Anterior Openbite Malocclusions in Adults: Recommendations, Treatment, and Stability

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STATEMENT OF COMPLIANCE

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

SIGNATURE PAGE

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

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

The signature below constitutes:

1) acknowledgement of having read this protocol version (as indicated in the upper right corner of this page) and the attachments, and agreement to follow this protocol version and all subsequent versions,

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, Practice Training Manual, and other applicable plans developed in the future).

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AAO	American Association of Orthodontists
AE	Adverse Event/Adverse Experience
AOB	Anterior Openbite
CC	Coordinating Center
CFR	Code of Federal Regulations
CRF	Case Report Form
DHHS	Department of Health and Human Services
FFR	Federal Financial Report
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
GPI	Grant Principal Investigator
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
National Dental PBRN	National Dental Practice-Based Research Network
NHANES	National Health and Nutrition Examination Survey
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
QA	Quality Assurance
QC	Quality Control
RAS	Regional Administrative Sites
RC	Regional Coordinator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SPI	Study Principal Investigator
TAD	Temporary Anchorage Device
US	United States

PROTOCOL SUMMARY

Title: Anterior Openbite (AOB) Malocclusions in Adults: Recommendations, Treatment, and Stability.

Précis: Almost all research on AOB treatment and stability is from retrospective case series. Therefore, this study has tremendous potential to provide practitioners with stronger evidence about AOB treatment outcomes and stability for adults. It will also provide information about retention outcomes. Additionally, the gathering of patient-reported data about the decision to pursue a specific treatment option and patient satisfaction after treatment may be extremely valuable.

This is a prospective, observational 3.5 year cohort study of approximately 840 adult patients in active orthodontic treatment for AOB who **expect** to have treatment completed within 24 months of enrollment into the study from approximately 210 National Dental Practice-Based Research Network (National Dental PBRN) orthodontists or dentists who routinely perform orthodontic treatment.

Objectives: ***Primary:*** The primary objective is to estimate the proportion of patients 1) treated successfully (determined at end of active treatment), and 2) whose treatment is stable (determined at one year post active treatment).

The primary outcome measure to determine success of treatment will be overbite at the end of treatment, and the primary measure to determine stability of treatment ascertained one year after removal of orthodontic appliances is the overbite measurement.

Secondary: The secondary objectives are to:

1. Identify how dentofacial characteristics, as well as patient and practitioner characteristics, influence:
    a. Treatment recommendations, and
    b. Acceptance of treatment recommendations.
2. Identify how treatment modalities, as well as dentofacial, patient, and practitioner characteristics, are associated with the following, both determined at the time orthodontic appliances are removed (end of active treatment):
    a. Treatment success, and
    b. Patient satisfaction.

3. Identify how retainer regimens, as well as treatment modalities, dentofacial, patient and practitioner characteristics are associated with the following, both determined one year after end of active treatment:
   a. Treatment stability, and
   b. Patient satisfaction.

Population:	The study will include approximately 840 adult National Dental PBRN practice AOB patients age 18 or older that are currently in active treatment, and **expect** to have treatment completed within 24 months of enrollment into the study.
Number of Sites:	Approximately 210 National Dental PBRN practitioners.
Study Duration:	Approximately 3.5 years
Subject Participation Duration:	Approximately 3 years
Estimated Time to Complete Enrollment:	Approximately 11 months

Schematic of Study Design:

Practitioner Screening/Enrollment

- Recruit, enroll, and train practitioners. Practitioner completes Practitioner Characteristics Form.

Patient Enrollment/Baseline, Active Treatment Stage (Stage 1 [S1])

At a routine orthodontic visit:

- Verify eligibility.
- Obtain informed consent and assign subject ID.
- Patient and Practitioner complete Enrollment Visit data collection forms.
- Submit initial cephalometric x-ray and intra-oral frontal photograph.

Appliance Removal, End of Active AOB Treatment (Stage 2 [S2], Visit 1 [V1]; complete within ~24 months after S1)

At the time of appliance removal:

- Measure the height of the right maxillary central incisor.
- Patient and Practitioner complete End of Active Treatment data collection forms.
- Obtain intra-oral frontal photographs, one taken in maximum intercuspation, and another one with the incisors slightly apart.
- Submit end of active treatment cephalometric x-ray and intra-oral frontal photographs.

Retainer Check Visits (Stage 2, Visits 2-x; varies based upon retention visit intervals)

At the time of **each** routinely scheduled retainer check appointment:

- Patient and Practitioner complete Retainer Use data collection forms.

Final Study Visit (Stage 3 [S3]) (S2, V1 + 10 to 24 months)

Approximately 1-year Post Appliance Removal:

- Measure the height of the right maxillary central incisor.
- Patient and Practitioner complete Final Study Visit data collection forms.
- Obtain intra-oral frontal photographs, one taken in maximum intercuspation, and another one with the incisors slightly apart.
- Submit intra-oral frontal photographs.

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Anterior openbite (AOB) may be defined as a condition in which the maxillary and mandibular incisors do not touch when patients bite (in their normal position) on their back teeth. Typically, when individuals bite on their back teeth, their incisors will touch lightly, and thus AOB is considered to be an abnormal bite relationship, or malocclusion. Severe AOB may also affect speech and function (Appendix B, Figure 1). Sometimes, patients may also be concerned about the appearance of their incisors.

Data from National Health and Nutrition Examination Survey (NHANES) III indicate that the prevalence of AOB in the US population is about 3.5% across all age ranges[1]. AOB is classified into two types: dental in origin, and skeletal in origin[2]. Dental AOBs are characterized by relatively normal vertical facial proportions, and the etiology of the AOB is primarily due to the intruded position of the incisors (Appendix B, Figure 2). This intrusion often may be caused by habits, such as sucking a thumb or finger. In children, dental AOBs may spontaneously resolve if the habit is discontinued in early mixed dentition. Skeletal AOBs are characterized by steep mandibular plane angles, as well as decreased posterior facial height and increased anterior facial height (Appendix B, Figure 3). The geometry of the mandible and maxilla in these patients can require significant extrusion of the incisors (as well as the canines and premolars) to achieve positive overlap of the teeth. Orthodontists generally agree that skeletal AOBs are more challenging to treat and retain, as the etiology is often due to inherent growth patterns, which are difficult to control. Also, as mentioned earlier, a large degree of extrusion may be necessary to compensate for the increased anterior facial vertical dimension, unless orthognathic surgery is considered.

The current evidence on AOB treatment and stability is based largely on retrospective case series. There are reports that surgery may be more stable than orthodontic therapy[3, 5], and that extraction therapy may be more stable than non-extraction therapy[7] (Appendix B, Figures 4 and 5). It is difficult to directly compare conventional to surgical treatment because studies measuring conventional orthodontic treatment typically report on adolescent patients, while the surgical literature reports primarily on adults. The success and stability for more recent techniques like temporary anchorage devices (TADs) and clear aligners have not been well investigated, with most of the literature consisting of case reports or case series[8-15].

Based on case reports[12-15], some orthodontists are using the clear aligner technique to treat AOBs. Many patients also favor aligners over conventional braces for esthetics and comfort. These are considerable advantages, and the case reports demonstrate that clear aligners can assist with bite closure. However, this technique does have limitations, including incomplete correction of tooth positions and difficulties in detailing the occlusion. Additionally, there are no published data about post-treatment stability

after treatment with clear aligners. Several case reports demonstrate that skeletal AOBs can be closed, but little information exists on the stability of the correction[8-11].

Conventional orthodontics is commonly recommended for AOB patients. It relies almost exclusively on dentoalveolar effects, mainly incisor extrusion, which may have a high potential for relapse. Because of this, additional strategies, such as Temporary Anchorage Devices (TADs) or surgery may be recommended. TADs are normally used in patients with skeletal AOB who might also be candidates for orthognathic surgery. TADs are used to assist with intrusion of molars, thereby allowing a closing rotation of the mandible, resulting in a deepening of the bite. TADs are invasive, but much less invasive than orthognathic surgery. They are also considerably less costly. Some researchers have reported that after treatment, molars may re-erupt, resulting in relapse of the AOB. If the treatment results and stability achieved with TADs are similar to that achieved with orthognathic surgery, then TADs would be preferable, due to their lower morbidity and cost. However, based upon the current literature, it is not known which treatment is better or more stable.

Of course, the most important outcome for AOB patients may be long-term stability, as closure of AOBs is often challenging to maintain (Appendix B, Figures 8-10)[3,5]. The literature does point to some factors that may play a role in stability. For example, some clinicians feel that extraction therapy is helpful, as the incisors are tipped backward during space closure, and as they tip back, they also tip downward[7]. This can lead to better stability compared to a situation in which a crowded arch is expanded, tending to cause forward tipping and a more shallow overbite relationship. Other studies suggest that the cessation or altering of oral habits could improve stability, as these could be etiologic factors. For example, there are some reports that crib therapy to stop digit or tongue habits can be relatively stable[16]. As mentioned earlier, there are several systematic reviews addressing stability of conventional orthodontics and orthognathic surgery, but they are based on low quality studies[3-6]. Currently, there are few studies reporting long-term stability of TAD or clear aligner treatment[9-11]. Additionally, only a few case reports describe the effectiveness of different types of retainers after treatment for AOB stability[17-19].

