQ Qx 18: response category 1 or declaration thereafter).
3. Is licensed in the U.S. to treat patients, treats patients in the U.S. on a recurring basis (EQ Qx 1: response categories 1-10) and
4. Has current contact information on file at which he or she can be contacted (EQ contact information).

5.2 Participant Exclusion Criteria

An individual who meets the following criteria will be excluded from invitation to this study:

1. Dental hygienists or dental specialists.

5.3 Strategies for Recruitment and Retention

5.3.1 Recruitment

The sampling frame includes all active general dentist members of the National Dental PBRN. From these, a random sample of 1,650 eligible dentists will comprise the recruitment pool. A random sample of all eligible dentists will receive an email invitation from the NCC inviting them to participate in the study. This email will contain a link to the electronic survey, housed on the NCC HUB website. Based on previous PBRN survey studies, we anticipate a response rate of approximately 50%. Calls will be held as needed with the Node Coordinators to review contact information for eligible practitioners, discuss recruitment issues and enrollment progress, manage study documentation and procedures, and troubleshoot problems related to enrollment.

5.3.2 Compensation

Participants will be offered \$50 remuneration for completing the questionnaire. If a participant completes the test-retest of the electronic questionnaire, they will be offered an additional \$50.

5.4 Participant Withdrawal

5.4.1 Reasons for Participant Withdrawal

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

5.4.2 Handling of Participant Withdrawals

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

5.5 Premature Termination or Suspension of Study

The study may be suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Study PI will promptly inform the IRB and will provide the reason(s) for suspension or termination.

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

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

6 STUDY SCHEDULE

6.1 Enrollment of Practitioners into the Study

Eligible practitioners will be identified based upon responses to the National Dental PBRN Enrollment Questionnaire.

Dentists will be invited to complete an online survey in waves to adjust for a balanced regional representation.

Completion of the questionnaire will indicate that study participants have read the consent information, and this will imply consent. A waiver of signed consent will be requested from the IRB.

The NCC and NCs will conduct email and telephone follow-up with invited practitioners to encourage completion.

6.2 Retest of the Questionnaire

- Dentists selected from among those study participants who completed the questionnaire will be sent a second online questionnaire request by email approximately two weeks after the receipt of their first completed questionnaire.
- Dentists will be informed they have one week to respond to the invitation to the retest. If the retest is not completed within the one-week timeframe, the link to the retest questionnaire will be disabled. Additional potential retest participants will be selected from those having already completed the questionnaire until a total of approximately 30 retests have been completed.

6.3 Merging Study Survey with Enrollment Questionnaire

- Enrollment Questionnaire data will be merged after all questionnaire responses are received.
- Questionnaire and Network enrollment data will be linked using practitioner identification numbers (PIDs) that are included in the practitioner database.
- Contact information will be removed from the final merged dataset and data will be stored/saved using the PID.
- During this phase, all data issues will be resolved, database locked, and data provided to study team.

7 STUDY PROCEDURES/EVALUATIONS

7.1 Questionnaire and Vignette Development

The study questionnaire and vignettes were developed by our study team, which had input from oral medicine professionals, hospital dentists, biostatisticians, a psychometrician, a hematologist, and questionnaire methodologists. Following the development of the questionnaire, the instrument has undergone review and evaluation by the NCC, a group with expertise in survey development and implementation, to ensure it is psychometrically sound and the data it collects will allow for adequate evaluation of the study objectives. Further, cognitive testing of the survey instrument was completed, in which dentists described their responses to a completed survey and were probed to assess possible respondent problems in understanding questions, recalling necessary information, and/or reporting accurately.

7.2 Questionnaire User Testing

The NCC will perform internal testing of the electronic study questionnaire including testing internet browser compatibility. Study team members will be given the opportunity to externally test the website prior to administration to study participants.

7.3 Questionnaire Testing-Retesting Format

The online version of the survey will be administered to a subset of approximately 30 online respondents to assess the test-retest reliability of the survey. Participants will be required to return the retest within 1 week of the invitation email. If the test is not completed within the timeframe, the link to the retest survey will be disabled. Administration of the testing-retesting will continue until 30 completed responses are obtained. The test-retest phase will be completed electronically only.

