

***In-Home Study of Intraoral Device for Reducing Snoring
among Habitual Snorers***

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Sponsor: Zyppah

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II. Purpose and Background

The purpose of this study is to evaluate the safety and efficacy of an over-the-counter (OTC) intraoral mouthpiece to reduce snoring. A secondary objective is to evaluate the behavior of patients at high risk for sleep apnea to determine whether they will seek a conclusive diagnosis with a sleep study.

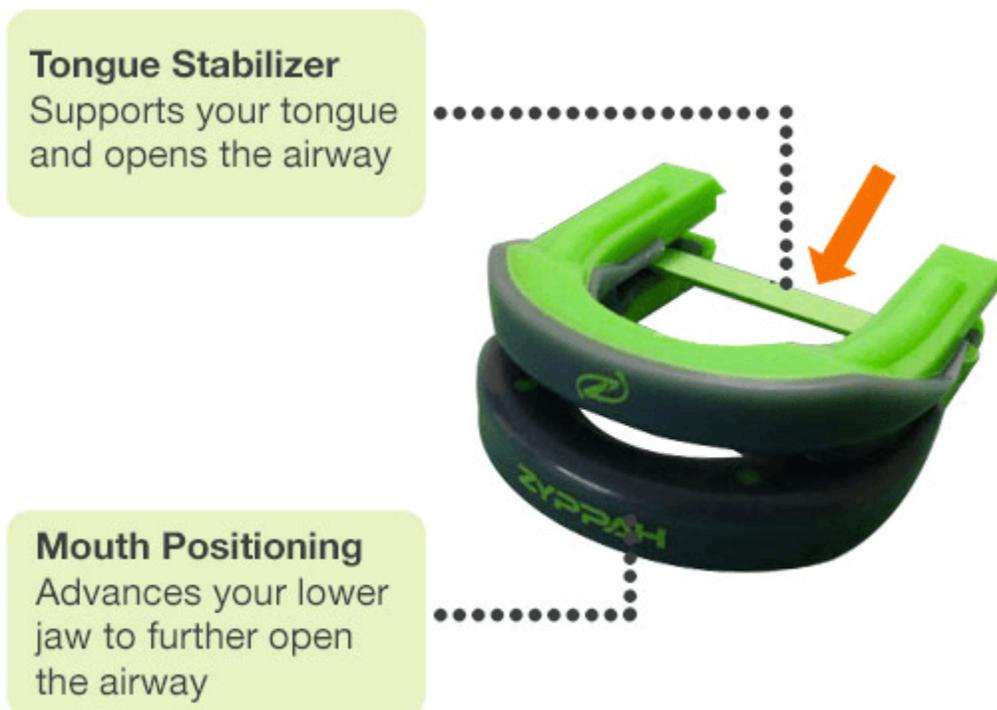
Background

Snoring is a common condition which negatively affects the quality of sleep for both snorers and their partners. It is estimated that nearly 30% of men and 9% of women suffer from habitual snoring, with risk factors including obesity, age (>40), smoking, and alcohol consumption. (Kara CO et al, *The prevalence of snoring in the adult population*, Kulak Buran Bogaz Ihtis, 2005, 14(1-2), 18-24).

Poor sleep quality has been shown to be a health risk for many conditions, including heart disease and hypertension, obesity, diabetes, mood disorders, reduces immune response and many others (<http://healthysleep.med.harvard.edu/healthy/matters/consequences/sleep-and-disease-risk>)

Snoring is often caused by a narrowing of the airway. As air is forced through this narrow passage it vibrates the skin of the airway, causing the distinctive sound of snoring. It is well established that slight changes in the positioning of the mouth, teeth, or tongue can significantly affect snoring.

This study is evaluating the safety and efficacy of an intraoral mouthpiece to reduce snoring. A similar intraoral mouthpiece, Zyppah Boil and Bite, is prescribed on the internet to more than 100,000 people every year. It is cleared under K111680.



The mouthpiece tested in this clinical trial is being evaluated as an over-the-counter product. It has the same features, except it does not move the lower jaw forward. The mouthpiece is designed to change the position of the mouth, and thereby increase the capacity of the airway. It also has a silicon strap placed over the tongue to stabilize it and open the airway. The mouthpiece is placed in boiling water to soften the plastic and then inserted in the mouth, customizing the shape for each user.



One concern in providing an OTC intraoral mouthpiece is the belief that a device intended to reduce snoring cannot reduce snoring associated with obstructive sleep apnea (OSA) and may cause patients not to enroll in a sleep study to diagnose (OSA). However, it is estimated by the American Sleep Apnea Association that 80% of moderate and severe sleep apnea remains undiagnosed. Our theory is that most patients are not making appointments for sleep studies to diagnose their sleep apnea, but are willing to buy an OTC mouthpiece to improve their snoring.

Obstructive Sleep Apnea (OSA)

Obstructive Sleep Apnea (OSA) is a sleep disorder where breathing stops and restarts multiple times during the night, interrupting sleep and often abruptly awakening the patient with a feeling of suffocation. There is significant overlap between snoring and patients with obstructive sleep apnea, which is estimated to affect 3-7% of men and 2-5% of women (Punjabi NM, *The Epidemiology of Adult Obstructive Sleep Apnea*, Proceedings of American Thoracic Society, 5:2, 2008).

The vast majority of those with sleep apnea also habitually snore, though the majority of habitual snorers *do not* have sleep apnea. From prevalence estimates, approximately 10% of male and 22% of female snorers may also have OSA. Women are eight times more likely to have their OSA undiagnosed than men.