Anterior openbite can be both a functional and cosmetic issue, and correcting it reliably, as well as retaining the correction, has proven to be challenging. Thus, conducting a well-designed study that addresses both treatment and stability may have high impact on the oral health of the public. This study may have significant benefits to future adult AOB patients. It may provide insight into the most effective and stable methods to treat and retain AOBs.

2.2 Rationale

The proposed study, which will take place in orthodontic and dental offices across the country that are part of the National Dental PBRN, is well-suited for a network study, as it will enable the assessment of practice trends for AOB from the entire country. At present, there are many strategies that are used to address AOBs. The

recommendations for treating a particular patient may depend on factors like the patient's age, the severity and nature of the AOB (dental vs skeletal), presence of habits, associated crowding, and each patient's goals and expectations. The treatment that a patient accepts can be influenced by all the factors above, as well as cost of the proposed treatments and a patient's willingness to consider surgical options like TADs or orthognathic surgery.

Further, since AOB occurs in less than 4% of the population, this National Network study will facilitate the collection of prospective data from a larger cohort of patients than could be obtained independently.

Almost all research on AOB treatment and stability is from retrospective case series. Therefore, this study has tremendous potential to provide practitioners with stronger evidence about AOB treatment outcomes and stability for adults. It will also provide information about retention outcomes. Additionally, the gathering of patient-reported data about the decision to pursue a specific treatment option and patient satisfaction after treatment may be extremely valuable.

2.3 Potential Risks and Benefits

There are no anticipated human subject safety risks to participating in this study. Research participants will not receive dental care as a study procedure, but will continue to receive normal clinical care as patients of the participating dentists and orthodontists. Risks of dental procedures provided as part of normal clinical care are not considered to be study-associated.

2.3.1 Potential Risks

Risks associated with routine orthodontic treatment, such as the risk of white spot lesions or root resorption, are not considered to be study-associated. 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 (CC), 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

Participation in the study will provide no direct benefit to participants. This study may have significant benefits to future adult AOB patients, as it may provide insight into AOB treatment, stability and retention outcomes.

3 OBJECTIVES

3.1 Study Objectives

Primary: The primary objective is to estimate the proportion of patients 1) treated successfully (determined at end of active treatment), and 2) whose treatment is stable (determined at one year post active treatment).

Secondary: The secondary objectives are to:

1. Identify how dentofacial characteristics, as well as patient and practitioner characteristics, influence:
    a. Treatment recommendations, and
    b. Acceptance of treatment recommendations by the patient.
2. Identify how treatment modalities, as well as dentofacial, patient, and practitioner characteristics, are associated with the following, both determined at the time orthodontic appliances are removed (end of active treatment):
    a. Treatment success, and
    b. Patient satisfaction.
3. Identify how retainer regimens, as well as treatment modalities, dentofacial, patient and practitioner characteristics are associated with the following, both determined one year after end of active treatment:
    a. Treatment stability, and
    b. Patient satisfaction.

3.2 Study Outcome Measures

The primary outcome measure to determine success of treatment will be overbite at the end of treatment. Overbite will be measured in two ways. The first method is to record whether the incisors have positive overlap at the end of treatment, which indicates success. This will be judged from the frontal photographs at all three time points (baseline/enrollment, end of active treatment, and one year after end of active treatment). Second, using lateral cephalograms, the overbite will be measured relative to a standardized reference line (for example, occlusal plane), at two time points. At the first time point, we will see that relative to occlusal plane, the initial overbite is negative (no incisal overlap), and the distance between the maxillary and mandibular incisor tips can be measured in millimeters perpendicular to the occlusal plane. At the second time point, the final overbite should be positive (incisal overlap), and this overlap can be measured in millimeters perpendicular to the occlusal plane. Based on the measurements from the initial and final cephalograms, we will assess whether the overbite has been treated successfully (positive incisal overlap), as well as how much the overbite has improved (in millimeters).

The primary measure to determine stability of treatment ascertained one year after removal of orthodontic appliances is the overbite measurement. Since a cephalogram will not be taken one year after the end of treatment, this measurement will need to be assessed from the photographs. Overbite will be measured in two ways. The first is the dichotomous assessment of incisal overlap at the follow-up time; this will be performed in the same manner as stated in the preceding paragraph. A positive incisal overlap will be considered stable. The second method will be performed by utilizing the proportions of teeth in order to determine how much overbite change has occurred (see Appendix C). The orthodontist will be asked to measure the height of the right maxillary central incisor at the time of deband and at the final visit. Using this measurement, along with the end-of-treatment and follow-up photos, the overbite can be calculated at each time point, as well as the amount of overbite change.

Secondary outcome measures to examine how dentofacial, patient and practitioner characteristics influence a) treatment recommendations suggested by the orthodontists and b) acceptance of treatment recommendations by the patient include the following:

- Practitioner treatment recommendations include the practitioner's general strategies for openbite treatment (from practitioner characteristics form, e.g., whether and how often surgery is recommended), treatment recommendations (e.g. surgical option) presented to the patient, and patient's treatment goals (practitioner perspective);
- Patient acceptance of treatment recommendations includes the patient's self-report of the primary (ideal) treatment plan, whether or not the plan was accepted and why, and the patient's treatment goals;
- Dentofacial characteristics will be ascertained through examination and include: dental or skeletal nature of the openbite, millimetric measure of AOB, and amount of crowding;
- Patient characteristics include age, race, sex, insurance, and education; and
- Practitioner characteristics include the following: age, race, sex, years since received orthodontic training and orthodontic program.

Secondary outcome measures to examine how treatment modalities are associated with treatment success and patient satisfaction at the end of active treatment include the following:

- Treatment success is described above for the primary objective.
- Treatment modalities: Which teeth were extracted, if any; which if any of four treatment modalities were used (surgical component, fixed appliances, removable aligners, and/or TADs (mini-screws, mini-plates)).
- Patient satisfaction: The primary satisfaction measure will be overall satisfaction with treatment, (and secondarily, satisfaction with esthetics and function separately), ascertained by patient report at the end of active treatment.
- Other factors of interest for each include dentofacial characteristics (molar class, crowding, facial pattern, magnitude (millimeters) of overbite), practitioner characteristics (age, race, sex, years since received orthodontic training) and patient characteristics (age, race, sex, insurance, education, treatment

preference (whether patient agreed with primary recommendation), and patient treatment goal).

Secondary outcome measures to examine how retainer regimens, as well as treatment modalities, dentofacial, patient and practitioner characteristics are associated with treatment stability and patient satisfaction one year after the end of active treatment include the following:

- Treatment stability is described above for the primary objective.
- Retainer regimens include: Type (Hawley, Essix, bonded), whether full-time or part-time (nights only) and compliance with these recommended regimens (ascertained through practitioner and, separately, patient self-report).
- Patient satisfaction: Overall satisfaction with retainers (and secondarily, satisfaction with esthetics and function separately), all of which will be ascertained by patient report at one year after end of active treatment.
- Other factors of interest for each include success of treatment at end of active treatment, and as described above, dentofacial characteristics (molar class, crowding, facial pattern, magnitude (millimeters) of overbite), treatment modalities (extraction, then surgical component, fixed appliances, removable aligners, TADs), practitioner characteristics (age, race, sex, years since received orthodontic training) and patient characteristics (age, race, sex, insurance, education, treatment preference (whether agreed with primary recommendation), and treatment goal).

