Nocturnal Mouth Guards, SOVA vs. Standard Acrylic Orthotic; Phase IV (SISU-SOVA)

NCT 02340663

04/10/2015

1. OVERVIEW AND OBJECTIVES

The **long-term objectives** of this research are to perform large-scale randomized clinical trials (RCT) with SISU mouth guards and SOVA night guards. Towards these long-term ends, the present proposal represents investigations into the most immediate issues that can be addressed in a preliminary study. The **outcome variables** for the present study fall into four categories: (1) fabrication efficacy, (2) compliance, (3) functional efficacy, and (4) user satisfaction. The **immediate goals of this preliminary proposal** will: (1) focus on the SOVA night guard, (2) conduct *in vivo* tests of the SOVA device under controlled clinical conditions, and (3) evaluate compliance and functional efficacy in the 'natural' environment of the patient's home. The clinical application involves protection of dental structures during nocturnal parafunction (sleep bruxism). Because of the potential co-morbidity of bruxism with temporomandibular disorders (TMD), a triad of masticatory myalgia, TM joint noises and/or joint arthritides, TMD signs and symptoms will be considered in future studies. **Future goals** will involve pursuing funding to perform large-scale RCT with both the SISU and SOVA night guards.

Specific Aim 1. Compare the SOVA night guard to the custom-acrylic bite splint in clinical laboratory conditions. Hypothesis: There will be no significant differences between the devices in terms of fabrication efficacy, functional efficacy or user satisfaction.

Specific Aim 2. Compare the SOVA night guard to the custom-acrylic bite splint under ecologically relevant conditions, i.e., the home environment. Hypothesis: There will be no significant differences between the devices in terms of compliance or functional efficacy.

2. BACKGROUND AND SIGNIFICANCE

Bite splints and bruxism. Tooth wear is an extremely prevalent condition, with > 4 teeth per dentition showing significant wear in over 50% of the population, and the prevalence increases with age to 60% by the 7th decade of life (Cunha-Cruz et al., 2010). Moreover, patients who have a history of previous bite splint wear have higher rates of tooth wear (Cunha-Cruz et al., 2010), suggesting that early intervention and long-term splint wear are required to reduce the impacts of bruxism.

Bite splints and TMD. Recent evidence suggests that bite splint use is efficacious in reducing pain symptoms in TMD patients who have been wearing splints for 1 – 6 months; however, within 15 days of terminating splint use, symptoms return (Rehm et al., 2012). These authors conclude that terminating bite splint use in TMD patients is not recommended. If this is correct, then bite splints for TMD symptom management require long-term, perhaps permanent, use. Given that no oral devices are permanent and that custom acrylic orthotics are expensive to replace, there exists a need for an alternative that is feasible in terms of cost, reliability, and regular replacement.

Current standards. There are three recognized oral devices (Maeda et al., 2009), (1) a stock type, which does not adjust to an individual's dentoskeletal morphology, (2) the mouth-formed or boil and bite type and (3) the custom-made appliance. The first two types are over-the-counter (OTC) devices. Bite splints for use with TMD and bruxism are most often custom-made. Either custom-made or the boil and bite type are most often used as mouth guards in contact sports.
Evidence varies as to which of the three oral devices is superior. Most experts presently recommend the custom-made mouth guards for sports purposes (Maeda et al., 2009). For sleep bruxism, custom-made hard acrylic or boil and bite night guards are apparently equally efficacious (Klasser et al., 2010). Finally, a review of RCTs indicates that hard acrylic orthotics were superior to soft appliances or repositioning appliances in managing TMD pain (Fricton et al., 2010).

The issue with custom-made hard acrylic appliances is that they are expensive and cannot be repetitively covered by insurance. Hence, there is a need for an inexpensive, reliable and replaceable alternative that has the functional efficacy of the custom hard acrylic appliances. It is also clear that, for such a device to be a legitimate alternative, it must undergo the appropriate clinical trials (ADA report. Using mouthguards to reduce the incidence and severity of sports-related oral injuries., 2006; Centers for Disease Control and Prevention. Promoting oral health: interventions for preventing dental caries, oral and pharyngeal

cancers, and sports-related craniofacial injuries. A report on recommendations of the task force on community preventive services., 2001; Fricton et al., 2010).