7.4 The anticoagulants in dentistry questionnaire and vignettes survey

Questionnaire items will include a series of multiple-choice questions and vignettes used to assess outcome measures. Some information will be collected from the National Dental PBRN Enrollment Questionnaire (e.g., practitioner and practice characteristics) and linked to participants' responses to the study questionnaire. More specifically the variables from the Enrollment Questionnaire that we will link to questionnaire respondents and use in our analysis include:

1. Practice characteristics:
 - 1) Region
 - 2) State
 - 3) Practice location, e.g., inner urban, urban, suburban, rural
2. Practitioner characteristics demographic information:
 - 1) Age
 - 2) Sex
 - 3) Years since graduating dental school
 - 4) Completed residency

5) Number of patients treated per week (average)

The questionnaire and vignettes will describe a comprehensive, detailed, multidimensional picture of dental practitioner management decisions for patients taking anticoagulation medication and undergoing dental procedures with risk for bleeding.

7.5 Questionnaire Administration

According to the inclusion criteria, eligible participants will be identified from their responses to the network's Enrollment Questionnaire.

Consistent with regulations outlined by the University of Alabama (UAB) IRB and any regional/local IRBs, information about the study will be provided to all eligible participants via an information sheet/questionnaire link in the email invitation. Completion of the questionnaire will indicate tacit consent.

After the invitation and two follow-up email reminders, the NCC will provide the Node Coordinators (NCs) with a list of non-responders and incomplete responders. The NCs will systematically contact non-responders and incomplete responders to encourage survey completion by email, phone, or fax.

If no feedback is received or the participant does not complete the questionnaire after multiple follow-up attempts over a period of up to three months, it is assumed the practitioner is not interested in the study. Node Coordinators may also contact participants as part of data cleaning conducted by the NCC.

8 ASSESSMENT OF SAFETY

8.1 Definitions of Safety Parameters

8.1.1 Unanticipated Problems

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 Specification of Safety Parameters

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

8.3 Reporting Procedures

8.3.1 Unanticipated Problem Reporting

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

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

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;

- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

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

- Unanticipated problem will be reported to the IRB as soon as possible but in all cases within 10 working days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made to NIDCR's centralized reporting system via the Clinical Research Operations and Management Support (CROMS) contractor:

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

9 STUDY OVERSIGHT

The PI will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The NCC will provide the PI with current data reports, and the PI will review the data for safety concerns and data trends at regular intervals, and will report to the IRB and NIDCR any Unanticipated Problem (UP) or any other significant event that arises during the conduct of the study, per the IRB's reporting time-frame requirements. To ensure data integrity, the PI, NCC, and study team will adhere to quality management processes (see Section 13).

10 CLINICAL SITE MONITORING

No outside clinical site monitoring will be employed for this study. The NCC is responsible for launching the study and collecting data received as part of the study. Quality Assurance/Quality Control activities associated with data collection and processing will be outlined in the Data and Quality Management Plan (DQMP). The NCC will ensure that the quality and integrity of the study data and data collection are maintained. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

11 STATISTICAL CONSIDERATIONS

11.1 Study Objectives and Research Questions

This is a cross-sectional questionnaire to assess general dentists' current understanding and approach to medical management of patients taking anticoagulants and planning to undergo dental procedures associated with a bleeding risk. As such, formal hypothesis testing will not be conducted to achieve the study objectives.

Below are the objectives and the research questions:

11.1.1 *Primary Objective:*

1. To describe general dentists' approach to managing dental treatment for patients taking conventional ACs and DOACs.

Research Questions:

- What is the frequency with which ACs/DOACs are stopped for a dental procedure that is associated with bleeding?
- Among those who stop ACs/DOACs, how long prior to dental procedures with risk for bleeding does the dentist/physician act to discontinue ACs/DOACs?
- What is the frequency with which the dentist makes his/her own decision, suggests to the patient's physician how to act, or defers to the physician's decision regarding discontinuing ACs or DOACs?
- What is the frequency with which dentists use laboratory tests to guide their approach towards patients taking ACs or DOACs?
- What post-procedure practices are in use when the dentist provides treatment associated with bleeding risk for patients taking ACs or DOACs?
- What is the frequency with which practitioners prefer to refer patients taking ACs/DOACs to another dental office?
- What is the level of practitioners' comfort in treating patients on ACs/DOACs?

11.1.2 *Secondary Objective:*

1. To examine the associations between stopping ACs/DOACS prior to a dental procedure that causes bleeding (and, if so, when) and practitioner/practice characteristics.