4 STUDY DESIGN

- This will be a prospective, observational 3.5-year cohort study of patients who are undergoing different types of orthodontic AOB treatment followed by retainers.
- The study population will consist of adult patients who are in active treatment for AOB, and expect to have treatment completed within 24 months of enrollment into the study. Approximately 210 orthodontists or dentists who routinely perform orthodontic treatment (approximately 35 in each of the six National Dental PBRN regions) will participate. Actual enrollment will be based on interest and enrollment into the Network, and likely will vary per region. Each practitioner will be requested to enroll approximately 3 - 8 adult patients in active AOB treatment over an approximate 11 -months enrollment period, with an enrollment goal of approximately 840 adult patients across the National Network. No practitioner will contribute more than 15 patients.
- Retrospective data will be collected to explore patient, practitioner, and dentofacial characteristics that influence the treatment recommendations and the accepted treatment plans for patients with AOB.
- The prospective cohort design will allow the investigation of how patient, practitioner, and dentofacial characteristics affect the success of treatment. The treatment provided to the patients will not be influenced at all by participation in the study.
- In addition, this study will allow the assessment of how treatment modalities, retainer regimens, and patient characteristics are associated with treatment stability and patient satisfaction one year after treatment.
- At each routinely scheduled retainer check visit, the patient will be asked to report on their retainer usage, and the practitioner will also be asked to judge retainer use.
- Patients will be asked again about satisfaction with their retainer regimen, as well as esthetics and function, at one year after treatment.
- Patients will participate in the study for approximately 3 years, on average, the duration of the treatment and follow-up phases. Practitioners' participation in the study will be approximately 3.5 years.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Practitioner:

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

- Is enrolled in the National Dental PBRN as a practitioner who is licensed in the United States (US), and does treat patients in the US on a recurring basis.
- Is a "full" participation level member, or willing to change from "information only" or "limited" to "full".
- Is trained and certified in Human Subjects Protection Training.
- Is willing to complete study-specific training.
- Has attended or viewed a National Dental PBRN orientation session or has attended at least one annual regional meeting of practitioners.
- Is an orthodontist or a dentist that routinely performs orthodontic treatment.
- Has a sufficiently large patient population such that the practitioner estimates he/she can recruit approximately 3 - 8 adult patients in active treatment for AOB, and expect to have treatment completed within 24 months of enrollment into the study.
- Routinely takes cephalometric x-rays before and after treatment.
- Has the ability to upload (via internet) de-identified cephalometric x-ray and digital intra-oral frontal photographs to a central repository.
- Affirms that the practice can devote sufficient time in patient scheduling to allow focused recording of all data required for the study.
- Does not anticipate retiring, selling the practice, or moving during the study.

Patient:

The patient population will come from the National Dental PBRN practices participating in this study.

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

- Must be at least 18 years of age.
- Must have AOB that is defined as one or more incisors that do not have vertical overlap with teeth in the opposing arch. The remaining incisors may have minimal incisor overlap, but none of them can contact teeth in the opposing arch.
  This will be determined by examining the patient's initial cephalometric x-ray, intra-oral photographs, and/or initial plaster or digital casts.
- Must be in active treatment for AOB, and expect to have treatment completed within 24 months of enrollment into the study.

- Must have an initial cephalometric x-ray (taken prior to the beginning of treatment). A cephalometric x-ray created from a cone-beam CT scan is acceptable.
- Willing to comply with all study procedures and be available for the approximate 3-year duration of the study.
- Allow the use of his/her x-rays and photographs that are obtained as part of normal treatment (i.e. before treatment began and at the time of appliance removal) for this research.
- Agrees to receive text messages, emails, and/or phone calls related to the study visits from the practice per the practice's routine contact method.
- Willing to be contacted as needed by each of these entities: the practice, Regional Coordinator (RC), and the Westat CC (the patient's preferred method of contact will be ascertained).
- Willing to provide contact information for at least one other person who will know the patient's whereabouts in the event the patient cannot be reached.

5.2 Exclusion Criteria

Practitioner: No adult AOB patients in active treatment.

Patient: An individual who meets any of the following criteria will be excluded from participation in this study:

- Adults with clefts, craniofacial conditions or syndromes.
- Patients who have significant physical, mental, or medical conditions that would affect their treatment compliance, cooperation, or outcome.
- Patients expecting to move before the completion of the study.
- Patients with initial treatment plans estimated at more than 36 months.

5.3 Strategies for Recruitment and Retention

5.3.1 Practitioner Recruitment and Retention

All National Dental PBRN orthodontists/dentist practitioners at full participation level, or willing to change to full participation level, will be approached for participation in the study. The study team will rely on the RC from the six Regional Administrative Sites (RAS) to help recruit current practitioner participants into the study. Additionally, practitioners will be recruited into the National Dental PBRN with the assistance from the American Association of Orthodontists (AAO). E-mails will be sent to AAO members to inform them of the study and to invite them to enroll in the National Network. Also, the AAO will make efforts to recruit orthodontists at their national and regional meetings.

Practitioners or their institution will be compensated for the time required to do the research, receiving $100 for each patient he/she enrolls and completes the data collection process for each of the three visits ($100 for Baseline/Enrollment, $100 for

End of Active Treatment, and $100 for Final Study Visit). The RAS will maintain a list of patients for each practitioner, along with key data regarding expected date of appliance removal and subsequent follow-up visit and can assist the offices in tracking the patients throughout the course of the study. Participating practitioners will also receive reminders regarding the expected completion dates for their patients, as well as their dates of recall.

Several other strategies will be employed to reduce practitioner burden. Special attention will be paid to making study procedures as simple and efficient as possible. Study procedures will be performed at enrollment, end of treatment, and at the one year post appliance removal. Additionally, several very short questionnaires will be completed during the retention phase. Many parts of the study forms can be completed outside of patient time, using notes from patient charts or records.

5.3.2 Patient Recruitment

To meet the patient recruitment goals of the study, the National Dental PBRN practitioner will create a list of all their adult AOB patients who are currently in active treatment, and expect to have treatment completed within 24 months of enrollment into the study. Once the list has been created, the practitioner or his/her staff will invite all patients to participate at their routine orthodontic visits. Offices may also elect to invite patients via phone calls. If a practitioner has more than 15 patients on this list, he/she should sequentially select the patients based upon their treatment start dates, beginning with the patient who started treatment the earliest. If some patients decline or withdraw, practitioners can move sequentially down the list to enroll up to 15 patients.

5.3.3 Patient Retention

Patient retention is vital to this study, and Appendix D provides a Patient Retention Plan for maximizing patient participation throughout the duration of the study.

Patients will receive a total $100.00 in patient incentives for participating in the study. He/she will receive $25 for the enrollment visit, $25 for the study visit when his/her braces are removed, and $50 for the study visit approximately one year after his/her braces are removed.

5.4 Patient 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:

- 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.
- The patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 Handling of Withdrawals

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 or other safety concerns. In these circumstances, only data related to the completion of reporting requirements for the unanticipated problem will be recorded. For patients withdrawn from the study for any other reason, the date and reason for withdrawal will be recorded, and no additional study data will be collected. Patients withdrawn from the study may continue to receive usual dental care as patients of the participating practitioner; however, additional study data will not be collected (except as noted above).

Replacement of patients who withdraw or discontinue early will be allowed, but only during the initial 11 months patient enrollment period. The practitioner may attempt to enroll one replacement patient for each patient enrolled who withdraws or discontinues during the practitioner-specific enrollment period. No practitioner will contribute more than 15 active patients in total to the analyses.

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 study principal investigator (SPI) will promptly inform the IRB and will provide the reason(s) for suspension or termination.

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

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

6 STUDY SCHEDULE

National Dental PBRN orthodontists/dentist practitioners who opt to participate will be provided information and instructions pertaining to the study. These instructions will provide information for the practitioner(s) and staff who will help to execute the study. A detailed Practice Training Manual will be provided to each practice in hard-copy form prior to initiation of the study in the practice. The Practice Training Manual will carefully describe the patient selection procedures, methods for approaching patients and obtaining Informed Consent (according to regional approvals), methods for data collection, and other study procedures. In addition, RCs will conduct in-person or remote protocol training with office staff prior to initiating the study to make sure that they and their office staff understand the study procedures and have received instruction in completing CRFs.

The study will proceed in stages:

1) Each region will enroll approximately 35 practitioners who have completed IRB-mandated training into the study. Actual enrollment will be based on interest and enrollment into the Network, and likely will vary per region;
2) Practice personnel will receive necessary IRB training, and practitioners will undergo informed consent procedures as required by each region's IRB. Individual Investigator Agreements, the University of Alabama at Birmingham (UAB) Master Service Agreement and similar documents will also be obtained prior to the start of the study as required;
3) RCs will ensure practices are trained in the appropriate study procedures (see below sub-sections);
4) Practitioners will complete the Practitioner Characteristics Form;

   The CC, along with the RAS and RCs, will coordinate the launch of the study. Once the RC has trained an office in the practice procedures, that practice should begin recruiting patients into the study immediately, or as soon as possible.
5) Practitioners and/or his/her designee who has completed human subject training will screen, consent and enroll eligible patients into the study.

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

6.1 Practitioner Screening/Enrollment

- Verify practitioner inclusion/exclusion criteria;
- Obtain and document consent from practitioner participant according to regional IRB requirements;
- Practitioner and applicable staff participate in training with RC;
- Practices will systematically search their current active patient lists to identify patients age 18 or older who are in active treatment for AOB who expect to have treatment completed within 24 months of enrollment into the study and meet study inclusion criteria;
- The maximum number (N) of patients from a single practitioner will be 15. If a practitioner has more than 15 potential patients, he/she should sequentially select the patients based upon their treatment start dates, beginning with the patient who started treatment the earliest. If some patients decline or withdraw, practitioners can move sequentially down the list to enroll up to 15 patients; and
- Practitioner completes Practitioner Characteristics data collection form.