Planned studies will escalate as follows. The initial studies will involve preforming a small RCT with 29 subjects in two groups (below). Subsequent future research will involve full-sized phase III trials of the SOVA night guard, while simultaneously developing a jaw function simulator. The technologies and insights developed from the simulator and phase III trials will provide solid methods for successful phase IV SOVA trials. Subsequently, the advances made with the SOVA studies will provide the necessary means for conducting phase III and IV trials of the SISU mouth guard device, which will take place under the hostile conditions attending contact sports. Of course, additional IRB approvals and funding will be required to pursue these future objectives.

3. METHODS AND STUDY DESIGNS

3.1 Subjects. Sample size estimations (**Table 1**) are based upon a recent review of RCTs for bruxism management, in which acrylic appliances were evaluated (see Appendix 2 in (Huynh et al., 2007)). The mean $\pm$ 1 SD number of bruxism episodes per hour with an occlusal splint (the gold standard) was 3.97 $\pm$ 0.58, and for a palatal splint, the mean $\pm$ 1 SD was 4.45 $\pm$ 0.63. Using these means and the higher SD (0.63), along with an α = 0.05 and β = 0.8, I determined that a study would be sufficiently powered with sample sizes of 29 per group. Based on other Michigan studies, I have estimated recruitment, exclusion and attrition rates, which suggest an estimated initial screening sample size of 120 necessary to end up with 29 per group (**Fig. 1)**. There will be two treatment groups: a group receiving supervised training in the fabrication of the SOVA night guard (SOVA) and a group receiving the Michigan custom-acrylic bite splint (MI BS). Two groups times 29 subjects per group equals 58 total needed for analysis (**Fig. 1**, bottom).

Table 1. Treatment (Tx) groups & sample sizes (N).

Tx	SOVA	MI BS
N	29	29

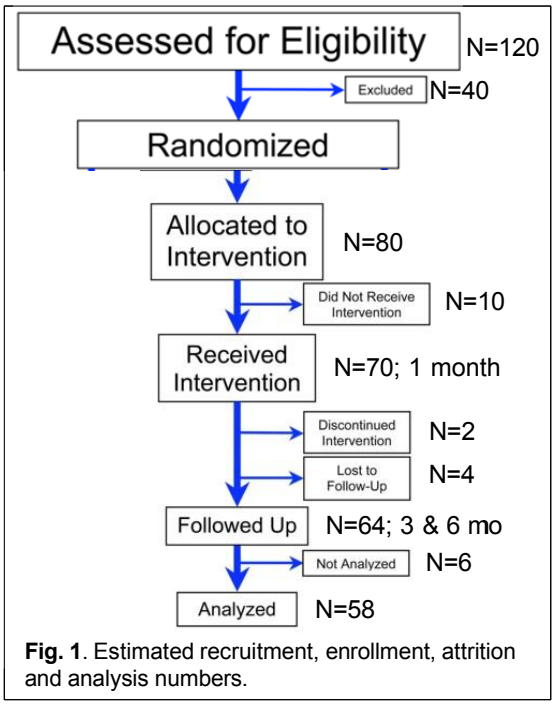

Fig. 1. Estimated recruitment, enrollment, attrition and analysis numbers.

Care will be taken to match the randomized groups for age, ethnicity, gender and TMD signs/symptoms. Alternatively these will be modeled as nuisance variables if attrition rates create bias and/or there is a lack of sufficiently sized screening pools. Subject inclusion criteria will be: (1) adults, male or female, (2) clinical signs of dental wear, (3) report from significant others of nocturnal grinding and clenching noises from potential subject, (4) absence of outstanding dental and medical conditions, including cardiovascular disease, sleep apnea, and diagnosed sleep disorders, (5) full dentition sans 3rd molars, (6) no movement or neurological disorders, (7) no active orthodontics, (8) no outstanding or previous periodontal problems, (9) no removable prostheses, (10) no medication use with movement disorders as known side effects, (11) ability to follow instructions, (12) ability to report to the clinical laboratory at appointed times over the course of the study. The presence or absence of TMD joint noises or masticatory myalgia will be permitted; however, joint arthritides will not be permitted.

