The Restful Jaw Device: A New Way to Support and Protect the Jaw During Third Molar Extractions

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STATEMENT OF COMPLIANCE

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

SIGNATURE PAGE

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

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ASA	American Society of Anesthesiologists
CFR	Code of Federal Regulations
CRF	Case Report Form
DCC	Data Coordinating Center
EC	Experimental Care
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FFR	Federal Financial Report
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
OMS	Oral and Maxillofacial Surgeons
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RJ2	Restful Jaw/ jaw support device
SAE	Serious Adverse Event/Serious Adverse Experience
TMD	Temporomandibular Disorders
UP	Unanticipated Problem
UC	Usual Care
US	United States

WHO	World Health Organization

PROTOCOL SUMMARY

Title:

The Restful Jaw Device: A New Way to Support and Protect the Jaw During Third Molar Extractions

Précis:

During mandibular 3rd molar (wisdom tooth) extractions, when a downward force is placed on the patient's jaw, the patient must tense his/her jaw muscles to oppose it. Patients under moderate/deep sedation or general anesthesia cannot tense their muscles to counter this downward force to prevent injury to the jaw including the temporomandibular joint (TMJ). Bite blocks hold the patient's mouth open but do not counter this downward force on the mandible. In this two-arm parallel randomized clinical trial (RCT) design, 294 patients undergoing 3rd molar extractions with moderate/deep sedation or general anesthesia will be randomly allocated to Usual Care (UC) or Experimental Care (EC). The study intervention for EC is use of the Restful Jaw version 2 (RJ2) device, which supports the jaw during the extractions, with concurrent use of a bite block. The study control is UC, which involves the dental assistant supporting the jaw during the extractions with concurrent use of a bite block. Patients will report temporomandibular disorders (TMD) pain via questionnaires at baseline and the 1-, 3-, and 6-month follow-up time points.

Objectives:

Primary: In patients undergoing mandibular 3rd molar extractions with moderate/deep sedation or general anesthesia, compare the incidence of TMD pain within a 6-month follow-up period between the two groups:

- UC group, using a bite block and with hand support of the jaw, and
- EC group, using a bite block and the RJ2 device to support the jaw.

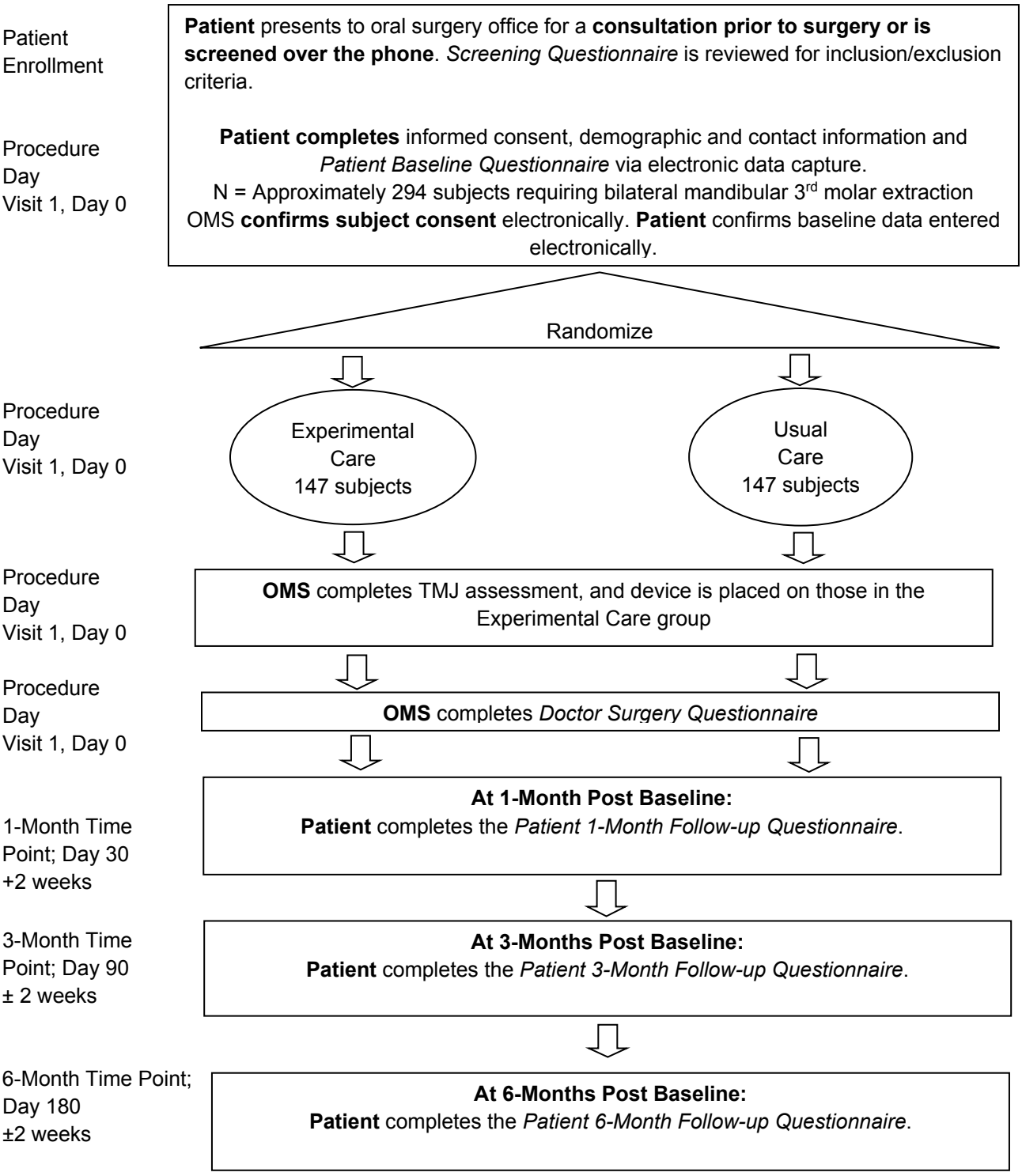
The primary outcome is the incidence of TMD pain within a 6-month follow-up period (binary dependent variable).

The secondary objectives of this study are to:

1. Compare the incidence of TMD pain between UC and EC groups using an alternate assessment instrument to identify TMD pain within a 6-month follow-up period
2. Compare TMD pain intensity between the UC and EC groups within a 6-month follow-up period: at 1-, 3- and 6 months.
3. Compare TMJ noise, pain characteristics (e.g., location in temple or jaw, and occurrence with wide opening of mouth) and change in jaw pain since it started, within a 6-month follow-up period: at 1-, 3- and 6 months.
4. (Exploratory Objective) Describe the experiences of surgeons and dental assistants with the new device at mid-way through recruitment of patients and at the end of recruitment.

Population:	Approximately 294 healthy, consenting adult patients, age 18-30, requiring surgical removal of bilateral mandibular 3rd molars (concurrent maxillary 3rd molar extractions allowed).
Number of Sites:	Approximately 4 clinical sites and 1 data coordinating center (DCC).
Description of Intervention:	The RJ2 device is used to support the jaw during dental procedures including surgical removal of 3rd molars (wisdom teeth) with moderate/deep sedation or general anesthesia. The device is designed to counter the downward forces placed on the mandible by clinicians during dental procedures and prevent jaw hyperextension (opening too wide) while providing a secure, stable jaw position. The RJ2 device has been determined by the Food and Drug Administration (FDA) to be a non-significant risk device.
Study Duration:	Approximately 36 months.
Subject Participation Duration:	Approximately 6 months.
Estimated Time to Complete Enrollment:	Approximately 14 months.

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Dental procedures can cause jaw pain, discomfort and fatigue from opening the mouth too long or too wide, or by placing too much force on the jaw. (1-15) Opening too wide can also cause hyperextension of the jaw. During and after long dental procedures, patients frequently report jaw pain, fatigue, or discomfort. This pain and dysfunction characterizes temporomandibular disorders (TMD), which can be short-term or may become chronic. TMD occurrence is frequently associated with trauma from dental procedures, including 3rd molar extractions. (1-15) Also, dental procedures may aggravate pre-existing subclinical TMD symptoms. (16)