6.2 Patient Enrollment/Baseline, Active Treatment Stage (Stage 1 [S1])

A potential patient may be recruited over the phone or at any visit when it is determined that a patient may be eligible for study participation. The designated office personnel will introduce the study to the patient and will ascertain that inclusion criteria are met. For patients who express interest in participating in the study, enrollment/baseline study procedures will occur during an in-office visit. Informed consent procedures and enrollment may occur during the same visit at which eligibility was confirmed.

- Verify eligibility and inclusion/exclusion criteria.
- Obtain and document consent from patient as required by IRBs.
- Obtain patient contact information and preferred method of contact (e.g., postal mail, email, telephone, text, other contacts).
- Patient and Practitioner complete Enrollment Visit data collection forms.
- Practitioner will obtain and upload initial cephalometric x-ray and intra-oral frontal photograph.

6.3 Retention Stage (Stage 2 [S2])

6.3.1 Appliance Removal, End of Active AOB Treatment: S2, Visit 1 (Complete within approximately 24 months after S1)

- Practitioner will obtain measurement of the height of right maxillary central incisor perpendicular to the incisal edges of the incisors.
- Practitioner will obtain intra-oral frontal photographs, one taken in maximum intercuspation, and another one taken with the incisors slightly apart.
- Practitioner will upload end of active treatment cephalometric x-ray and intra-oral frontal photographs.
- Patient and Practitioner will complete End of Active Treatment data collection forms.
- Verification of patient contact information and preferred method of contact.

6.3.2 Retainer Check Visits: S2, Visits 2-x (Varies; based upon retention visit intervals)

Information from routinely scheduled retainer check visits will be gathered during the first year after active treatment has terminated.

- Patient and Practitioner will complete Retainer Use data collection forms.
- Verification of patient contact information and preferred method of contact.

6.4 Final Study Visit (Stage 3 [S3]): Approximately 1-Year Post Appliance Removal (S2, V1 + 10 to 24 months)

- It will be acceptable to allow the Final Study Visit to occur as early as 10 months after appliance removal. The maximum limit for the timing of the final study visit will be 24 months post appliance removal or until end date of the study, whichever occurs first.
- Practitioner will obtain measurement of the height of right maxillary central incisor perpendicular to the incisal edges of the incisors.
- Practitioner will obtain and upload final intra-oral frontal photographs, one taken in maximum intercuspation, and another one taken with the incisors slightly apart.
- Patient and Practitioner will complete Final Study Visit data collection forms.
- Practitioner will provide final instructions to participant, if applicable.

6.5 Withdrawal Visit

- Record date and reason for withdrawal.
- If withdrawal occurs during an in-office visit, and if the consent was not withdrawn, obtain the applicable study data using the visit specific data collection forms/steps listed in the sections above.

7 STUDY PROCEDURES/EVALUATIONS

7.1 Study Procedures/Evaluations

Practitioner:

Prior to enrolling patients, the practitioner will complete a Practitioner Characteristics Form which will ascertain types and frequency of typical treatments and retention techniques used to treat adult patients presenting with an AOB.

Patient:

Enrollment. For each patient enrolled, the practitioner will complete an Enrollment Visit Form based upon clinical examination and review of records recording: 1) patients' reasons for seeking treatment; 2) pre-treatment diagnoses (dentofacial characteristics); 3) goals of treatment (practitioner perspective); and 4) treatment plan options, including adjunctive treatment, and treatment plan chosen.

De-identified initial cephalometric x-ray and intra-oral frontal photographs taken prior to treatment initiation will be uploaded for measures of dentofacial characteristics, such as overbite, mandibular plane angle, and incisor angulation (as described above in outcome measures).

At enrollment, after consent, the patient will complete a Patient Enrollment Visit form, which elicits 1) age (from year of birth and date), race/ethnicity, sex, insurance, education; 2) reasons for seeking treatment; 3) treatment recommended as ideal (patient perspective); 4) whether or not accepted ideal recommendation, and if not, why not; and 5) previous orthodontic treatment, if any.

End of active treatment. The practitioner will complete an End of Active Treatment Form based upon clinical examination and review of treatment records recording: 1) any changes in originally accepted treatment plan; 2) treatment result and expected stability outcome; 3) any residual oral habits; 4) patient compliance and adjunctive treatments; 5) current molar relationship; and 6) retention techniques recommended.

De-identified end of active treatment cephalometric x-ray and intra-oral frontal photograph taken in maximum intercuspation will be uploaded for measures of overbite. Practitioner will also obtain an additional intra-oral frontal photograph taken with the incisors slightly apart and upload the de-identified photo for measures of overbite. The practitioner will also measure the height of the right maxillary central incisor using the provided metal ruler.

Patients will complete an End of Active Treatment Form eliciting whether or not AOB was closed, if they were satisfied overall, satisfied with esthetics, satisfied with function, and if they would recommend the treatment they received to a friend if they had similar problem.

Routine visits within the year following end of active treatment. Practitioner will complete a Retainer Use Form based upon clinical history and examination, recording: 1) AOB status and any changes in alignment of upper or lower incisors; 3) assessment of patient's compliance; 4) any retainers and/or regimen changes; and 5) whether any additional adjunctive treatments have been completed since retention began.

Patients will complete a brief Retainer Use Form eliciting whether or not AOB is closed, how much they are wearing upper/lower retainers, and whether or not they are wearing retainers as requested.

Final visit, one year after end of active treatment. Practitioner will complete a Final Visit Form based upon clinical history and examination, recording the same information as on retainer use form and the current molar relationships.

Final intra-oral frontal photographs, one taken in maximum intercuspation, and another one taken with the incisors slightly apart, will be de-identified and uploaded for measurement of overbite. The practitioner will also measure the height of the right maxillary central incisor using the provided metal ruler.

Patients will complete a brief Final Visit Form eliciting whether or not AOB is (still) closed, current usage, if satisfied with retainer experience, satisfied with esthetics, satisfied with function, if they would recommend the treatment received to a friend if they had similar problem, and if satisfied with type of retainers received after treatment.

7.2 Questionnaire Administration

Patient satisfaction will be assessed using a five-point Likert-like scale (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, very dissatisfied), followed by open-ended responses for somewhat/very dissatisfied responses. Whether or not treatment would be recommended to a friend will also be assessed using a five-point Likert-like scale. Patient's compliance with retainer regimens will be ascertained from the perspectives of the practitioner as well as the patient.

For all patient data collection forms completed in the practitioner's office after the enrollment visit, the dentist's staff will be responsible for mailing the study data collection forms to the RAS.

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.

8.1.1 Unanticipated Problems

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

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

8.1.2 Serious Adverse Events

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

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

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:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the AE, incident, experience, or outcome;
- An explanation of the basis for determining that the AE, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

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

- Unanticipated problems that are SAEs will be reported to the IRB and to NIDCR within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 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:

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

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

- US: 1-888-746-7231
- International: 919-595-6486

9 STUDY OVERSIGHT

The GPI and SPI will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. In addition to the SPI's responsibility for oversight, study oversight will be under the direction of the NIDCR Medical Monitor. The SPI will submit reports to NIDCR Medical Monitor for review at six months after study initiation until enrollment targets have been met, and then annually thereafter. Medical Monitor reports will include data regarding enrollment and retention, unanticipated problems and protocol deviations, primary outcome measures, quality management findings and other relevant parameters. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

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 will perform quality management and clinical site monitoring activities, to evaluate study processes and documentation based on NIDCR standards and principles of good clinical practice (GCP).

Quality management procedures are detailed in the protocol, Section 13, as well as the study-specific Manual of Procedures (MOP). This study will follow the general guidelines for conducting monitoring for the network's observational clinical studies documented in Chapter 6 of the National Dental PBRN Manual of General Operations. Documentation of monitoring activities and findings will be provided to the practitioner, GPI, SPI, NIDCR Office of Clinical Trials Operations and Management, and the NIDCR Program Official. The NIDCR reserves the right to conduct independent audits as necessary.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

The primary objective is to estimate the proportion of patients 1) treated successfully (determined at end of active treatment), and 2) whose treatment is stable (determined at one year post active treatment).

11.2 Sample Size Considerations

Previous studies have reported success rates around 80% for treatment of AOB, and among those successfully treated, from 65% to 100% have been reported to be stable. These success and stability rates are likely overestimated due to reporting bias. We want to estimate both success and stabilization rates with 10% precision. Power is weakest when success and stabilization rates are lower (need larger sample size [patients], see table below).