3.2 Project design.
Fig. 2 provides an overview of the project flow. Each aspect will be described below.

3.2.1 Screening. Candidates will undergo a screening to assess co-morbidities and to identify inclusion and exclusion criteria. Standard questionnaires and screening instruments include the Research

Diagnostic Criteria for TMD (TMD-RDC) (Dworkin and LeResche, 1992), Jaw Function Limitation Scale (JFLS) (Ohrbach et al., 2008), the TMD Pain Screener (Gonzalez et al., 2011), Measure of Symptoms Sleep Scale (MOS), Perceived Stress Scale (PSS). Additionally, a brief clinical exam will be performed to evaluate dental and medical health, including an intra-oral and extra-oral head and neck examination, heart rate and blood pressure. Subjects meeting the acceptance criteria will be randomly assigned to one of the two groups (**Table 1**) using stratified randomization procedures (Suresh, 2011). Subjects will then have alginate impressions taken, and impressions will be poured up in stone. The models will be used either to fabricate the MI BS or to assess SOVA appliances for fabrication efficacy.

3.2.3. Splint delivery. For the SOVA group, subjects will be asked to fabricate SOVA devices in the clinical laboratory while receiving feedback from trained and calibrated study 'instructors'. Fabrication will proceed according to manufacturer instructions. Calibrated instructors will be blinded to the study's objectives, as will subjects. A "Michigan" acrylic bite splint will be fabricated using standard clinical practice and checked for fit and quality on subjects assigned to the MI BS group.

3.2.4 Subjective fabrication assessment. Standardized questionnaires will be provided to participants and will cover issues of ease of fabrication, ease of instructions, and other related issues for the devices. Box scales will be used to evaluate items individually and separately.

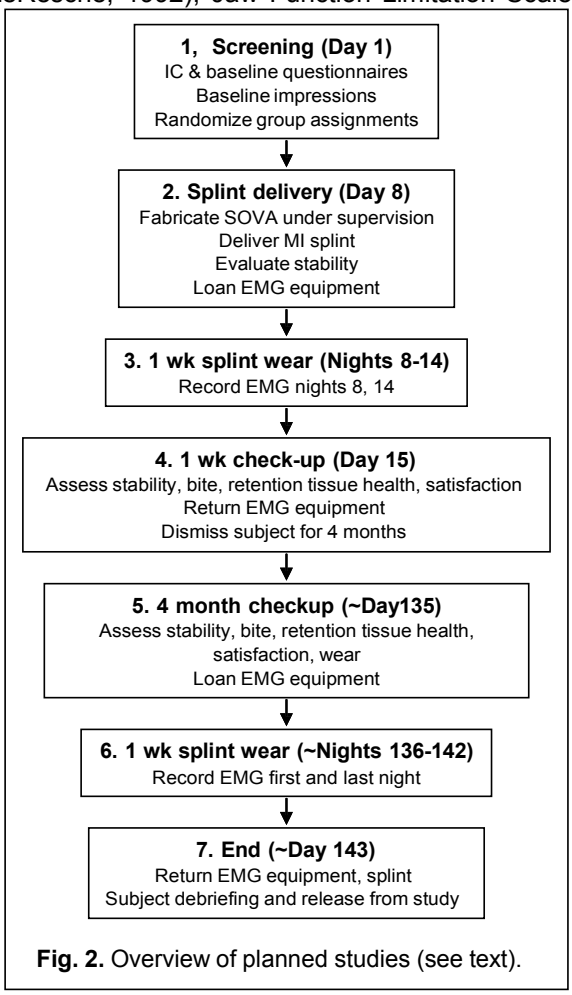

Fig. 2. Overview of planned studies (see text).

3.2.5 Quantitative fabrication assessments. Four aspects of fabrication will be evaluated by investigators: (1) stability—does the device move independently of the maxilla and is the mandible stabilized by the device, (2) retention—does the device resist displacement, (3) tissue adaptation—how much spacing exists between the maxilla and the device and between the device and mandible, and (4) health of the teeth, gingival, tongue, palate and lips.

3.2.5a. Stability and retention will be quantitatively assessed with jaw movement (custom jaw tracking devices in conjunction with a MaxTraq motion analysis system [Innovision, Columbiaville, MI] and EMG [LabChart, ADInstruments, Colorado Springs, CO] data) and force sensors (T-scan, Tektronix, South Boston, MA). For position-stability assessment, maxilla, mandible and the splint will be simultaneously recorded from at least three sites each (to capture 6 degrees of movement freedom). Subjects will clench, grind, perform closed border movements and vacuous chewing (verified with EMG and force sensors). For retention assessment, subjects will perform a series of tests designed to dislodge the device, e.g., tapping, forced blowing, coughing, chewing on gum. Stability and retention indices will be created based on whether device movements vary independently of jaw movements and applied bite forces, and how force sensor output varies during dislodgement exercises. (Note, the force sensors will be placed between the device and the maxilla, so that reductions in sensor output will indicate that the device is being dislodged.) Deviations will be used to form standardized indices of stability and retention, with smaller values representing greater stability and retention.