Research Questions:

What are the associations between stopping ACs/DOACs prior to a dental procedure that causes bleeding and each of the following variables (and, if so, when) -

- The practice's region (6 National Dental PBRN regions).
 - The practice's location (urban or suburban vs rural).
 - How long ago the dentist graduated from dental school.
 - Whether the dentist completed a general dentistry residency (AEGD or GPR or not).
 - Experience with treating patients on ACs/DOACs.
2. To describe how general dentists classify the severity of post-operative bleeding.
- Classification of intra-oral bleeding scenarios after a simple extraction (minor, moderate, or major).

11.2 Sample Size Considerations

11.2.1 Sample size calculation details:

1) Generate point estimates with good precision (narrow confidence intervals) of proportions or means for survey items (Primary Objective and Secondary Objective 2). A sample size of 825 would allow us to construct two-sided 95% CIs of width $\pm 3.47\%$ (i.e., margin of error) for a binary item with proportion of .50. For items assuming an approximately interval scale (e.g., Likert-type items) and a standard deviation of 1, a sample size of 825 would allow us to construct two-sided 95% CIs of width ± 0.068 .

2) Statistically test for bivariate relationships described in the final analysis plan for Secondary Objective 1. With a sample size of 825, we will have 80% power to detect multiple correlations (R) as small as .10 in a linear regression at a two-tailed alpha level of .05. For the analyses involving logistic regression, we will have 80% power to detect an odds ratio as large as 1.48 (or 0.67 in the opposite direction), assuming a 50% split on a binary independent variable and 50% rate in the outcome for the reference group and an odds ratio as large as 1.22 (0.82 in the opposite direction) for a one standard deviation unit change in a continuous independent variable at a two-tailed alpha level of .05.

11.2.2 Overall summary of sample size estimations:

To achieve a sample size of 825, 1650 Network clinically active dentists will be invited to participate; this assumes a conservative completion rate of 50% based on prior National Dental PBRN participation rates.

11.3 Final Analysis Plan

We will examine the distribution of all variables prior to analyses and verify all missing and out-of-range values. We will evaluate all inferential analyses at an alpha level of .05.

For the primary objective and secondary objective 2, we will use descriptive statistics for each of the items in the questionnaire and vignettes. Descriptive statistics will also be used for analysis for each of the practitioner and practice descriptors in the network's Enrollment Questionnaire database. We will also calculate confidence intervals around proportions for categorical items and around means for interval level items.

For secondary objective 1, we will use logistic regression for binary outcomes (items 11.I, 13.I, 14.I, 15.I, 16.I, and Vi1.7 & V1.8 [option a vs b-d]), ordinal logistic regression for ordinal outcomes (Vi1.7 & V1.8 [option b vs c vs d]), and linear regression for the reasonably continuous outcomes (2.IV, 3.IV, 7.IV, 8IV). For each regression analysis, we will test the following independent variables separately: practice region (categorical with six levels representing each PBRN region), practice location (binary with urban/suburban vs rural), duration since graduating dental school (continuous), completion of residency program type (categorical, with three levels representing AEGD vs GPR vs none), number of patients seen in the past three months taking ACs (continuous), familiarity with DOACs (continuous), and number of patients seen in the past three months taking DOACs (continuous). Categorical independent variables will be dummy coded. Also, because of the large number of tests being conducted, we will adjust for multiplicity using the Benjamini and Hochberg method.³⁷

Missing data. Data from incomplete questionnaires may be included in data analyses. Participants will be able to submit questionnaire with incomplete data as 22 % (6/27) of the questions do not require responses. Depending on the extent of missing data and available resources for analyses, the study team may consider statistically appropriate methods for imputing missing information.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source data/documents will be maintained by the NCC for this study. The NCC will program the electronic survey and vignettes into their electronic data capture (EDC) on the HUB website. Participants will be sent an email invitation with a direct link to the electronic survey and vignettes. After completion of the electronic survey, data will be collected and maintained through the EDC.

Only study personnel (i.e., the NCC, PI, and designated study team members) will have access to the data. All research computers and associated study documents will be password-protected and maintained in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of study safety, progress, and data validity.