Total number of patients needed to estimate proportions with 10% precision	
%succeed/stabilize	3/dentist
50%	422
60%	406
70%	355
80%	271
90%	153
Assumes interclass correlation coefficient (ICC) of 5%	

Assuming a 70% success rate, a 50% stabilization rate, an average of 3 patients per practitioners and an ICC of 5%, 600 patients are needed. To allow for a 10% attrition for success (end of treatment) and 20% attrition for stabilization (one year post treatment), this study would need to enroll 840 patients. This means we need to recruit about 210 orthodontists, who each need to recruit about 4 patients each.

11.3 Final Analysis Plan

Analysis plan for Primary Objectives:

Primary objective #1 is to estimate the proportion of patients who are successfully treated. As described in section 3.2 (outcome measures), successful treatment is defined as occurring when patients have positive overlap at the end of treatment; this will be calculated with a 95% confidence interval.

Though not an explicit hypothesis, we expect those that are "successfully" closed will have had a smaller distance between the maxillary and mandibular incisor tips prior to treatment, i.e., at enrollment, than those not successfully closed. We will calculate the mean distance improved separately for those successfully treated and those not. It may be that those not successfully treated had more improvement than those who were successfully treated (if the former had a greater distance that needed to be corrected) and we want to capture this. Thus, as an additional but secondary measure of improvement, we will also calculate mean and median distance improved as descriptive measures.

Primary objective #2 is to estimate, among patients who are successfully treated, the proportion of patients whose treatment is stable. As described in section 3.2 (outcome measures), stability will be assessed one year after end of active treatment. The primary measure (strictest, most conservative classification) will be among patients who are determined to have been successfully treated at end of active treatment (having closed their AOB), what proportion of these have positive overlap at the one-year follow up time. This proportion will be estimated with a 95% confidence interval. Additional assessments of stability will include the proportion of all who had improvement in overbite (positive increases) during retention, no change in overbite during retention, and worsening of overbite (negative increases) during retention. We will calculate these mean and median changes as descriptive measures.

11.4 Secondary Analyses

11.4.1 Sample Size Considerations

For secondary objectives, we wish to detect differences of 20% in success and stabilization rates between subgroups, e.g., differences between patients for whom extraction was recommended and those for whom it was not. In general, we will need 110 patients for each group that is being compared (assuming 80% power, 5% significance level, and an ICC of 5%). For example, for the assessment of success between extraction and non-extraction cases, we need 110 patients treated with each technique. For the comparison of the four treatment modalities, we need 110 patients treated with each of the 4 techniques, or 440 patients total. If we recruit 840 patients at baseline, we should have adequate power for most secondary objectives, even allowing for attrition.

11.4.2 Proposed Secondary Analyses

Analysis plan for Secondary Objectives:

Secondary objective #1a will examine how dentofacial, as well as patient and practitioner characteristics influence treatment recommendations suggested by the orthodontists. The association of each of the dentofacial, patient and practitioner characteristics specified below with different treatment recommendations will be ascertained using a chi-square test for categorical variables and either t-test or Wilcoxon rank-sum test (nonparametric equivalent). Dentofacial characteristics: profile, molar classification, maxillary crowding, mandibular crowding, posterior cross-bite, facial pattern. Patient characteristics: age, sex, race/ethnicity, insurance, education, treatment goals. Practitioner characteristics: age, sex, race/ethnicity, year received orthodontic training. For each domain of the three domains, namely, dentofacial, patient and practitioner characteristics, characteristics with $p<0.2$ will be entered in the model, retained if $p<0.1$. Final Generalized Estimating Equations (GEE) regression model (adjust for clustering within practice) will start with those $p<0.1$ for each domain, and retained if $p<0.05$ for final analysis ascertaining how dentofacial, as well as patient and practitioner characteristics influence treatment recommendations (extraction, then surgical component, fixed appliances, removable aligners, TADs).

Secondary objective #1b will examine how dentofacial, as well as patient, practitioner, characteristics influence whether or not treatment recommendations suggested by the orthodontists are accepted by the patients. Method described above will be repeated for acceptance of recommendations. Separate analyses, i.e., stratum specific, will be performed for recommendations involving extraction and those not. Of interest (though not a primary objective or specific hypothesis to be tested) within this secondary objective is exploring what factors influence whether or not patients accept treatment recommendations involving an extraction or surgical component.

Secondary objective #2a will identify how treatment modalities, as well as dentofacial, patient and practitioner characteristics, are associated with treatment success. Success is defined above, first as positive overbite, then as amount of millimetric improvement, even if AOB is not completely closed as described in analysis for primary objective #1 above. Separate analyses, i.e., stratum specific, will be performed for treatment involving extraction and those not. The association of treatment modalities used will be assessed with whether or not treatment was successful using chi-square. The dentofacial, patient and practitioner characteristics described above, and the process to ascertain their influence on treatment recommendations, will be used to determine their association with treatment success. The process, being domain specific, will model criteria entry if $p<0.2$; retain at $p<0.1$. Final model, all domains combined, entry if $p<0.1$; retained if $p<0.05$. For this secondary objective (2a), treatment modalities will be included, first as a domain in the same manner that dentofacial, patient, and practitioner characteristics are. Then, stratum specific analyses will be performed separately according to whether or not there was an extraction.

Secondary objective #2b will identify how treatment modalities, as well as dentofacial, patient and practitioner characteristics, are associated with patient satisfaction. The above process will be repeated except the “outcome” will be patient satisfaction instead of treatment success. Separate models will be developed for overall or general

satisfaction, and for satisfaction with esthetics and with function. For this objective, whether or not treatment was successful, will be analyzed as an independent variable. A high association is expected, namely, more patients will be satisfied when treatment is successful than when not; however, it will not be a 100% (perfect) association. Some patients who are treated successfully will not be satisfied, and in contrast, some patients who are not treated successfully will be satisfied. Quantification of these proportions is of interest, as well as identifying characteristics (treatment modalities, dentofacial, patient and practitioner) that are associated with satisfaction (or dissatisfaction).

Secondary objective #3a will examine how retainer regimens, as well as treatment modalities, dentofacial, patient and practitioner characteristics are associated with treatment stability. Stability is defined above, namely, at one year after end of active treatment there is positive overbite. First, the association of retainer regimens, namely, type of retainer (Hawley, Essix, bonded) and frequency of use prescribed (full or part-time) with treatment stability will be assessed with chi-square test. The treatment modalities (extraction, then surgery, fixed appliances, removable aligners, or TADs), dentofacial, patient and practitioner characteristics described above, will be used to ascertain their association with treatment stability. The process, being domain specific, will model criteria entry if $p<0.2$; retain at $p<0.1$. Final model, all domains combined, entry if $p<0.1$; retained if $p<0.05$. For this secondary objective (3a), retainer regimens will be included, first as a domain in the same manner that treatment modalities, dentofacial, patient, and practitioner characteristics are. Then, stratum specific analyses will be performed separately according to whether or not treatment included extraction and whether or not treatment was successful (AOB closed at end of active treatment).

Secondary objective #3b will examine how retainer regimens, as well as treatment modalities, dentofacial, patient and practitioner characteristics are associated with patient satisfaction, assessed one year after end of active treatment. The above process will be repeated except the “outcome” will be patient satisfaction at one year after end of active treatment instead of treatment stability. Separate models will be developed for overall or general satisfaction, and for satisfaction with esthetics and with function; all ascertained at one year after end of active treatment. For this objective, whether or not treatment was stable will be analyzed as an independent variable. A high association is expected, namely, more patients will be satisfied when treatment is successful than when not; however, it will not be a 100% (perfect) association. Some patients who are treated successfully will not be satisfied, and in contrast, some patients who are not treated successfully will be satisfied. Quantification of these proportions is of interest, as well as identifying characteristics (treatment modalities, dentofacial, patient and practitioner) that are associated with satisfaction (or dissatisfaction).

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate dental and research records for this study, using the principles of GCP and complying with regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

The following clinical records will be considered source documents where they are used to complete case report forms (CRFs): clinical and office charts, memoranda, recorded data from automated instruments, cephalometric x-rays, and intra-oral frontal photographs of the patient's teeth.

The following CRFs or portions of CRFs will be considered source documents: Practitioner Characteristics Form, Patient's and Practitioner's Enrollment Visit Forms, Patient's and Practitioner's End of Active Treatment Forms, Patient's and Practitioner's Retainer Use Forms, and Patient's and Practitioner's Final Visit Forms.

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 Health Insurance Portability and Accountability Act (HIPAA) regulations. These records will be subject to examination and copying as stated in this section.