3.2.5b. Tissue adaptation will be assessed by using a 3D laser scanner. The occlusal, facial and lingual surfaces of the upper arch will be scanned as will the inner surface of the night guards. An index of

adaptation will be developed based on the volumetric spaces separating the teeth from the device, using topological software. Smaller volumes will represent better tissue adaptation. Volumetric indices will be compared between devices via ANOVA or appropriate statistical methods.

3.2.5c Tissue health will be assessed via appropriate, standard methods currently used in cariology and periodontology clinical studies (Monse et al., 2012; Tirapellia et al., 2010). Baseline measurements will be compared with post-device wear measurements. Between-group differences will be studied with a repeated measures ANOVA or appropriate statistical methods.

3.2.6 Compliance assessment. Compliance assessments will focus on: (1) how often the device is worn, (2) whether the device is removed at inappropriate times during the night, (3) whether alternative devices are used. Compliance will be assessed via subject self-report (daily log), nocturnal EMG recording devices and microwear methods. Subjects would be blinded to the purpose of the technological methods. Occlusal microwear patterns are unique to the surfaces against which occlusion occurs, and the microwear changes on a daily basis (Ungar et al., 2003). Hence, microwear assessment provides definitive evidence regarding splint compliance.

3.2.7 Functional efficacy. Two questions will be addressed under functional efficacy: (1) does the device alter bruxing activity, and (2) how do the teeth and device hold up under bruxing activity. Some of the technology used for compliance assessment, above, can be used here. 'Gold standard' methods for evaluating bruxing activity rely on polysomnography (PSG) and EMG activity; therefore, it will be important to employ these technologies for purpose of peer-review publications. To address the second question, how do the teeth hold up, 3-D laser scanning technology will be used to measure changes in macroscopic tooth structure, and confocal microscopy and scale-sensitive fractal analysis will be useful for addressing microwear.

3.2.8 User satisfaction. This will be assessed through a series of standardized questionnaires adopted from other clinical studies, e.g., the Oral Health Impact Profile (Slade and Spencer, 1994), the Tampa Scale for Kinesiophobia: TMD (Visscher et al., 2010), the TMD pain screener (Gonzalez et al., 2011). Questionnaires used in the SISU field tests (SISU mouthguards preliminary results), as well as forced choice, box scales and statistical methods developed in another study (Lin, 2008; Lin et al., 2013) will also prove useful for assessment of patient satisfaction. Also such questions as, does the device hurt or pinch anywhere, does your bite feel 'off' when you first remove the guard, how often do you take out the splint before the night is over, do you experience excessive salivation or dry mouth, do you ever wake up with the splint out for unknown reasons, does the device build up plaque and other deposits through time, do you ever just feel like not wearing it and if so why not, will be used to assess specific aspects of user satisfaction.

Table 2. Summary of objectives, methods and when performed

Assessment	Method or modality (equipment)	When
Subjective fabrication	Questionnaires (na)	Step 2
Stability	Performance during jaw function, bite force and muscle use (MaxTraq + EMG + T-Scan)	Steps 2, 4, 5
Retention		
Tissue adaptation	Shape conformity (3-D laser scanner, topology)	Steps 4,5
Tissue health	Tooth wear and gingival health (standard dental)	Steps 4,5,6
Compliance	Self-report (questionnaires), Evidence of nocturnal use (EMG-sleep + microwear)	
Functional efficacy	Bruxism/TMD evidence, dental changes (EMG-sleep + 3-D scanning + microwear)	
User satisfaction	Questionnaires (na)	

3.2.9 Repeated measures (Step 4 Week 1 check-up and Step 5 4 Month check-up). Compliance, stability, retention, tissue adaptation and health, functional efficacy and user satisfaction will be assessed two times, viz., 1 week after delivery and 4 months after delivery (Fig. 2, Table 2). This will provide a

rigorous data set, reduce subject attrition and thus allow for both publications and further proposal applications to be pursued.