Over 10 million 3rd molars (wisdom teeth) are extracted from about 5 million people in America each year.(1) More than 11 million patient days of “standard discomfort or disability” – pain, swelling, bruising and malaise – result postoperatively.(1) Although the American Association of Oral and Maxillofacial Surgeons guidelines state that consent forms for 3rd molar extractions should include injury to the temporomandibular joint (TMJ) or associated muscles(17), there are few reports of the trauma to the TMJ or jaw muscles from this procedure.(1) One of the best studies assessing development of TMD after 3rd molar extractions is a large prospective cohort study of young adults.(3) Huang et al. assessed the onset of jaw joint symptoms (i.e., TMJ noise and jaw pain) in individuals who had 3rd molar extractions compared to those who did not. Of the 517 participants with follow-up data, 39% (n = 201) had a total of 720 3rd molars extracted, with 68% reporting that 'intravenous sedation' or general anesthesia was used. Among patients undergoing 3rd molar removal, the rate of TMD lasting more than 1 month was 34.3 per 100 person-years compared to 8.8 among those who did not have 3rd molar extractions. The relative risk of developing TMD was 3.8 and the rate of TMD reported by patients undergoing this surgery was greater than 30%. This study's findings are limited by its low follow-up rate (40 to 50% for follow-up questionnaires at different intervals). Further, a retrospective study reported that almost a quarter of new onset TMD cases in young adults were associated with 3rd molar removal.(2) In a cross-sectional study of patients aged 18.7 + 1.1 years, the occurrence of 3rd molar extractions was significantly associated with TMD ($P<0.001$). (7) Finally, in an age and sex matched case-control study, at 6 months follow-up, patients who had 3rd molar extractions had significantly more TMJ and jaw muscle pain than controls who did not have this surgery ($P<0.05$). (6) These findings suggest removing 3rd molars is associated with development of TMD and that this patient safety issue is not addressed by current methods to protect the jaw during this surgery. Providing better support for

the jaw during 3rd molar extractions to prevent hyperextension and excessive force on the jaw would be expected to alleviate the physical stress on the jaw and reduce patient suffering and jaw injury. (18, 19)

2.2 Rationale

This study will test whether the new RJ2 device, when supporting the jaw during surgical removal of 3rd molars, reduces the incidence of TMD pain compared to usual care where the dental assistant supports the jaw. **Hypothesis:** The risk of developing TMD pain in patients undergoing 3rd molars (wisdom teeth) removal in the experimental care (EC) group will be statistically lower than in the usual care (UC) group within the 6-month follow-up interval.

Rationale: When a downward force is placed on the patient's jaw to surgically remove the mandibular (lower) 3rd molars, the patient must tense his/her jaw muscles to oppose it. This can result in jaw pain, discomfort or fatigue, especially if the force is high or prolonged. Patients under moderate/deep sedation or general anesthesia cannot tense their muscles to counter this downward force to prevent injury to the jaw. Bite blocks hold the patient's mouth open but do nothing to counter this downward force on the jaw. Opening a patient's mouth too wide can cause jaw hyperextension; a long extraction procedure time can also lead to injury of the jaw. This can result in patient suffering, lost time for the dentist to manage the symptomatic patient, and potential medico-legal problems. Currently, oral and maxillofacial surgeons (OMSs) when surgically removing 3rd molars (wisdom teeth) with moderate/deep sedation or general anesthesia have at least 2 dental assistants present. The first dental assistant provides suction and gives the surgical instruments to the surgeon. The second dental assistant is a certified anesthesia dental assistant who monitors the patient's vitals as well as oxygen and carbon dioxide levels while providing the patient with medications intravenously. This second dental assistant also inserts the bite block and then stands behind the chair and places their hands on both sides of the jaw to support it and oppose the downward force on the patient's jaw during the extractions. If additional intravenous medications are needed during the surgery, the surgery has to stop (lost time) and the OMS or the first dental assistant supports the jaw until the second dental assistant completes the medication administration. Based on clinical experience, the second dental assistant often experiences fatigue and pain in their hands, arms, neck and shoulders during long or difficult procedures, which can affect his/her ability to support the jaw. Given the second dental assistant's many duties and responsibilities, it is hard for the assistant to provide constant good jaw support while anticipating the direction and amount of force placed by the OMS on the patient's jaw during 3rd molar surgical removal. This may

explain the finding that almost a quarter of new onset of TMD cases in young adults is associated with 3rd molar removal.[2] This **patient safety issue** can be addressed during 3rd molar surgical removal by using a bite block to hold the mouth open and concurrently using a jaw support device under the jaw to provide a stable counter force to downward forces on the jaw, thus preventing jaw hyperextension and injury to the jaw. This would also free the second dental assistant from holding the jaw so he/she can concentrate on his/her other duties, which would **improve patient safety**.

The currently patented **Restful Jaw® 1** (RJ1) device is designed to support the jaw when downward forces are placed on it and it has been shown to significantly reduce jaw pain during dental procedures (*restfuljaw.com*).[18,19] However, significant changes have been recommended by users of the RJ1 device who utilize moderate/deep sedation or general anesthesia. We have addressed these concerns and suggested changes in Phase I of this small business grant with an innovative design for the new **Restful Jaw 2** (RJ2) device (see Section 6 for a description of the new device). These changes included providing support on both sides of the jaw which mimics the dental assistant's placement of his/her hands. Also, the device attaches to the dental chair head post so the only contact to the patient is under his/her jaw. Finally, if the device needs to be removed from the patient during the procedure, the dental assistant presses on the foot pedal or the quick release control box and this deactivates the device so it can be quickly removed from the surgical field and away from the patient. Specifically, in Phase I step 1 of this grant, the OMSs and dental assistants (DAs) provided us with critiques of the prototypes of the RJ2 device. Then during Phase I step 2, they used a working prototype of the device on consenting patients having 3rd molar surgical removal with moderate/deep sedation or general anesthesia and provided additional feedback on the device. We continued this process to the point of saturation where we are confident the device is satisfactory for use in the oral surgery environment with the minor modifications which have been incorporated in the design.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

There are potential risks of using the RJ2 device. If excessive force is placed on the device by the OMS, then the device could slide to a slightly different position. However, as soon as this force is stopped, then the device will stop moving. There is potential that the device could malfunction and lose pressure during the procedure. If this occurs, the passively controlled arms will fall away from the patient's jaw which could also compromise the support of the patient's jaw. To mitigate these risks, the dental assistant will be present behind the dental chair to support the jaw. Patients have similar

risk of jaw injury when their jaw is supported only by the dental assistant's hands since their hands can slip in position if excessive force is placed on the jaw, and their supporting arms and hands can become fatigued during procedures compromising their ability to support the jaw. In addition, patients could report that the padded jaw brace when placed under their jaw feels uncomfortable. If this occurs, then the dental assistant can reposition the brace to a position that is comfortable. There are no other anticipated safety risks to participating in this study beyond those risks inherent in 3rd molar extractions with moderate/deep sedation or general anesthesia. Patients do not receive 3rd molar extractions as a study procedure. Consequently, risks of 3rd molar extraction with moderate/deep sedation or general anesthesia will be discussed with the patient as part of normal clinical care and are not considered to be study-associated. Finally, if any adverse event (AE) occurs, then it will be documented and assessed by the study team.

2.3.2 Potential Benefits

This trial may ascertain whether use of the RJ2 device provides a more effective way to support the jaw that reduces the incidence of TMD pain compared to the dental assistant supporting the jaw for patients having removal of 3rd molars.

3 OBJECTIVES

3.1 Study Objectives

Primary: In patients undergoing mandibular 3rd molar extractions with moderate/deep sedation or general anesthesia, compare the incidence of TMD pain within a 6-month follow-up period between the two groups:

1. UC group, using a bite block and with hand support of the jaw, and
2. EC group, using a bite block and the RJ2 device to support the jaw.

The secondary objectives of this study are to:

1. Compare the incidence of TMD pain between UC and EC groups using an alternate assessment instrument to identify TMD pain within a 6-month follow-up period
2. Compare TMD pain intensity between the UC and EC groups within a 6-month follow-up period: at 1-, 3- and 6 months.
3. Compare TMJ noise, pain characteristics (e.g., location in temple or jaw, and occurrence with wide opening of mouth) and change in jaw pain since it started, within a 6-month follow-up period: at 1-, 3- and 6 months.
4. (Exploratory Objective) Describe the experiences of surgeons and dental assistants with the new device at mid-way through recruitment of patients and at the end of recruitment.

3.2 Study Outcome Measures

3.2.1 Primary

The primary outcome is the incidence of TMD pain within a 6-month follow-up period (binary dependent variable). TMD pain is deemed to have occurred if the patient's self report in the *Patient 1-, 3- and 6-month Follow-up Questionnaires* endorses *either or both* of the following questions: Pain in jaw with wide opening, or pain in temples, jaw joints or jaw muscles.[3] The primary analysis will include all available follow-up measures (1, 3, and 6 months) for each patient to estimate the incidence of TMD pain.

3.2.2 Secondary

1. The incidence of TMD pain, as measured with the validated *TMD Pain Screener Questionnaire[22] (binary dependent variable)*, will be compared between the UC and EC groups within a 6-month follow-up period based on patients' self report in the

Patient 1-, 3- and 6-month Follow-up Questionnaire.

2. TMD pain intensity, as measured with the validated *Characteristic Pain Index (CPI)* within a 6-month follow-up period (treated as a continuous measure), will be compared between the UC and EC groups based on patients' self report in the *Patient 1-, 3- and 6-month Follow-up Questionnaire*.

3. The UC and EC groups will be compared for TMJ noise, pain characteristics (e.g., location in temple or jaw, and occurrence with wide opening of mouth) and change in jaw pain since it started, within a 6-month follow-up period based on patients' self report in the *Patient 1-, 3- and 6-month Follow-up Questionnaire*.

4. A final secondary outcome is descriptive: a summary of the experiences of surgeons and dental assistants with the new RJ2 device at mid-way through recruitment of patients and at the end of recruitment based on their self report in the *Doctor Questionnaire Regarding Use of the Device* and *Dental Assistant Questionnaire Regarding Use of the Device*, respectively.