13 QUALITY CONTROL AND QUALITY ASSURANCE

For the Quality Assurance (QA)/Quality Control (QC) activities associated with data collection and processing, the CC will develop a DMP in which the specific data QA/QC procedures will be provided and a Quality Management section in the MOP to further detail the QA/QC process. In the DMP, the procedures will include the development of automatic data quality checks in the database system 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 MOP will detail a QA/QC process associated with data collection on paper CRFs (pCRFs) that will include quality checks at the participating practices, followed by QA/QC review at the RAS prior to and after data entry into the web system. Data entered into the system will be compared against pCRFs. The RAS staff will ensure that 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. The Data Manager at the CC will work with the RCs to ensure that all procedures are followed and that the data are checked according to the validation requirements specified from the study protocol. At the end of the study, the RCs will ensure that all data collected by the regional offices are entered and cleaned. The Data Manager at the CC 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 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, which will be provided to the Statistician if requested. The datasets will be provided to the Statistician via secure data transfer method.

The cephalometric x-rays and intra-oral frontal photographs obtained as part of routine orthodontic care before treatment and at the time of appliance removal will be used for this research. Practitioners will obtain an additional intra-oral frontal photograph at the time of appliance removal and two other intra-oral frontal photographs at the Final Study Visit (approximately one year after appliance removal/end of active treatment). Practitioners will be asked to de-identify the x-rays and photos and upload them electronically to a central data collection site created and maintained by the CC. De-identification procedures will be detailed in the Practice Training Manual. The RCs will be asked to verify that x-rays and photographs uploaded are de-identified and of good quality. At the end of each data collection period, the SPI or designee will review the x-rays and photographs to measure overbite, mandibular plane angle, and incisor angulation. The related quality management procedures will be specified in the MOP. The measurements obtained will be used to assess the study outcome measures.

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

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

Once the local institution has decided to use the National Dental PBRN Central IRB review, the National Dental PBRN Central IRB is the IRB responsible for the review of the protocol. The National Dental PBRN Central IRB then performs all future continuing protocol and informed consent reviews and amendment (new protocol version) reviews. Additionally, when recruitment and/or educational materials are to be used by all participating local institutions, the National Dental PBRN Central IRB will review and approve the language. The Central IRB also reviews unanticipated problems distributed by the Administrative Unit to local institution PIs.

Once the National Dental PBRN Central IRB has approved a protocol, local institutions are able to perform a Local Context Review and open the protocol in a shorter time than required by the traditional local institution IRB review process. Once the decision to open the protocol has been made, local institutions have the prerogative to use the National Dental PBRN Central IRB review or conduct their own local review on a protocol-by-protocol basis. If an RAS or other local institution elects not to use the National Dental PBRN Central IRB, the protocol, consent form(s), recruitment materials and all participant materials will be submitted to the RAS or other local institution IRB for review and approval.

Approval (either centrally for those regions who agree to central approval, or regionally for those who do not) of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

The National Dental PBRN Central IRB approved sample ICF will contain locked sections that may not be revised and unlocked sections that may be revised or added to by the Local Context Reviewer. The revisions or additions should be made to comply with state and local laws; professional and community standards; institutional policies, such as applying the institution’s letterhead and adding local contact information; and the needs of differing populations. However, no content should be deleted, no additions or modifications should be made that might change the meaning of any sections, and no

"wordsmithing" may be done to the locked sections of the ICF. The local institution PI will provide a redline version of the sample ICF, incorporating local institution requirements, to the Administrative Unit for review PRIOR to submission to his/her local institution.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. If required by the responsible IRB, a consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee who has received human subjects training will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document or give verbal approval of the consent process (depending upon central or regional IRB requirements) 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. A copy of the informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

Participating practices will designate who will execute informed consent for the study. In most cases this will be the dentist practitioner(s). Any personnel who will be assigned to obtain informed consent will be defined as designee and will complete required IRB training. Informed consent will be obtained in the practice prior to enrolling a patient into the study.

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

The population is being restricted to individuals aged 18 years or older in order to eliminate a potentially confounding variable that could be quite significant in stability – facial growth. Based upon the results of this study, adolescents could be targeted for a future study.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Practitioners and patients will be assigned unique identification numbers, which will be used to maintain study records and organize data transcripts. A file or database at the CC linking practitioners' and patients' names with their unique identification number will be password-protected.

The study monitor and 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 records (e.g., office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

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.

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

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the SPI. All CRFs must be reviewed by the RC and data entry staff, who will ensure that they are accurate and complete. All practices will be trained on de-identifying and transmitting cephalometric x-rays and intra-oral frontal photos in a standardized manner, in order to assure the quality and integrity of the images. Unanticipated problems must be reviewed by the SPI or GPI.

Staff at the RAS will receive pCRFs from practitioners and will enter data into the web system. For the pCRFs that are to be used as source documents (see Section 12), the RAS staff will ensure the forms are completed, and they will be maintained at the RAS. 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, the CC will provide pCRF completion and electronic data entry guidelines.

15.2 Data Capture Methods

Study-specific pCRFs will be developed to include fields for all data elements required for participant assessments. A Web-based system will be used for the upload and storage of the cephalometric x-ray and intra-oral frontal photographs. All data from pCRFs will be entered into a Web-based data collection system to 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. Reports with a summary of data completion by participants will be made available on the network web site.

After the paper data collection has been completed for a patient at enrollment and at each follow-up visit, study materials for the patient will be placed in a secure location. Participating practices will maintain a patient participant log with the name of the patient corresponding to the study ID number printed on the CRFs. After completion of a study

visit, the practitioner will sign the pCRFs (if necessary), and the designated staff member will transmit the pCRFs to RCs.

15.3 Types of Data

Data for the present study consist of the following:

- Practitioner level data from the National Dental PBRN enrollment questionnaire and practitioner characteristics form;
- Patient characteristics data from baseline/enrollment data collection form;
- Patient-reported treatment preference, treatment compliance, and patient satisfaction data on baseline and follow-up visit data collection forms;
- Patient clinical data, and treatment-related data on baseline and follow-up visit data collection forms;
- Cephalometric x-rays and intra-oral frontal photographs; and
- Unanticipated problems data.

15.4 Schedule and Content of Reports

Reports to monitor enrollment will be produced every two weeks during the patient enrollment period, until enrollment targets are attained and enrollment is closed. These reports will provide accrual information in aggregate and by important data variables of interest (e.g. extraction status) and will also contain separate sections regarding patient accrual by practitioner.

Reports to monitor patient participation will be produced every three months after enrollment is closed. These reports will provide ongoing monitoring of patient participation during the active phase of treatment, and will contain information on when the patients are expected to begin the retention stage of treatment and/or final follow-up.

Patient participation reports will also be produced every three months for patients who enter the retainer use phase of their treatment. Data from these reports will be closely monitored, and futility analyses will be performed as needed. In addition, every six months 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. For patients who are lost to follow-up, reports to assess reasons for loss will be produced after data has been obtained following the data collection period for each study follow-up assessment.

Medical Monitor reports will be produced at six months after study initiation until enrollment is closed, and then annually thereafter, and may be produced more frequently at the request of the NIDCR Medical Monitor. Data elements for inclusion in the Medical Monitor reports are stated in Section 9, Study Oversight. In addition to enrollment and retention reporting, the Medical Monitor reports will contain safety data as well as frequencies and descriptive statistics for primary outcome variables and key

variables, and quality management findings. The identification of key variables will be determined by the SPI and other study team members.

As portions of the study objectives can be addressed at the end of recruitment and at the end of active treatment, it is anticipated that some full analyses will be performed after each phase of 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 CC Statistician, in consultation with the SPI, and other study team members. The content of these reports will be determined by the CC 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 Section 13 of the study DMP, in accordance with the Westat CCs Standard Operating Procedure (SOP) DSD-001: Development of a Data Management Plan and SOP DSD-405: Data Lock. Briefly, the Oracle Clinical (OC) data will be locked and the final SAS datasets will be generated at the end of the study. Prior to locking the database, the Clinical Data Manager (CDM) or designee will ensure all data are complete and clean. Then, the CDM will obtain approval from the Project Manager to proceed with the data lock. The CDM 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 CDM 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 National Institutes of Health (NIH) or longer as dictated by local IRB or state laws/regulations.

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way (e.g., 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, 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 GCP principles. The noncompliance may be on the part of the patient, practitioner, SPI, or study staff. As a result 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 Medical Monitor report, all previously unreported PDs must be reported in the Medical Monitor report independent of when they are reported to IRBs.