4. STATEMENT OF COLLABORATION AND TIMELINE OF ACTIVITIES

Table 3. Timeline

Task	Sp/Su				F				W				Sp/Su				F				W			
IRB																								
Screening and recruitment																								
Splint fabrication and first week																								
Follow-up 4 months																								
Analysis and Publication																								

Table 3 estimates the timeline for the proposed studies. Each cell represents one month, with years being stratified into trimesters (Spring/summer, Fall, Winter). Based on clinical studies performed on TMD subjects at MICHR and current projects assessing jaw function, I estimate that screening can be completed in 14 months. Actual participation can begin upon receiving IRB approval and identification of appropriate candidates. Studies involve subjects for 6 months. Accounting for lag times involved in stratified randomization, enrollment will probably lag by 1-4 months, indicating that studies will wrap up after 2 years as shown, with enrollment finalized by early fall of the 2nd year, and all follow-ups being completed during the Winter of the 2nd year. The final trimester will be heavily devoted to analysis and publication. Obviously, preliminary analyses (not shown) will begin as soon as data are available (approximately mid-Fall of year 1) in order to assure that experimental procedures are ideal

PI Gerstner has a long-standing collaboration with Dr. Tom Braun, a biostatistician with MICHR, and he has published papers, served on graduate student MS committees and taught in courses with Dr. Braun. Statistical aspects of this project can be handled through this collaboration. PI Gerstner has also collaborated with Dr. Daniel Clauw's chronic pain group, Dr. Shih's mechanical engineering group and movement science groups in the School of Kinesiology. Any and all of these collaborations can be brought to bear on this project to move it forward with scientific rigor and state-of-the-art methods.

5. BUDGET

Personnel
No personnel costs are being requested. The project will be carried out by dental students in the Pathways program of the school of dentistry and undergraduate pre-dental students who will be earning course credit. In this way, these costs can be curtailed.

Equipment
Funds are being requested for a sleep monitoring system (*Biocapture*, EMG sleep system) in order to evaluate compliance and efficacy issue (**Table 2**). The system monitors polysomnographic (PSG) variables to confirm sleep and bruxing events and is a clinical research standard and necessity. The system is critical for evaluating the night guard for compliance and functional efficacy in the home environment. No such system current exists in the Gerstner laboratory.

Amplifiers and jaw tracking system upgrades are being requested for evaluation of bite splint stability and retention in the controlled laboratory setting (Table 2). The EMG system to which the amplifiers will be attached, will be purchased through other funding mechanisms in order to reduce costs to Delta Dental. Funds for the jaw tracking system represent an upgrade to an existing system; the upgrade will automate the analysis. The automation is critical, because it will allow students to do the data acquisition; otherwise non-automated analysis requires trained experts, which would require substantial personnel costs.

Funds are being requested for a *T-scan* bite-force analysis system. This system, currently unavailable in the Gerstner laboratory, is the only system in existence that can reliably and quantitatively check how intra-oral forces impact stability and retention of the splint. Without this system, these aspects of the project would be difficult if not impossible to do.

All equipment and upgrade prices reflect 20% academic price reductions.

Supplies
Funds are being requested to purchase software to analyze tooth and bite splint wear, which are critical for evaluating tissue health, compliance and functional efficacy. The prices reflect large academic price reductions. Laboratory fees are needed for fabrication of the Michigan bite splints necessary for the "gold standard" control group of subjects. The microscope provides an essential and inexpensive means of quality-screening the microwear on stone models before they are shipped for analysis with the confocal microscope (see Other Expenses, below). The use of an inexpensive microscope in the Gerstner laboratory will effectively reduce the costs of the latter analysis by over $2000, thus reducing budget costs by at least $1700.

Other software as well as dental and technical supplies (> $19,000 worth), which are necessary for successful completion of the project, will be purchased through other funding sources.

Other Expenses
Subject fee expenses have been calculated as $20 per visit. As Fig. 1 shows, we estimate that 70 subjects will finish the first appointment. After accounting for dropouts, we estimate that 64 will finish the next two appointments. Hence the fees are calculated as shown on the budget page.
Confocal microwear processing fees are requested. These fees reflect a negotiated $45 / subject rate, and since these microwear processing can be done after other analyses, we can target only those 58 subjects that will be included in the final analysis (Fig. 1, bottom). The processing is necessary to evaluate and fulfill the compliance and functional efficacy aspects of the project.

Indirect costs have been figured based on the modified total direct cost rate (i.e., less equipment) and at 8% as per Delta Dental Foundation's ICR.

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