4 STUDY DESIGN

- **Study design**

  This is a multicenter, two-arm, parallel RCT design in which approximately 294 patients undergoing 3rd molar (wisdom teeth) extraction will be randomized to either UC or EC, with data obtained at baseline, and at 1-, 3- and 6-months follow-up after surgery. Patients in the EC (study intervention) arm will undergo 3rd molar extraction with the RJ2 device supporting the jaw and concurrent use of a bite block. Patients in the UC (study control) arm will undergo 3rd molar extraction with the dental assistant supporting the jaw and concurrent use of a bite block.

  The study will be conducted at the following sites:

  - University of Minnesota School of Dentistry, Moos Tower, Oral Surgery surgical suite; 7th floor Moos Tower, 515 Delaware St SE, Minneapolis, MN 55455.
  - HealthPartners Como Clinic, Oral Surgery Department, 2500 Como Ave, St. Paul, MN 55108
  - HealthPartners Eden Prairie Clinic, 8455 Flying Cloud Dr. Eden Prairie, MN 55344
  - Metro Dentalcare Specialty Center Burnsville, 14344 Burnhaven Dr., Burnsville, MN 55306

- **Study population**

  Approximately 294 healthy (ASA 1 & II), consenting adult patients, age 18-30, requiring surgical removal of bilateral mandibular 3rd molars (concurrent maxillary 3rd molar removal allowed). All patients presenting to participating surgeons' practices for surgical removal of their 3rd molars will be considered for eligibility. See eligibility criteria described in Section 5.

  Approximately seven (7) OMS will participate in the study. They represent three diverse practice settings; the University of Minnesota Dental School Department of Oral Surgery, HealthPartners (a large group practice) and a private practice setting. All surgeons are board certified and currently treat patients with 3rd molar extractions. Dental assistants at each of these sites will be invited to participate in the study.

- **Data Collection**

  Patient-reported data will be collected via tablets, smart-phones, or computers at baseline during in-office visit(s) with the surgeons. To assist with in-office data collection, participating OMS will be offered tablets. OMS, dental assistants, and patients will provide baseline and follow-up data directly into the electronic data capture (EDC) system that is maintained by the HealthPartners Data Coordinating Center (DCC); data can be entered via tablets, smart-phones, or computers. After baseline, patient-reported data will be ascertained independent of office visits, and all follow-up patient, OMS and dental assistant data collection will be managed by HP DCC. Follow-up contacts to non-responders will also be managed by the DCC.

- **Overview of Study Schedule**

  - The electronic data system used to collect patient and OMS/dental assistant data will be assessed for acceptability and compatibility prior to administration of any questionnaires.
  - OMS and their office staff will receive study training from the Study Coordinator (SC), after which the OMS is authorized to begin enrolling study patients.
  - An in-office patient log will be kept regarding the reason patients were excluded or declined to participate.
  - Once the patient is screened using the *Screening Questionnaire* that comprises the inclusion and exclusion criteria, patients who are eligible will be invited to participate in the study. Potential patients who are interested in study participation will undergo consent procedures.
  - Patients will complete these baseline forms and questionnaire before surgery: *Patient Contact and Patient Demographics information,* and *Patient Baseline Questionnaire.*
  - Randomization procedures will occur, and patients will receive their randomized assignment.
  - The OMS will complete the *Doctor Surgery Questionnaire* after completing the 3rd molar extractions.
  - At 1, 3, and 6 months post-baseline, patients will complete follow-up assessments via an online questionnaire. Non-responders will be followed up with email, telephone, and/or texting. All patients will be followed up regardless of whether they report TMD pain at any follow-up.

- Midway through and at the end of the enrollment phase of the study, the OMS and dental assistants will complete a questionnaire regarding their experience with the use of the device.
- Approximately 3 months into recruitment, Dr. Schiffman, Ms. Kloser, study engineers and OMS will meet to discuss their experience with using the device.

First Month Follow-up of Study Patients by study staff

Patients will receive emails with active links to the online web-based *Patient One-month Follow-up Questionnaire* for electronic completion. The DCC will attempt email, telephone and/or text contact for non-responders to remind them to complete the questionnaires online or over the telephone. Completion of questions over the telephone is an option for those patients who do not complete the form by close of data collection window.

Months 3 and 6 Follow-up of Study Patients by study staff

Similar procedures, as in the first month time point, will be repeated at months 3 and 6.

5 STUDY ENROLLMENT AND WITHDRAWAL

The target sample size for this study is 294 patients. To meet this target, we anticipate that 500 patients will need to be screened. Enrollment will include patients who present to the participating oral & maxillofacial clinics for surgical removal of mandibular bilateral 3rd molars (concurrent removal of maxillary 3rd molars is allowed). Each OMS will enroll no more than 60 patients into the trial.

5.1 Subject Inclusion Criteria

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

- Between 18 to 30 years of age at time of enrollment;
- Willing to provide informed consent to be randomized to either using the device or not when having surgical removal of 3rd molars with moderate/deep sedation or general anesthesia;
- Requires surgical removal of bilateral mandibular 3rd molars with moderate/deep sedation or general anesthesia; concurrent maxillary 3rd molars removal allowed;
- American Society of Anesthesiologists (ASA) Physical Status category 1 (normal healthy patient) or Category 2 (patient with mild systemic disease);
- Available to be contacted for study purposes by e-mail, phone and/or text;
- Willing to provide contact information for one other person who will know the patient's whereabouts in the event the patient cannot be reached. This contact information must be different from the patient's contact information;
- Willing to comply with all study procedures and be available for the six month duration of data collection.

In order to participate in this study, **dental assistants** must meet all the following criteria:

- Holds a certification as a dental assistant
- Willing to provide informed consent according to their IRB requirements and procedures.

- Willing to comply with all study procedures.
- Willing to provide feedback on the device at the midpoint and end of the data collection.

In order to participate in this study, **OMS** must meet all the following criteria:

- Willing to provide consent according to their IRB requirements and procedures.
- Has the ability to receive emails and access online surveys.
- Willing to comply with all study procedures and be available for the duration of the study.
- Successfully completed a CODA certified program in advanced specialty education program in oral and maxillofacial surgery.
- Currently certified in moderate/deep sedation or general anesthesia.
- Currently certified in Advanced Cardiovascular Life Support (ACLS).

5.2 Subject Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in this study:

- In the past 3 months, reports the presence of TMD pain in their temples, jaw joints or jaw muscles;
- Contraindication(s) for moderate/deep sedation or general anesthesia;
- Any condition or situation the surgeon determines that would prevent the patient from participating in this study;
- Inability to understand study procedures or provide consent in English;
- Device does not fit mandible;
- Supernumerary 3rd molars present.

5.3 Strategies for Recruitment and Retention

All patients presenting to participating surgeons' practices will be considered for eligibility. For patients without TMD pain in the last 3 months, the surgeons or their office staff will discuss the study and review eligibility criteria with the patient. Patients who meet eligibility criteria and consent to participate in the study will complete their baseline data collection forms, undergo randomization procedures, and then have their 3rd molars surgically removed.

Patients will be told that their treatment will not be affected by participation in the study except that they will be randomized to UC or EC.

Patient retention is important to this study, and follow-up data will be collected independently of in-office visits. Study patients will be asked to complete follow-up assessments online at 1-, 3-, and 6- months after the baseline visit. Patients will be paid $125 total for completed questionnaires; $25 at baseline, $25 at 1-month follow-up, $25 at 3-month follow-up and $50 at the 6-month follow-up.

Study patients will be contacted by email prior to each data collection time point at 1-, 3-, and 6-months post-surgery. The initial email contact for each survey period will contain the request to complete the questionnaire and an active link to the online web-based questionnaire. Email, telephone and/or text follow-up attempts will be implemented for non-responders. The HealthPartners DCC will email, call and/or text patients who do not complete the follow-up questionnaires by the close of the target data collection window to encourage them to complete surveys. When contacted, patients will be given the option to complete the questionnaire by telephone with the DCC.

5.4 Treatment Assignment Procedures

The specific randomization procedure and methods are described below. Generally, participants will be randomized between the two study treatments, stratified by surgeon (7 surgeons and thus 7 strata total). This stratification addresses variation between surgeons in surgical technique and variation between practices in postoperative rehabilitation protocol.

5.4.1 Randomization Procedures

The OMS or dental assistant will provide a participant with the randomization assignment after the participant's eligibility is confirmed and his/her consent is obtained. The random assignment will be obtained from the study tablet used by the OMS or dental assistant. The study tablet, which will be programmed by the HP DCC, will (among other things) use randomized treatment assignments from a stratum-specific

(i.e., surgeon-specific) sequence of randomized assignments created as described in the following paragraph. Each surgeon-specific randomization sequence will be loaded into the tablet by the programmer at the HP DCC in such a way that it will be impossible for clinical study personnel, in particular for the OMS or dental assistant to access this sequence or to infer any treatment assignment in the sequence until the moment that assignment is given to a particular participant.