16 PUBLICATION/DATA SHARING POLICY

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

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APPENDICES

Appendix A: Schedule of Events

Appendix B: Examples of Anterior Openbite

Appendix C: Method to Measure Millimetric Vertical Relapse from Photographs

Appendix D: Patient Retention Plan

APPENDIX A: Schedule of Events

Procedures	Practitioner Screening/ Enrollment	[1]Patient Enrollment/ Baseline (Stage 1 [S1])	[1, 2]Appliance Removal, End of Active AOB Treatment (Stage 2 [S2], Visit 1 [V1]; ~24 months after S1)	Retainer Check Visits (S2, V2-X)	[3]Final Study Visit (Stage 3; S2, V1 +10 to 24 months)
Practitioner Recruitment and Enrollment	X				
Obtain Practitioner Characteristics	X				
Informed Consent		X			
Assessment of Eligibility Criteria		X			
Review of Medical/Dental History		X			
Obtain/confirm contact information and preferred method of contact		X	X	X	X
Patient Demographics		X			
Enrollment Visit data collection (Patient and Practitioner)		X			
Cephalometric x-ray		X	X		
Intra-oral frontal photograph		X	X		X
Measurement of the height of right maxillary central incisor			X		X
End of Active Treatment data collection (Patient and Practitioner)			X		
Retainer Use data collection (Patient and Practitioner)				X	
Final Visit data collection (Patient and Practitioner)					X

Foot notes:
1 = Cephalometric x-rays and intra-oral frontal photographs obtained as part of routine orthodontic care before treatment and at the time of appliance removal/end of active AOB treatment will be used.
2 = One additional intra-oral frontal photograph will be obtained at the time of appliance removal/end of active AOB treatment for this research.
3 = Two intra-oral frontal photographs will be obtained approximately one year after end of active treatment for this research.

APPENDIX B: Examples of Anterior Openbite

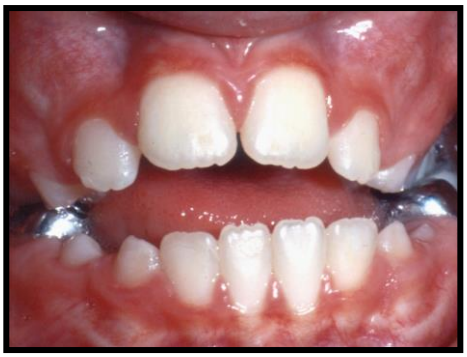

Figure 1. Severe Anterior Openbite

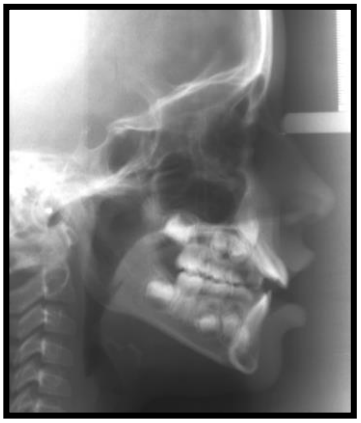

Figure 2. Dental Openbite

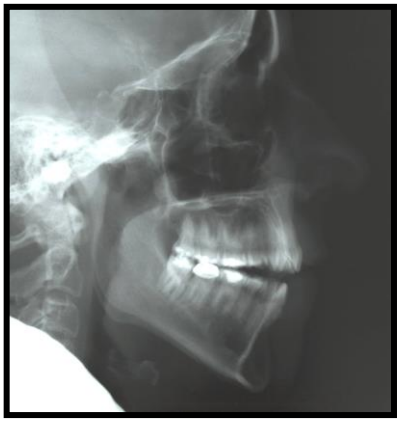

Figure 3. Skeletal Openbite

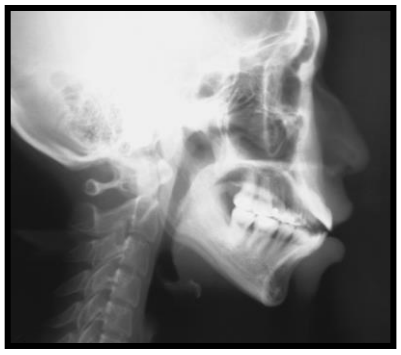

Figure 4. Initial

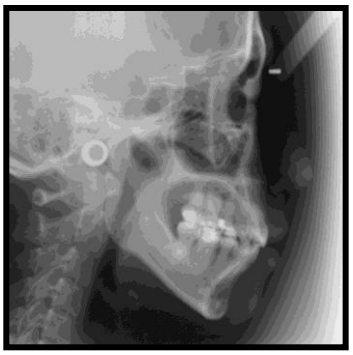

Figure 5. Post-Treatment

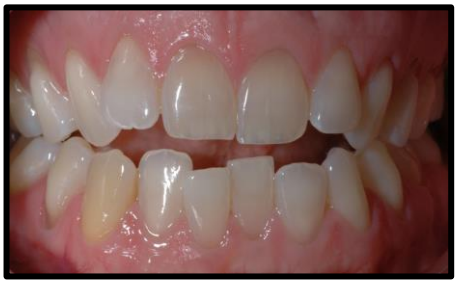

Figure 8. Initial

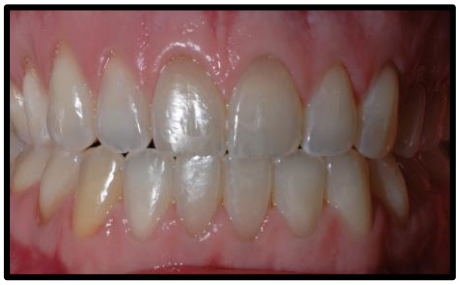

Figure 9. End of orthodontic treatment

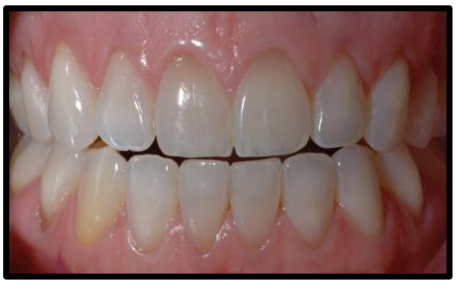

Figure 10. 1 year post-treatment

Appendix C: Method to measure millimetric vertical relapse from photographs

1. Two intra-oral frontal photos will be taken at the end of treatment, as well as at the one-year follow-up time, to measure overbite. One photo will be taken in maximum intercuspation (Fig A), while the other will be taken with the incisors apart so that the entire length of the mandibular incisor can be visualized (Fig B).
2. The practitioner will also measure and report the clinical height of right maxillary incisor at the end of active treatment and at the one-year follow-up, to the nearest tenth of a mm. This measurement will be used to calculate the magnification factor.
3. At each time point, both photos are cropped to exactly capture the width of the four maxillary incisors, with an image size of 6 inches in length to facilitate measurement. Then, the height of the maxillary right central is measured, and the length of the visible portion of the mandibular right central incisor is measured in both photos.

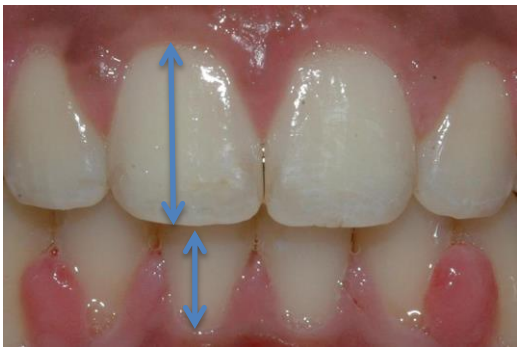

Figure A: Maximum intercuspation

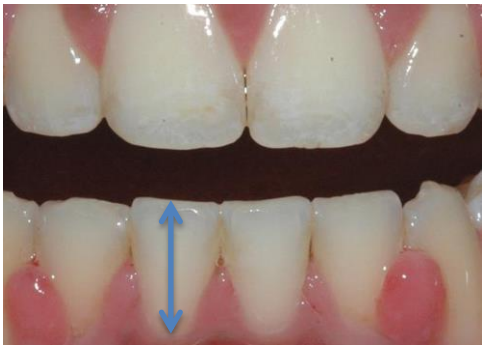

Figure B: Incisors apart

4. If the photos above were viewed with a length dimension of 6 inches, then the maxillary right incisor height would be measured at 61 mm, and the lower incisor would be measured at 36 mm in Fig A and 43 mm in Fig B. We can then calculate the overbite by this method:

   61 mm divided by 15.3 (clinically measured height of incisor) = 3.99 mm. This is the magnification factor.
   43 mm - 36 mm = 7 mm. This is the overbite prior to adjusting for magnification.
   7 mm divided by 3.99 = 1.8 mm of overbite

5. The same method will be employed to calculate the overbite at the end of the one-year retention period, and then the change in overbite can be calculated by subtracting the end of treatment overbite from the one-year follow-up overbite. For example, if the patient's overbite is measured at 1.1 mm using one-year follow-up photos, then the amount of change is 2.4 – 1.1 = 1.3 mm.

Appendix D: Patient Retention Plan

This Patient Retention Plan provides an outline of the issues associated with patient retention and the procedures for maximizing retention during the course of the Anterior Openbite (AOB) Study. For studies that involve longitudinal follow-up of study patients, retention is a key requirement. High retention rates increase the validity and generalizability of study data by ensuring that bias due to incomplete follow-up of patients does not affect study findings.

Retention of study patients is a multifaceted problem. Difficulties with maintaining complete follow-up can be due to a variety of causes. It is important to identify and delineate the different types of retention issues because the way to address them will depend on the type. The four types of retention issues are:

Lost: Patients move and their new location cannot be found.