The source documents for this study are:

- Electronic anticoagulants in dentistry questionnaire administered through the NCC EDC on the HUB website
- Data collected in the Network Enrollment Questionnaire

13 QUALITY CONTROL AND QUALITY ASSURANCE

For the quality control (QC) and quality assurance (QA) activities associated with data collection and processing, the NCC will develop a DQMP in which the specific data QA/QC procedures will be provided. These procedures will include the development of automatic data quality checks in the EDC for the questionnaire and processes related to data accuracy and completeness. The EDC will be programmed with edit checks and response limiters to reduce data response errors.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

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

14.2 Institutional Review Board

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

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

14.3 Informed Consent Process

The standard waiver of documentation of signed informed consent for Internet-based surveys will be requested for this study. Consistent with regulations outlined by the Central IRB, informed consent language will be provided on the entry page to the survey and will indicate that consent is provided if the respondent chooses to enter the survey via the link they have been provided (tacit consent).

14.4 Exclusion of Women, Minorities, and Specific Age Groups

National Dental PBRN dentists of any age, sex/gender or racial/ethnic group may participate if they meet eligibility criteria. Minors (< 18 years-old) will not be enrolled in this study.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the study sponsor.

Participants' pre-assigned identification numbers (practitioner IDs assigned by the National Dental PBRN) will be used to maintain study records and organize data files.

A dataset linking participants' names with their unique identification numbers will be stored at the NCC behind a secure firewall.

The study monitor or other authorized representatives of the NIDCR may inspect all study documents and records required to be maintained by the investigator.

The National Program Manager, who will be responsible for ensuring National Dental PBRN dentists completing the questionnaire are remunerated \$50 (if they chose to/are able to accept it), will be provided the minimum information necessary from the questionnaire to fulfill the responsibility of appropriately directing practitioner payments to their desired address. This information will be made available through reports on the HUB.

14.5.1 Certificate of Confidentiality

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

14.5.2 Confidentiality of Data Sharing

As described in section 16, it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see <https://grants.nih.gov/policy/sharing.htm>). PIs and funding recipient institutions will ensure that all mechanisms used to share data include proper plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research.

15 DATA HANDLING AND RECORD KEEPING

The study team is responsible for ensuring the accuracy and completeness of the data reported and following the data collection procedures as outlined in the DQMP. Access to study data will be provided to study team members by NCC staff.

15.1 Data Management Responsibilities

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

The NCC will develop and maintain an EDC system including the study questionnaire/vignettes. The DQMP will include details on the EDC and procedures that will be followed to launch and monitor the study. The data reported in the network's Practitioner Database will be used by the NCC staff to identify eligible general dentists for this study.

15.2 Data Capture Methods

Research Electronic Data Capture (REDCap) will be the EDC system for this study, with integration into the HUB for reports and other study monitoring. The NCC will conduct preliminary testing and review of data fields in the initial programming and online launching of the survey.

Survey study data will be backed up on a regular basis during the data collection period via servers that offer data security.

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

15.3 Schedule and Content of Reports

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

Final data analysis reports that address objectives of the study will be produced by the NCC for review by the NIDCR and study team. The content of these reports will be determined by the study team and the NCC.

The procedure for locking the database prior to final analysis will be detailed in the study DQMP. Briefly, the EDC data will be locked once all data queries are resolved and final datasets will be generated at the end of the study. Prior to locking the database, the Study Manager (SM) or designee will ensure all data is complete and clean as determined by the study team. Then, the SM will obtain approval from the PI to proceed with the data lock.

15.4 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH or longer as dictated by IRB or state laws/regulations. In addition, a de-identified public use dataset will be created and stored on the National Dental PBRN public website maintained by the University of Alabama (UAB).

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way no sooner than three years from the date that the grant federal financial report (FFR) is submitted to the NIH and with the PI permission. The file connecting subjects' names with their unique identification number will be kept in a dataset stored at the NCC behind a secure firewall, in accordance with IRB regulations, before being securely erased on agreement by ARC Director, NCC director and the PI.

15.5 Protocol Deviations

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

Protocol deviations will be assessed for their impact on safety, study operations, and data integrity. Appropriate corrective and preventive actions will be implemented if warranted.

16 PUBLICATION/DATA SHARING POLICY

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

NIH Public Access Policy

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

As a National Dental PBRN activity, this study will abide by the network's publications policy, which is publicly available at <https://www.nationaldentalpbrn.org/publications/> .

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