For each stratum (i.e., surgeon), the randomization sequence will be created by the project statistician using custom-written code in the R system (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/), as follows: The sequence will use randomized permuted blocks of size 2 and 4, in each of which the two treatments are present equally often. The R code will first generate a random sequence of block lengths, so that study personnel will never be able to tell which block they are in, and then in each block, the treatment assignments will be randomly permuted, so that each sequence of possible treatments within a block is equally probable.

5.4.2 Masking Procedures

In this RCT, it is not feasible to blind patients, surgeons, or dental assistants to treatment after the intervention assignments have occurred, so they will not be blinded. It is, however, feasible to mask the sequence of treatment assignments until the moment each assignment is made, and this will be done, as described in Section 5.4.1, above.

The DCC will also be un-blinded to treatment arm assignment. However, study staff and investigators will not have access to any interim outcome data. Unmasking procedures during the surgery will not be necessary as the patient, surgeon, and dental assistants will be un-blinded to the treatment group for each patient. The patient's record in the OMS office will include documentation of study participation and their group assignment (i.e., UC versus EC).

5.5 Subject Withdrawal

5.5.1 Reasons for Withdrawal

Patients may withdraw voluntarily from participation in the study at any time upon request, including at baseline and at any follow-up time points.

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

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient. All patients who provide consent and are randomized to one of the treatment arms will remain in the study even if they are not able to follow through with their group assignment through the completion of the surgical procedure. This includes an event that occurs during the surgical removal of their 3rd molars that precludes completion of the surgical procedure at that time. Only patients who no longer consent to provide data will be withdrawn.

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

- If an enrolled patient declines to provide any of the essential baseline data on the Patient Contact Form, the Patient Demographics Form, and/or the Baseline Patient Questionnaire, this decision will be considered a voluntary withdrawal from the study by the patient and the PI will withdraw the patient from the study.

5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

All patients who provide consent and are randomized to one of the treatment arms will continue to provide data unless and until they explicitly withdraw their consent for further data collection. Only participants who no longer consent to provide data will be excluded from further data collection, and data collected during the duration of their participation will be included.

For patients who cease to receive their assigned treatment or who withdraw from study participation, the date and reason for this change in status will be recorded. Patients who have withdrawn consent for study participation may continue to receive usual care as patients of the participating OMS.

OMS ***will not*** replace patients who have withdrawn from the study; the study's sample size was chosen to account for 10% of patients not providing follow-up data.

If any OMS or DA withdraws from study participation, he/she will be replaced, and the replacement(s) will be trained on study procedures prior to participating in the trial.

5.6 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 to the investigator, funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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 INTERVENTION

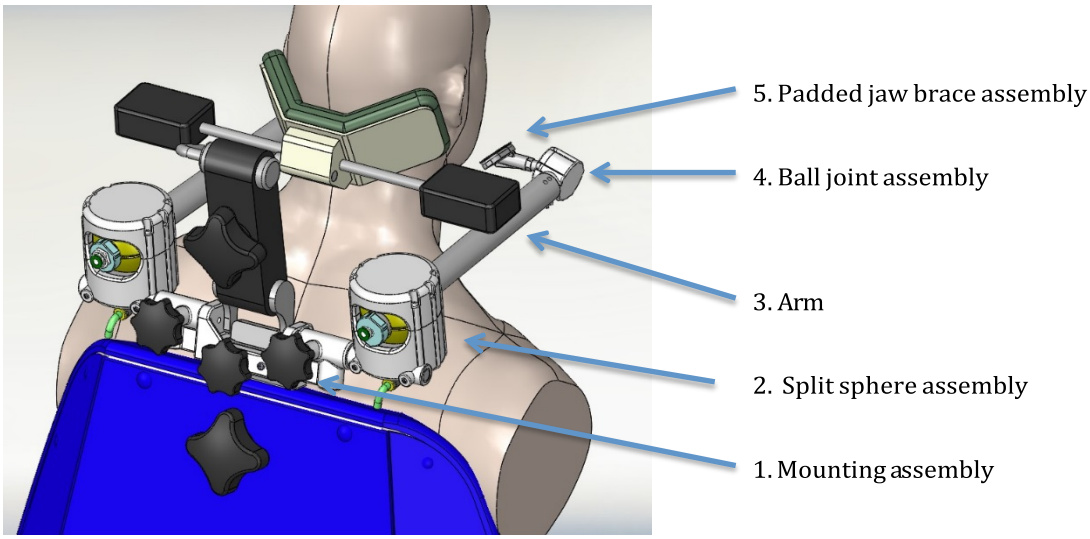
6.1 Study Product Description

Description of the Restful Jaw Device (RJ2)

The RJ2 device is used to support the jaw during dental procedures including surgical removal of 3rd molars (wisdom teeth) with moderate/deep sedation or general anesthesia. The device is designed to counter the downward forces placed on the mandible by clinicians during dental procedures and prevent jaw hyperextension (opening too wide) while providing a secure, stable jaw position.

Figure 1 shows a side view of the device mounted to the head rest post with the jaw brace (#5) under the patient's jaw

Figure 1. Side view of device mounted to the chair head rest

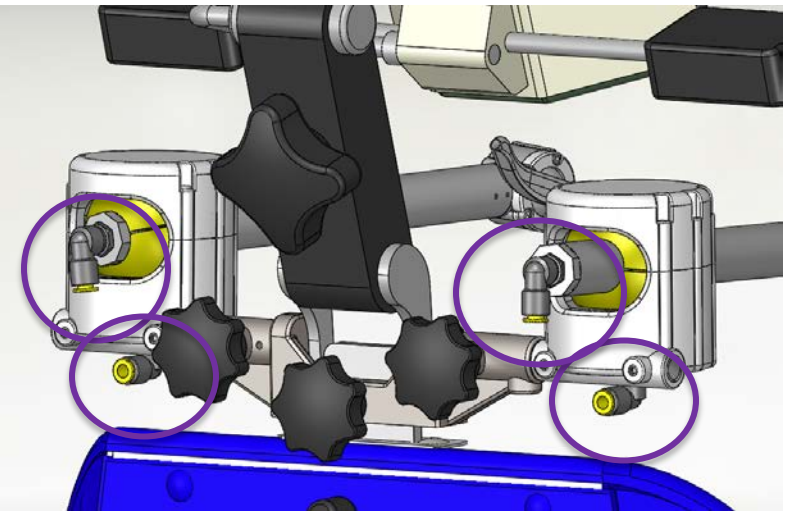


The device is designed to replicate the dental assistant's shoulders, arms, wrists and hands. The device has 5 components (see Figure 1): the first component is the *mounting assembly* that attaches the device to the dental head rest post (Figure 1. #1). The second component is the *split sphere assembly* which replicates the movements of the dental assistant's shoulder (Figure 1. #2). The third component is the *"arm"* of the device, replicating the dental assistant's arms, which can be rotated and moved in and out of the split ball assembly (Figure 1. #3). The fourth component is the *ball joint assembly* which replicates movements in the dental assistant's wrist (Figure 1. #4). The fifth component is the *padded jaw brace assembly* that replicates the dental

assistant's hands (Figure 1. #5). Please refer below to the "*Instructions for Use"* for more details regarding the device.

This device requires pressurized air to operate. Air hoses are provided with the device to connect it to the air supply in the surgical suite. If there is no air supply available, then a free-standing air compressor or pressurized tank is used. The control box that sits on the floor is where the air into and out of the device is controlled. The air hoses from the air compressor or tank connect to the "input" port on the control box. The 4 "output" ports on the control box connect, via hoses, to the shoulder and end of each arm (Figure 2, purple circles).

Figure 2. Device Air Valves



A foot switch is used to activate the device (pressurize the system) and to deactivate the device (remove pressure from the system). The foot switch is attached via tubing to the control box port. A pressure gauge is present on the control box to verify the pressure in the system. An emergency stop (e-stop) button is also present on the control box in the event of an emergency to evacuate all air from the system.

Use of the device

When using the device, the dental assistant stands behind the chair and holds the "wrists" and "hands" of the device in each hand. The dental assistant then moves the jaw braces into place relative to the patient's jaw with no air pressure in the system. When there is no air pressure present, the "shoulder", arm", "wrist", and

"hand" move freely without resistance. When the brace is positioned correctly on the patient's jaw, the dental assistant presses on the foot switch to pressurize the system with air. This pneumatically locks all parts into the desired position. When removing the device, the dental assistant stands behind the chair and holds the brace with their hand and pushes on the foot switch to eliminate the pressure in the system. Then the assembly can be freely moved and placed behind the dental chair. There is also an e-stop button on the control box that can be used to evacuate the air in the system whereby the assembly is again de-activated and can be moved.

6.1.1 Acquisition

The device will be provided to the participating OMS by the sponsor. The study engineer and study coordinator will bring the device to the OMS's office, set it up and provide instruction on use of the device. The office will also receive a FDA Label and Instructions for the device.

6.1.2 Formulation, Packaging, and Labeling

Label and Instructions for Use of the Jaw Support Device
INTENDED FOR PREMARKET PRACTITIONER PREFERENCE TESTING ONLY

MANUFACTURED and Packed by:
Lab 651
550 Vandalia Street
Suite 224
Saint Paul, MN 55108

DISTRIBUTED BY:
The Restful Jaw Company, LLC
1596 Northrop St.
St. Paul, MN 55108

For product or technical information, contact 1-651-964-2529.