Missing Data: Patients still within the practice but follow-up visit is missed or data are not collected during visit.

Refused: Patients decide they no longer want to continue participating in study.

Unable: Patients no longer seeing their original/enrolling practitioner.

Below the National Dental PBRN describes the plans for addressing each of these retention issues. Also provided are other administrative and design methods that will help to increase retention rates.

Methods to Minimize "**Lost**"

1) At patient enrollment, emphasize study requirements to patients:
   a. They are part of a long-term (three year) follow-up study, and the importance of all study assessments.
   b. RCs or the CC will contact them by telephone to arrange follow-up visits even if they change dentists.
   c. Entry criteria will include the ability and likelihood of maintaining participation throughout the study.
   d. Collect information on:
      i. Home address
      ii. Home telephone number
      iii. Cell phone and text numbers
      iv. E-mail address(es)
      v. Contact information (including cellular telephone and email) of two persons, one of whom that does not live in the same household as the patient and who will know of the patient's whereabouts.

2) During study visits, confirm contact information (of patient and the two contact persons).

3) Make contact with participating offices every three months to review progress of patients in treatment, upcoming appliance removal dates, and upcoming one-year post treatment dates. Offices will then contact patients, as needed, to remind them of key upcoming dates. The patient's preferred method of contact (e.g., postal mail, email, telephone, text message) will be ascertained at the baseline appointment. Experience has shown that it is personal relationships, both between the patients and offices, and the offices and the RCs, that promote successful execution of PBRN studies. In other words, it will be more meaningful for patients to hear from their personal dental offices regarding a reminder for a study appointment. In turn, it will be more meaningful for the office to hear from its RC that it is time for them to contact patients. Experience has also shown that it is beneficial for the network to relieve burden on the practices. To that end, the National Dental PBRN will request IRB approval for the RCs and for the CC to receive the patient contact information and the contact information of two persons, one of whom that does not live in the same household as the patient, so that both can assist the practices with follow-up contacts (e.g., birthday cards, appliance removal visit reminders, etc), particularly with patients who have had difficulty attending visits. The regions will have some latitude in determining the best means for maintaining contact with study patients and ensuring their ongoing participation.

4) Number of Patients per Practitioner Considerations:
    a. Ask practitioners to enroll approximately 3 - 8 patients, but no more than 15 patients per practitioner, preferably in an approximately 11 months enrollment period. Recruiting in a limited time period will make it easier to recall and follow the patients.

5) Given the above design features, patients should not be "lost". However, if a patient moves and contact is lost, the CC has extensive experience with using tracing resources such as National Change of Address services, motor vehicle departments, and LexisNexis databases. In those cases, the CC will implement those tracking procedures.

6) The process for contacting patients for appliance removal and subsequent follow-up visit and reminders will be for the practice to make the initial contact attempts, then inform their RC if there was no response within three weeks of the second contact attempt. In this situation, the RC will discuss the circumstances with the practice staff, and a decision will be made on allowing the office to attempt additional contacts, or if the RC should attempt to contact the patient. (For example, a phone number that is discontinued would prompt the RC to attempt to contact the patient, whereas a patient who has a history of periodic out-of-town travel for work might not.) If the office feels the RC should get involved, the RC will attempt to contact the patient. If the RC is unable to contact the patient after

2 attempts, then the RC should inform the CC, and the CC will initiate tracking procedures to identify updated patient contact information. If the office feels the RC should not get involved, then the RC will check again with the office every 2 weeks to see if the office has been successful in contacting the patient, or if the RC needs to get involved. Initiating tracking procedures promptly when there is no patient response to contact attempts will minimize missed study visits and also minimize loss to follow-up.

Methods to Minimize "**Missing Data**"

1) Because patients will be in various stages of participation, it will be important to fully train office personnel about all stages of the study, as well as the data that must be collected at each stage. Having said that, enrollment will be emphasized during the first 6 months, followed by the active treatment stage, and finally, the retention stage. RCs will periodically remind offices about the active treatment and retention data collection procedures, as well as to assist them with tracking the progress of each patient through the course of the study. It can be challenging to remember to perform study procedures when the enrollment phase is over and data collection is only occurring in the office every few months.

2) Ask participating offices to develop a system to flag records of patients in their practices who are participating as patients in the study, as well as to flag study patients in the office schedule. In this way, study personnel will be alerted to the fact that the patient is at the office, and can ensure that data collection takes place if indicated. Flagging the patient in the schedule will help to ensure that patients are not inadvertently scheduled when the practitioner will not be in the office. In the same way, if a patient's record is requested by another office, study personnel can inform the RC and attempts made to maintain the patient in the study.

3) Emphasize to practitioners as part of their initial study packages that the dentist has to be the motivational director of the study, especially regarding follow-up appointments, and make sure that the staff understands that the office is committed to participating in the study and seeing it through to completion.

Methods to Minimize "**Refused**"

1) The method described in the 1st point above under "Lost" will also help reduce the number of patients who refuse to continue participating. At enrollment, patients are informed that they are agreeing/consenting to participate in a long-term follow-up study. Patients who enroll are required to state a willingness to participate throughout the study.

2) The method described in the 3rd point above under "Lost" (making contact between visits) should also help reduce refusals. The CC has found that

retention is increased if patients are kept engaged and interested in the study through the use of periodic newsletters and other study updates, postcards, birthday cards, phone calls, using the patient's preferred mode of contact. Additionally, follow-up involvement will be kept as simple and convenient for the patient as possible.

Methods to Minimize "**Unable**"

1) There are several scenarios in which a patient stops seeing the original/enrolling practitioner:
   a. Patient does not move, but:
      i. Patient changes practitioner - in same practice
      ii. Patient changes practitioner - in different practice
      iii. Patient stops seeing any practitioner
   b. Patient moves
      i. Patient sees new practitioner
      ii. Patient stops seeing any practitioner
   c. Practitioner retires or dies
   d. Practitioner moves
   e. Practitioner refuses to continue participating (low likelihood)

2) The operational impact of all of the above scenarios can be summarized by two scenarios:
   a. Patient has a new practitioner (not a National Dental PBRN member)
   b. Patient stops seeing any practitioner

3) Locating the patient should not be a problem (see Methods to Minimize "Lost"), and having the patient agree to continue participating should not be a problem (see Methods to Minimize "Refused").

4) The main operational issue is: How to get study follow-up visit information from patients seeing a non-National Dental PBRN practitioner or not seeing any practitioner. If allowable by the IRB, we propose the following options:
   a. Invite the new dentist into the Network so the patient can continue to be followed by the new practitioner.
   b. Ask the patient to return to the original practitioner only to collect the end of treatment and one year post-treatment data.
   c. Ask the patient to visit a different network practitioner who is participating in the study only to collect study related data.
   d. If the patient is moving, provide a list of network practitioners in the area the patient is moving to.

Other Administrative and Design Methods to Increase Retention Rates

1) IRB/Informed Consent Considerations to Reduce Attrition

a. Incorporate into the informed consent form (ICF) permission for all relevant study personnel, both in the dentist's office as well as the study investigators, and RCs to contact the patient. This will allow communications with the patient by study personnel without having to go through the dental office.
b. Incorporate into the ICF permission to see a National Dental PBRN practitioner other than the initial provider for the purpose of data collection. This will expedite data collection in those instances where a National Dental PBRN practitioner retires or sells his/her practice, or where a patient goes to a different non-National Dental PBRN practitioner, or stops seeing a practitioner for routine care.

2) Financial, but non-coercive incentive to patients to encourage continuing participation.
   a. Patients will receive $25 each for the enrollment and end-of treatment visits. For the final study visit, which is approximately after one year of retainer use, they will receive $50. This amount is purposely larger than the other two, as it is always more difficult to retain patients after active treatment has been completed.

<u>Additional methods for patients who have missed an appliance removal or subsequent follow-up Visit</u>

1) If an enrolled patient misses the <u>appliance removal or subsequent follow-up</u> window for a visit, his or her contact information will be confirmed through the CC tracking procedures prior to the practice initiating contact attempts for the recall visit scheduling and the recall reminder for the next recall visit.

2) The practitioner's office will use the confirmed contact information to attempt to contact the patient by telephone (or other preferred means of contact) to schedule the next recall visit in a timely fashion, or remind the patient of the recall visit.

3) If successful in contacting the patient, there will be special emphasis on reminding the patient of the importance of his/her participation in the study and the importance of complying with the study visits.

4) If the patient cannot be reached, the two individuals designated as additional connections to the patient will be contacted to confirm the patient's contact information and/or determine the patient's whereabouts and additional attempts will be made to make contact with the patient.

5) If their designees cannot be contacted, CC tracing resources will be used in an attempt to locate the patient to schedule the visit, or remind them of the visit.