CONTENTS: 1 Jaw Support Device

CAUTION: INVESTIGATIONAL DEVICE. LIMITED BY US FEDERAL LAW TO INVESTIGATIONAL USE.

INTENDED PURPOSE:
This device is for use during the premarket clinical investigation to support the mandible of a patient during oral and maxillofacial surgical procedures including surgical removal of third molars with moderate to deep sedation or general anesthesia.

USE:
This device is fully assembled when shipped. To use, the device MUST be securely attached to the dental chair head rest post. See the chair manufacturer's instructions for removing and reinserting the chair head rest post.

The device requires air pressure to operate. Air hoses are provided with the device to connect it to the air supply in the operatory. If there is no air supply available, then a free-standing air compressor or pressurized tank is used. The air hoses are attached to the back of the chair where quick disconnect fittings are provided to hold them in place.

ATTACHING THE DEVICE TO THE CHAIR

1. Remove the head rest post from the chair.
2. Hold the device with the three black knobs facing you. Turn the center black knob to loosen the head rest mounting plate. See red circle on Figure 1a.
3. Slide the device onto the head rest post so that the knobs are facing away from the front of the head rest towards the back of the chair as shown in Figure 1a.
4. Adjust the position of the device on the head rest post so the device shoulders (shown in Figure 1a in a yellow circle) can rotate freely below the arm rest pads as shown in the blue circles in Figure 1a. If needed, remove the arm rest pads from the head rest.
5. Hand-tighten the center black knob securely to lock the position of the device on the head rest post.
6. Slide the head rest post back onto the chair. Make any adjustments so the device is positioned evenly on the chair head rest post. Note: The device can contact the top of the chair.
7. Once in position, follow chair manufacturer's instructions to lock the head rest post onto the chair, commonly a large knob on the back of the chair. Once the head rest is locked, check that you can still freely rotate the arms without obstruction from the chair or arm rest pads.
8. Ensure a tight fit of the device on the post AND the post in the chair before using the device on any patient. Tighten as needed. Before every procedure always tighten the middle black knob securely. See red circle on Figure 1a.

9. See Figure 1b for a view of the device from the front when the device is in place on the chair and the patient.

FIGURE 1a: Jaw Support Device (Back View)

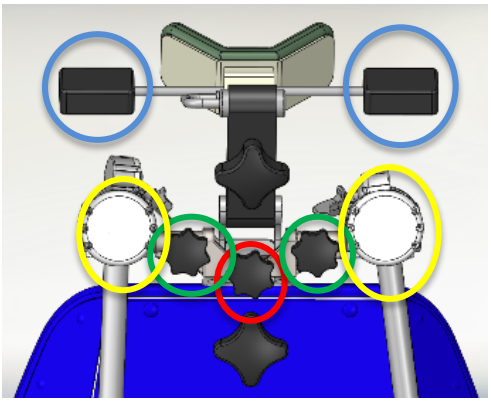
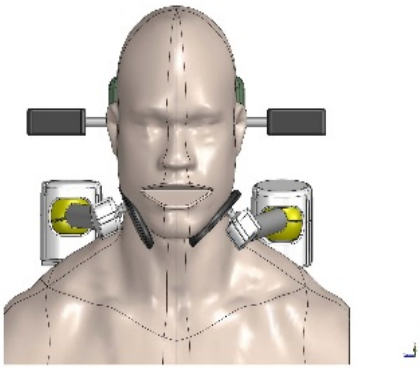


FIGURE 1b: Jaw Support Device (Front View)



CONNECTING THE DEVICE TO AIR

1. Turn on the in-office air compressor, or if using a free-standing air compressor turn it on and charge to maximum tank pressure. A pressurized free-standing tank can also be used. Connect the air compressor or tank hose to the 'supply' port on the device control box shown in the orange circle on Figure 2. Note: The control box is strapped to the back of the chair.
2. Attach air hoses to all four air intake connectors on the shoulder and the end of each arm. See purple circles in Figure 3.
3. Connect air hoses to control box 'output' ports shown in purple-dashed circles in Figure 2.
4. Connect the input and output of hoses of the foot switch (Figure 4) to their respective ports on the control box shown in the blue square Figure 2. The foot switch will be used to lock and unlock the arms (Figure 4).

FIGURE 2 Control Box

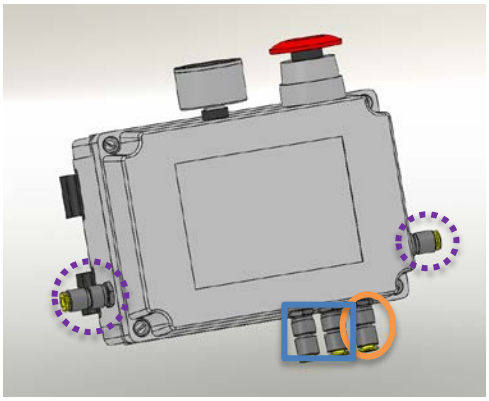


FIGURE 3 Device Air Ports

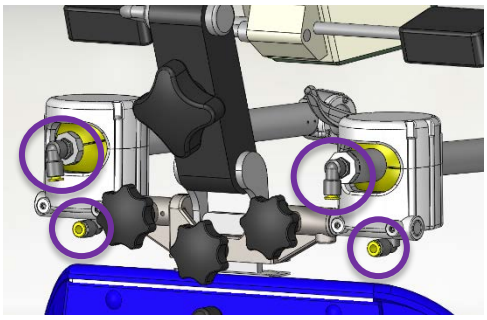


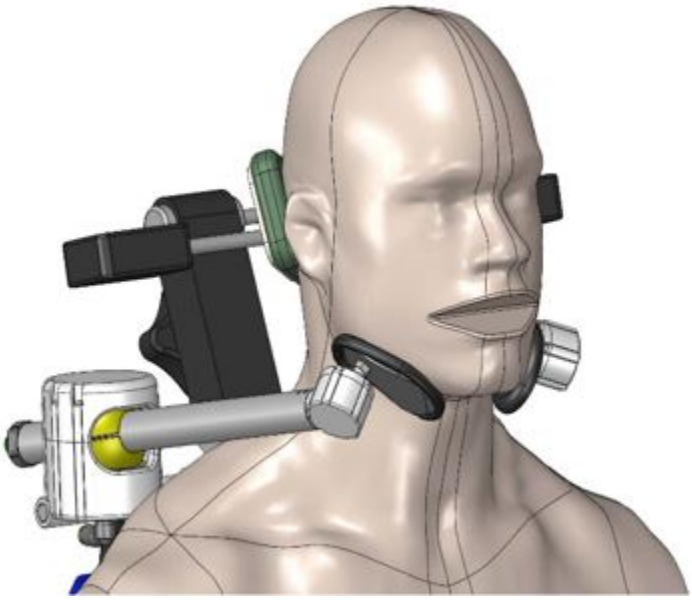
FIGURE 4 Foot Switch

POSITIONING THE DEVICE ON THE PATIENT ON BOTH SIDES OF THE MANDIBLE

1. Seat the patient in the chair.
2. Adjust the head rest position as needed. Ensure the arm rests do not inhibit motion of the shoulder joints (see blue circles in Figure 1a).

3. Loosen the left and right knobs shown in green circles in Figure 1a.
4. Rotate the left shoulder part so the arm will extend slightly above the patient's left shoulder. Tighten left knob.
5. Repeat #3 and 4 with right shoulder.
6. Stand behind the patient and position ***both*** padded jaw braces at the same time under the mandible on both sides. Figure 5 shows the approximate position of the brace on the patient.
7. Press the foot switch to secure the device's position on the patient.

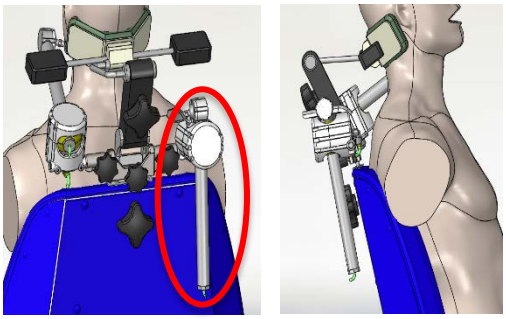
FIGURE 5 Bilateral Mandible Support



REMOVING THE DEVICE

1. To remove the device, press the foot switch to release pressure in the arms. This will make the arms relax.
2. Slide the arms back to their original position near head rest.
3. Loosen the left and right knobs shown in Figure 1a, and rotate the arms back to the stored position behind the chair. Figure 6 shows the right arm in stored position.

FIGURE 6: Device in Stored Position



STORAGE

1. The device can be stored on the head rest post with the arms slid back and folded in a 90º angle as shown in Figure 6.
2. It can also be completely removed from the chair and stored in a dry place at room temperature for future use.
3. Review the chair manufacturer's instructions for removing and re-inserting the head rest on the chair post.

MAINTAINANCE AND INFECTION CONTROL

Disposable pads are placed on the jaw brace. If bodily fluids are present on the device, thoroughly clean all surfaces of blood and other bodily fluids using a standard EPA-registered low or intermediate level disinfectant clinic wipes, or sprays, on all surfaces in contact with the patient, clinician or bodily fluids. The padding on the jaw braces should be discarded and replaced after each use.

PRECAUTIONARY STATEMENTS

If excessive force is placed on the device by the surgeon, then the device could slide to a slightly different position. However, as soon as this force is stopped, then the device will stop moving. If the device malfunctions and loses pressure during the procedure, the passively controlled arms will fall away from the patient's jaw; and the clinician or dental assistant need to be immediately available to provide support for the patient's jaw.

A red emergency air release valve *is located on the back side of the control box* and should be pushed in the event of an emergency and/or if the foot switch is malfunctioning to evacuate all air from the system.

Do not use on any patient where the device cannot be positioned correctly or appropriately adjusted on them for stability and support of the mandible.

PROCEDURES TO FOLLOW IN THE EVENT OF PATIENT EMERGENCY

Remove device from patient contact:

1. If this is an emergency, support the patient's jaw and then press the foot switch. This will release air from the arms which will lose pressure and become relaxed.
2. Slide the arms back to their original position near head rest.
3. Loosen the right and left knobs turning the green-circled knobs as shown in Figure 1a.
4. Rotate the arms back behind the chair as shown in the stored position in Figure 6.
5. Follow clinic's protocol for emergencies.

6.2 Accountability Procedures for the Study Product

The device will be set up for the OMS and will be removed by the study engineer and/or the study coordinator.

7 STUDY SCHEDULE

7.1 Screening

Patients who are planning to undergo mandibular 3rd molar surgical removal with moderate/deep sedation or general anesthesia at the office of a participating OMS will be screened for possible study participation; this may occur in the OMS office prior to or on the day of the surgery, or screening may occur *over the phone.* Office staff will review inclusion/exclusion criteria with the patient via the *Screening Questionnaire* to determine if the patient meets eligibility criteria for the trial. A laminated version of eligibility criteria (see Section 5) as well as a picture of the device will be available for use by the OMS, dental assistants or office staff when discussing the study with the patient.

The procedures listed below are consistent with those included in the Schedule of Events (Appendix A).

7.2 Enrollment/Baseline

If eligible and interested in study participation, the patient will undergo consent procedures via tablet technology. A designated office staff member, most likely the OMS, will execute the consent process according to IRB requirements.

If an enrolled patient declines to provide any of the essential baseline data on the *Patient Contact Information, Patient Demographics*, and/or the *Baseline Patient Questionnaire*, this decision will be considered a voluntary withdrawal from the study (see Section 5.5.1).

Enrollment/Baseline Visit (Visit 1, Day 0)

- Verify, obtain and document consent from potential patient via electronic data capture consent form based on IRB requirements.
- Verify and document Health Insurance Portability and Accountability Act (HIPAA) authorization for use of the patient's Personal Health Information (PHI) in Research, based on IRB requirements.
- Patient completes patient contact information, patient demographics information, and *Baseline Patient Questionnaire*.
- Record results of TMD examination from OMS on *Doctor Surgery Questionnaire*.

- After a patient eligibility is confirmed and they have provided consent, the patient's random assignment to EC or UC is then automatically available to the OMS and their dental assistant on the tablet. The patient is then informed of their group assignment.

- OMS completes usual care extraction of 3rd molars with moderate/deep sedation or general anesthesia and bite block. If patient is randomized into the UC group, the procedure will be completed with a bite block and a DA holding the jaw. If patient is randomized into the EC group, the procedure will be completed with a bite block and the RJ2 device.

- OMS completes *Doctor Surgery Questionnaire*.

7.3 Intermediate Follow-up

Follow-up 1 at 1-Month (Day 30 +2 weeks)

- Patients will complete their *Patient One-Month Follow-up Questionnaire* one-month post baseline independent of an in-office visit.

Follow-up 2 at 3-Months (Day 90 ± 2 weeks)

- Patients will complete their *Patient Three-Month Follow-up Questionnaire* three-month post baseline independent of an in-office visit.

7.4 Final Study Follow-up

Follow-up 3 at 6-Months (Day 180 ± 2 weeks)

- Patients will complete their *Patient Six-Month Follow-up Questionnaire* six-months post baseline independent of an in-office visit.

7.5 OMS and DA Data Collection

Middle of Enrollment Data Collection (when participating office has reached middle of patient enrollment)

- OMS completes mid-data collection *Doctor Questionnaire* Regarding Use of Device.

- DA completes mid-data collection *Dental Assistant Questionnaire* Regarding Use of Device.

End of Enrollment Data Collection (when participating office has completed patient enrollment)

- OMS completes Doctor Questionnaire Regarding Use of Device at the end of patient enrollment.
- DA completes Assistant Questionnaire Regarding Use of Device at the end of patient enrollment.

7.6 Withdrawal From Study

- Record date and reason for withdrawal.
- Consistent with Section 5.5.2, the only evaluations and data collection authorized will be information needed to address an unanticipated problem or other safety issue that may have led to his/her withdrawal from the study.

7.7 Unscheduled Visit

For the purpose of the study, the patient does not need to see the surgeon after their 3rd molars are surgically removed. However, the patient may return to the OMS with concerns after surgical removal of their 3rd molars, including that they are having TMD pain. If the OMS determines that the concern is related only to 3rd molar removal, as described in their inter-office consent form for 3rd molar removal, then they will manage the patient for this. This includes the presence of TMD pain. If the OMS cannot determine if the concern is related to the study or believes it is related to the study, including use of the device, then they will inform the study coordinator who will discuss this event with the project PI. If they deem the event to be an adverse event related to the study, then it will be reported as described in Section 9.4.

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

OMS and DAs – Training:

- The study coordinator will visit each OMS office, review the study protocol and *Manual for Surgeons and Dental Assistants* and demonstrate how to use the device. OMS will be consented, when required by their IRB, at the time of study training. For those dental assistants who are willing to participate, consent will be obtained by the study coordinator at the time of training.

- OMS and dental assistants will be formally and uniformly trained on site by the research coordinator in the dental office where the device will be employed prior to any procedure being performed by the OMS.

Patients – Baseline:

- Patients who have consented to study participation will provide contact information for study follow-up, demographic information and a baseline questionnaire, which will assess: 1) presence of any TMJ noise in past 3 months, 2) presence of any jaw or temple pain, 3) current pain or discomfort associated with their wisdom teeth, 3) Presence of any oral habits, and 4) and general health status.

- Patient will be randomized to: 1) Usual Care (UC) with a bite block and hand support of the jaw, or 2) Experimental Care (EC) with a bite block and the Restful Jaw device to support the jaw.

- The device will be positioned (EC group only) and placed prior to the surgical procedure.

OMS – Baseline:

- The OMS will complete the *Doctor Surgery Questionnaire* for each of the consented patients in both the EC and UC groups after the surgery is completed. The target is to have the OMS complete the questionnaire on the day of the surgery. This questionnaire assesses: 1) TMD pain present in the last 3 months, 2) any TMJ noise present, 3) information on surgical procedures (e.g., teeth extracted, eruption status, presence of pericoronitis or

infection, reason for extraction, procedure employed for removal, estimate of time to extract the tooth and sequence of extractions). In addition, if the device was used, OMS will record whether the use of the device was discontinued during the surgery.

Patient – Follow-up:

- At 1, 3, and 6 months post-baseline, patients will complete follow-up questionnaires via an online questionnaire, which will assess: 1) presence of TMJ noise, 2) presence of jaw or temple pain including frequency, duration, intensity, 3) pain-related disability; 4) factors that increase or decrease their pain, and 4) whether the jaw pain is getting better, worse or staying the same.

OMS and DAs – During data collection phase:

- Both the OMS and any DA(s) who assisted in the procedure(s) and was responsible for using the device during the procedure, and consented to study participation, will each complete a questionnaire about their experience with the jaw support device once during recruitment and once at the end of recruitment. This questionnaire assesses; 1) use of the device compared to a dental assistant holding the jaw, 2) ease and stability of device use, 3) provider's comfort and posture when using the device, 4) fit and manipulation of device before and during procedure, 5) ease of removal of device, 6) efficiency of procedure with device, 7) interference with working field when device is used, 8)airway support with device, 9) impact of dental assistant's other duties with use of the device, 10) use of device in future, 11) thoughts on minimizing injury during procedures, 12) overall opinion of device and 13) any suggestions for modification of the device.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

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

9.1.1 Unanticipated Problems

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

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

Per the definition, only a subset of adverse events would be characterized as UPs. There are other types of incidents, experiences, and outcomes that are not considered adverse events (AEs), but are characterized as UPs (e.g., breach of confidentiality or other incidents involving social or economic harm).

9.1.2 Adverse Events

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.1.3 Serious Adverse Events

A 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

UPs will be recorded in the data collection system throughout the study.

The PI will record all safety events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

9.3.2 Expectedness of AEs

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

9.3.3 Severity of Event

The following scale will be used to grade AEs:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting to IRB and NIDCR

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as a UP 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 a UP;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs that are serious adverse events will be reported to the IRB and to NIDCR within 1 week of the investigator becoming aware of the event.

- Any other UP will be reported to the IRB and to NIDCR within 2 weeks of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All UPs, including UPs that are SAEs, will be reported to NIDCR through the Rho Product Safety centralized reporting system:

- 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

For any UP meeting the SAE criteria, the study surgeon will complete a Serious Adverse Event Form and will submit via fax or email within the timelines stated in Section 9.4.1 to NIDCR's centralized safety system via Rho Product Safety. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

9.4.2 Reporting of SAEs and AEs to FDA

The FDA determined that the RJ2 device is a non-significant risk (NSR) device, and thus the FDA determined that an IDE application is not required to be submitted or approved by the FDA. The FDA further stated that IRB approval of the investigation as a NSR study must be obtained. Therefore, reporting of SAEs and AEs will be to the University of Minnesota and HealthPartners IRBs. NIDCR will be copied on any reports.

9.5 Halting Rules

For monitoring purposes, all AEs will be recorded throughout the trial, and the DCC will track all AEs, including all SAEs.

Decisions about stopping the trial will be made either by the investigators or by the NIDCR in consultation with the Medical Monitor. A formal stopping rule will use the group sequential method of Lan and DeMets, described in more detail in Section 12.3.2, applied separately to the two outcomes "Any AE" and "Any SAE", with P-values computed comparing the groups according to these outcomes using Fisher's exact test. As noted in 12.3.2 regarding efficacy, the exact sequential monitoring plan must be reviewed and approved by the NIDCR in consultation with the MMOR before any interim formal tests occur.

The investigators can stop enrollment in the study at any time based on the occurrence of an AE or UP that they deem of sufficient concern.

10 STUDY OVERSIGHT

NIDCR's Medical Monitor reviewed this clinical trial based upon the trial study design described in the grant application and the non-significant risk (NSR) letter from the FDA that was provided by Dr. Schiffman to NIDCR. In addition to the PI's responsibility for oversight, it has been determined that the trial will be overseen via Medical Monitor Oversight Reporting (MMOR). The MMOR will be requested at 6-month intervals during the data collection phase of the trial. NIDCR's program officer, Dr. Dena Fischer, will provide more information about timelines for reporting after the clinical trial is activated.

11 CLINICAL SITE MONITORING

Clinical site monitoring will not be conducted for this trial. The NIDCR reserves the right to conduct independent audits as necessary.

Quality and integrity of study data and data collection methods will primarily involve quality management (QM) procedures to ensure adherence to human subject protections, including completeness of consenting procedures, and completeness and accuracy of data collection. These QM procedures are detailed in the protocol, Sections 14 and 16, as well as the Manual of Procedures (MOP).

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

The risk of developing TMD pain in patients undergoing 3rd molars removal in the EC group will be statistically lower within the 6-month follow-up interval than in the UC group.

12.2 Sample Size Considerations

This study's sample size is based on the incidence of TMD pain following 3rd molar removal reported by Huang et al.[3] That observational study reported that among patients undergoing 3rd molar removal, the incidence of jaw joint symptoms lasting more than 1 month was 34.3 per 100 person-years. Among those who did not have a 3rd molar extraction, the rate was 8.8, for a relative risk of 3.8. The incidence of TMD pain reported by patients undergoing surgery was over 30%.

Primary analysis. We present a conservative power calculation that assumes we have a single binary outcome (TMD pain yes vs. no) instead of the three measures per person we will collect. The calculations shown below assume two-sided tests and a false positive rate of 5% (alpha = 0.05).

Table 1. Sample size per group

TMD pain incidence	Relative risk		
	2.0	**2.5**	**3.0**
14%	132	65	39
20%	81	38	22
25%	58	26	14
30%	42	18	9

Table 1 shows that 132 patients per group gives 80% power to detect a conservative relative risk of 2.0. To estimate this, we considered a TMD pain incidence of 14% and alpha (type I error) 5%. Table 1's incidences and relative risks are based on data from Huang *et al* .[3] Note that Huang *et al*. reported TMD pain incidence over 30%; the current study will have adequate power if the control group's TMD pain incidence is much lower.[3] We will randomize 294 subjects into the study. Assuming 10% loss to follow-up (90% retention), the total sample size will be 264 (132 per group). The assumed retention of 90% is a conservative estimate based on Dr. Schiffman's experience in his previous RCT, where 98 of 106 (92%) TMD participants completed their 5-year follow-up visit. [20] Therefore, we anticipate, with patient incentives, that we will obtain 90% or more retention at the 6-month follow-up.

12.3 Planned Interim Analyses (if applicable)

No interim analyses are planned.

12.3.1 Safety Review

If the device becomes loose or excessive force is placed on it during the procedure, there is a potential risk this could compromise the support of the patient's jaw, resulting in jaw injury.

While the proposed intervention does not include changes to practice that may harm patient participants, a special focus will be the safety of patients exposed to the study intervention.

We have no specific outcome measures related to safety but participating surgeons will be required to record all AEs, including SAEs, according to procedures specified in Section 9.2

12.3.2 Efficacy Review

Interim analyses are not planned for this clinical trial. However, should it be determined that an interim analysis should occur, the exact sequential monitoring plan must be reviewed and approved by the NIDCR in consultation with the MMOR before any interim formal tests occur. For the repeated tests of efficacy, we will use the group sequential method of Lan and DeMets [21] for which neither the number of tests nor the increments between tests needs to be pre-specified. The approach requires specification of a so-called alpha spending function, chosen to give a low probability of stopping in the early formal analyses. We will propose the well-known O'Brien-Fleming spending function with total alpha 0.05.

12.4 Final Analysis Plan

All analyses will be by intention-to-treat, with participants included in the group (UC or EC) to which they were randomly assigned.

Primary analysis. The primary outcome is incidence of TMD pain <u>within</u> a 6-month follow-up period (a binary dependent variable). The incidence of TMD pain post-surgically will be compared between UC and EC groups. This primary TMD outcome is deemed to have occurred if the patient's self report in the *Patient 1-, 3- and 6-month Follow-up Questionnaires* endorses <u>*either or both*</u> of the following questions: Pain in jaw with wide opening, or pain in temples, jaw joints or jaw muscles.[3] The primary analysis will include all available follow-up measures (1, 3, and 6 months) for each participant to

estimate incident TMD pain. The UC and EC groups will be compared using an analysis that has the form of logistic regression, but which accounts for correlation of visits within participants using generalized estimating equations (GEE) with each participant being a cluster. The analysis will include group (UC vs. EC), which tests whether the two groups differ in overall frequency of TMD pain; time (1, 3, and 6 months, as a categorical factor); and their interaction (i.e., the time-by-group interaction), which tests for different patterns of change over time in frequency of TMD pain.

In the event of noteworthy amounts of missing data (e.g., patients lost to follow-up or questionnaires not completed), we will check the primary analysis by using standard multiple imputation methods, as implemented in the most recent version of the SAS software (SAS Institute Inc., Cary NC, v. 9.4 or higher), to multiply impute missing data and perform tests. Specifically, we will use SAS's FCS method to create 20 "complete" datasets and otherwise use the defaults in SAS's procedures.

Secondary analysis. The primary analysis will not include adjusters, as the randomization should balance the groups. As a check on this, an adjusted version of the primary analysis will include adjusters differing substantially between the two randomized groups, selected from the list of potential adjusters given below (see "Potential Adjusters", below).

Other secondary analyses are as follows:

1. The incidence of TMD pain, as measured with the validated *TMD Pain Screener Questionnaire*[22] *(binary dependent variable)*, will be compared between the UC and EC groups within a 6-month follow-up period based on patients' self report in the *Patient 1-, 3- and 6-month Follow-up Questionnaire*. These analyses will have the same form as the primary analysis.

2. TMD pain intensity, as measured with the validated Characteristic Pain Intensity (CPI) within a 6-month follow-up period (treated as a continuous measure), will be compared between the UC and EC groups based on patients' self report in the *Patient 1-, 3- and 6-month Follow-up Questionnaire*. Unadjusted and adjusted analyses (using adjusters selected as described above) will be performed using GEE as in the primary analysis.

3. Baseline characteristics, specifically all of the potential adjusters listed below (see "Potential Adjusters", below), will be compared between the UC and EC groups. Analyses will use t-tests, possibly after transforming the measure because it has a skewed distribution, Chi-squared test and Fisher's Exact Test.

4. The UC and EC groups will be compared for TMJ noise, pain characteristics (e.g., location in temple or jaw, and occurrence with wide opening of mouth) and change in jaw pain since it started, within a 6-month follow-up period based on patients' self report in the *Patient 1-, 3- and 6-month Follow-up Questionnaire*. These analyses will have the same form as the primary analysis.

5. A descriptive summary of the experiences of surgeons and dental assistants with the new device at mid-way through recruitment of patients and at the end of recruitment based on their self report in the *Doctor Questionnaire Regarding Use of the Device* and *Dental Assistant Questionnaire Regarding Use of the Device*, respectively,

All analyses will use SAS version 9.4 or later (SAS Institute Inc., Cary, NC). All tests will use a significance threshold of 0.05 (2-tailed).

Potential adjusters: The following characteristics will be compared between the UC and EC groups as potential adjusters:

- Patient demographics
- Baseline patient-reported symptoms (e.g., TMJ noise, pain or discomfort around wisdom teeth, frequency of oral habits as measured with the Oral Behaviors Checklist (OBC), and health status; see *Patient Baseline Questionnaire*.
- Baseline clinical findings by the surgeon (e.g., TMJ noise, eruption status, pericoronitis, soft-tissue infection, reason for extraction, difficulty of extraction, length and duration of the surgery, and pain or discomfort around third molars); *see Doctor Surgery Questionnaire*.
- Procedural characteristics, identified by the surgeon (e.g., type of extraction, amount of bone removal, use of grafting); *see Doctor Surgery Questionnaire*.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating office will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

The following will be considered source documents maintained by the DCC via electronic data management system or paper:

- Surgeon log of eligible and ineligible patients who did not enter study
- OMS consent (if applicable)
- Dental Assistant consent
- Patient consent
- Patient HIPAA
- Patient contact information
- Patient demographics information
- Patient Baseline Questionnaire
- Patient One-Month Follow-up Questionnaire
- Patient Three-Month Follow-up Questionnaire
- Patient Six-Month Follow-up Questionnaire
- Screening Questionnaire
- Doctor Surgery Questionnaire
- Doctor Questionnaire Regarding Use of Device
- Dental Assistant Questionnaire Regarding Use of Device

14 QUALITY CONTROL AND QUALITY ASSURANCE

Data collection for this trial will occur via an electronic data capture (EDC) system that employs on-screen data validation and alerts. In addition, key data elements may need to be double entered, or reviewed and affirmed, to confirm correct data entry.

Prior to EDC system development, the system specifications will be carefully evaluated by the study team, DCC, and other stakeholders as necessary (e.g., NIDCR program official). Prior to study launch, the EDC system will undergo user acceptance testing, which will be documented in the Test Summary Report. Further, a data management plan developed by the DCC details quality management procedures including the development of data quality checks in the database system and processes related to quality review and management of data entered.

The architecture of the EDC system and rigorous testing of it prior to study launch provide built-in procedures for maintaining data quality. Additionally, the DCC will produce reports, periodic (at least monthly) and real-time, to monitor data quality. For example, this includes monitoring to ensure present and valid entries in given data fields. Report design will consider available resources in the NIDCR Toolkit for Clinical Researchers (e.g., the NIDCR Quality Management Subject Participant Data Review Tool).

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

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

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB at the University of Minnesota and HealthPartners for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

15.3 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 patients and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the patient. Consent forms will be IRB-approved, and the patient is required to read and review the document or have the document read to him or her. The OMS and staff, with appropriate training, will explain the research study to the patient and answer any questions that may arise. The patient will sign the informed consent document prior to any study-related assessments or procedures. Patients 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 patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. When consenting the OMS (when applicable) and dental assistants, they will be informed that their participation is voluntary and employment is not contingent on participation.

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

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

Racial and ethnic minorities will be included in the study at least proportional to the composition in the dentist's patient population. Individuals of any sex or racial/ethnic group may participate. Patients 18 – 30 years of age will be included in this study.

15.5 Subject Confidentiality

Patient confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to any study information relating to patients.

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.

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

The security features of the data capture system will enforce strict limits on data access for various members on the team. The system will be configured to give study personnel "minimum necessary" access to data given the role of the person in the project.

Certificate of Confidentiality: To further protect the privacy of study participants, the NIH will issue a Certificate of Confidentiality. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

15.6 Future Use of Stored Specimens and Other Identifiable Data

No identifiable data will be maintained after this study beyond what is required by the FDA.

16 DATA HANDLING AND RECORD KEEPING

The study team is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs) and source documentation.

Only study personnel (i.e., PI, Co-Investigator's, study statistician, study coordinator, and DCC personnel) will have access to the study data elements in the study database as described in Section 16.3 Types of Data. All study personnel will have completed the human subjects' protection training elements as required by their IRB.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the PI. All source documents must be reviewed by the study team, who will ensure that they are accurate and complete. The DCC will provide support and processes to allow for accuracy and completeness of data collected. AEs must be recorded by the OMS and staff, and all UPs must be reviewed by the OMS and staff.

The DCC will be responsible for developing, monitoring, maintaining, locking, and closing databases capturing study data. In collaboration with the study team, the DCC will conduct quality control and quality assurance measures to monitor and maintain study data quality. Participating OMS and office staff will be trained on the EDC system by the study coordinator prior to patient enrollment.

16.2 Data Capture Methods

This study will utilize a centralized electronic data capture (EDC) system, developed and maintained by the DCC, for practitioners and patients to enter data onto web-based CRFs. The EDC system employs on-screen data validation utilizing univariate and multivariate alerts, as needed, including valid-value, valid-range, and missing-value alerts. These validations will prevent users from continuing with study data collection if invalid or missing data entries are provided.

The EDC system provides comprehensive and extensible support for both Authentication and Authorization through role-based access control. Access to the EDC system will be available to specific study team members, site study staff and DCC study staff. Staff eligible to access the web application will be assigned an application-specific

user account and will create a unique password to access the application. All access to the systems is based on authorization by the PI and/or the DCC manager or their delegates. Access to sections within the EDC application will be role-based, thereby limiting the user's access only to pertinent information for their role with patients at their assigned study site.

Practitioner- and patient-entered information on CRFs through the application is transmitted to and stored in the EDC system essentially in real time. While practitioners can access the web application, and practitioners and patients can access web-based CRFs, only key study and DCC staff will have direct access to core EDC system and its data. Therefore, each user of the EDC system is permitted access to only the minimum necessary data required to fulfill their role in the study.

16.3 Types of Data

The OMS or their DA will complete the:

- Screening Questionnaire
- Doctor Surgery Questionnaire
- Doctor Questionnaire Regarding Use of Device
- Dental Assistant Questionnaire Regarding Use of Device

The patients will complete:

- Patient Contact Information
- Patient Demographics
- Patient Baseline Questionnaire
- Patient 1-, 3- and 6-Month Follow-up Questionnaires.

16.4 Schedule and Content of Reports

Reports to monitor enrollment will be produced at least monthly during the participant enrollment period, until enrollment targets are attained and enrollment is closed and will be provided to the PI, study team and NIDCR. These reports will contain accrual information in aggregate and by important data variables of interest. These reports will also contain separate sections for each site and the surgeons in each site.

Reports will also be developed to describe protocol deviations, UPs, quality management/monitoring and identified study challenges and solutions.

The MMOR will be produced approximately every six months after enrollment begins until data collection is completed. The exact timeline for the report will be decided by NIDCR. The purpose is to review cumulative enrollment data, participant safety and protocol adherence, and data integrity. The progress report will provide study site status, enrollment and retention status, status of outcome measures, and major protocol changes since last reported, protocol deviations, UPs, quality management/monitoring and identified study challenges and solutions.

Reports to assess study retention will be produced at least monthly until data collection is complete and will be provided to the PI, study team and NIDCR. These reports will provide ongoing monitoring of participant retention. Retention data will be closely monitored overall, by region, and by practice, and futility analyses will be performed as needed. For patients who are lost to follow-up, reports to assess reasons for loss will be produced following the data collection period for each study follow-up assessment.

The procedure for locking the database prior to final analysis will be detailed in the study Data Management Plan. Briefly, the data will be locked and final datasets will be generated at the end of the study. Prior to locking the database, the DCC Data Manager or designee will ensure all data is complete and clean and will obtain approval from the PI to proceed with the data lock. The date and time of database lock will be documented.

16.5 Study Records Retention

Study records will be maintained for at least 3 years from the date that the grant federal financial report (FFR) is submitted to the NIH.

Study documents should be retained for a minimum of 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by FDA or local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual for Surgeons and Dental Assistants requirements. The noncompliance may be on the part of the patient, the investigator, or study staff. As a result of deviations, corrective actions may be developed by the study staff and should be implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and reported to the local IRB(s), according to their requirements. Deviations must also be reported to NIDCR at the timeframe for which the deviations are reported to the local IRB(s).

17 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.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials."

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific *steps to ensure compliance* with NIH implementation of FDAAA.

18 LITERATURE REFERENCES

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SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Manual for Surgeons and Dental Assistants
- Case report forms
- Quality Management Plan
- Data Management Plan

APPENDICES

These documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items require a protocol amendment.

- Appendix 1: Schedule of Events
- Appendix 2: Consent Form(s)

APPENDIX A: SCHEDULE OF EVENTS

Procedures	Oral surgery screening	Baseline	1-month follow-up +2 weeks	3-month follow-up ± 2 weeks	6-month follow-up ± 2 weeks	Middle of data collection device evaluation	End of data collection device evaluation
Assessment of Eligibility	X	X					
Administration of consent		X					
Patient contact information		X					
Patient demographics		X					
Patient Baseline Questionnaire		X					
Randomization		X					
Oral Exam (not a study directed procedure)		X					
Treatment administered by the OMS (not a study directed procedure)		X					
Doctor Baseline Questionnaire		X					
Patient Follow-up Questionnaires			X	X	X		
OMS & DA middle of data collection evaluation of device questionnaire						X	
OMS & DA end of data collection evaluation of device questionnaire							X