The instructions for use of the mouthpiece helps the patient assess their risk of mild, moderate or severe OSA and may encourage them to register for an inexpensive home sleep study. It is hoped that this device may help some habitual snorers identify their risk of OSA and seek treatment. This clinical trial will also monitor the behavior of these users, looking to see whether they i) seek a sleep study, ii) return the device for a refund or iii) decide to use the snoring device. In the first two cases, they will be dropped from the clinical trial.

Study Design

Patients will enroll in the study online. The on-line experience has been carefully designed to mimic the experience of buying the device in a retail store or on a website without consulting a sleep professional or dentist. After filling out a short online questionnaire to determine their initial symptoms and signing the informed consent, the product and instructions will be shipped to them. The device is used for a period of 10 days in the clinical trial. An email prompting them to complete a follow-up questionnaire will be sent ten days after the device has been received. Upon completion of the follow-up survey, the cost of the device will be refunded to the patient, incentivizing completion of the study.

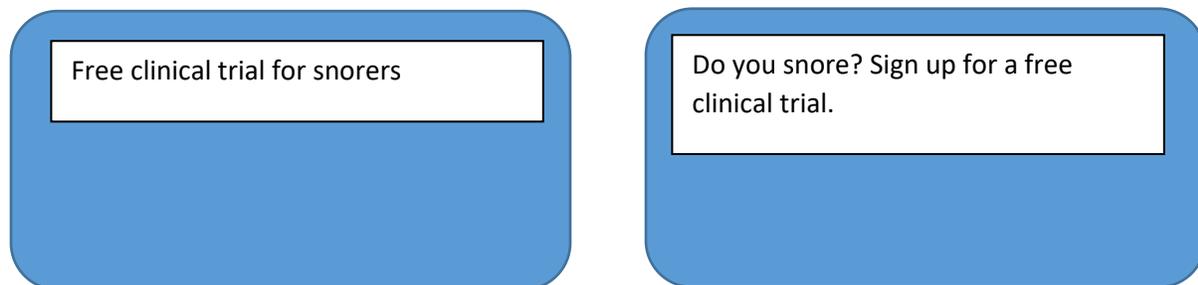
The surveys will ask the patients to qualitatively and quantitatively compare their snoring before use of the device and after 10 days of using the device.

As part of the follow-up survey, users will be asked if they self-identified (on the basis of the product instructions) as being at risk for OSA. If they answer positively, they will be asked about their response, including whether they sought medical care, enrolled in a sleep study, or discontinued use of the device.

A two-sample t-test will be used to analyze the change from the initial survey to the follow-up survey, with patients serving as their own controls.

Subject Selection

When patients go on-line to investigate the current Zypah boil and bite design, they will see one of the following buttons on the web page.



Subjects will be recruited online. A total of 500 patients will be recruited to the trial. Even assuming a 30% drop-out rate or failure to complete the study questionnaires, the remaining patients should be sufficient to generate statistically significant data if the device is effective.

Gender

No effort will be made to differentiate users based on gender, and there are no gender-specific enrollment restrictions. It is anticipated that the enrollment in the study will reflect the prevalence of the condition in the general population, with men comprising a higher percentage of the study population. Pregnant women will be allowed to enroll in the study, as this is a non-significant risk study and there is no rationale for any additional risk associated with pregnancy.

Age of Subjects

The only restriction on age is over the age of 18. It is anticipated there will be a broad range of ages represented.

Racial and Ethnic Enrollment

There are no racial or ethnic limitations on enrollment, and it is anticipated the study population will match the patient population at large. No data will be collected on racial or ethnic identification.

Inclusion Criteria

- Over 18 years of age
- Living in the United States
- Signing the Informed Consent Form

Exclusion Criteria

- Missing teeth (as the device won't be properly fitted)
- Any severe breathing or respiratory disorder, such as chronic asthma, emphysema, COPD, or a similar condition
- Poor dental health, such as severe gum disease, loose teeth, an abscess, mouth sores, or bleeding gums
- A dental implant placed within the last three months
- Diagnosed with a Temporomandibular joint condition (TMJ)
- Actively experiencing any mouth or jaw pain, including clenching of the teeth, grinding, or any other physical injury to the jaw or teeth
- Full dentures
- Braces
- Diagnosis of sleep apnea
- Less than 18 years of age

Vulnerable Subjects

No vulnerable subjects will be recruited for this study.

Methods and Procedures

Methods and Procedures

Subjects who are interested in reducing their snoring will be recruited online. In order to participate in the trial, they will complete a pre-trial questionnaire, as well as review and sign the Informed Consent.

Assuming they satisfy the Inclusion and Exclusion criteria and sign the Informed Consent (includes the inclusion/exclusion criteria), they will purchase the device for \$90. The intraoral device and patient instructions will be mailed to them (Attachment E).

Once the subject is able to participate in the study, the device is placed in boiling water to soften it. While still warm, the device is placed in the mouth and molded to the individual patient. This is the same procedure used with many intraoral mouthpieces and devices including the Zyppah Boil and Bite.

The subject will be asked to use the intraoral device each night for ten consecutive nights. After they have used the device for ten days, a follow-up survey will be emailed to the subject. The patient will respond to the questions in the survey. After they have completed the follow-up survey and returned it, the subject will receive a full refund for the cost of the device (\$90). This is intended to increase compliance with the protocol.

This study will also evaluate the response of subjects who are at high risk of obstructive sleep apnea. The product instructions will contain a brief questionnaire (Attachment D, STOP-BANG Survey) assessing the subject's risk for OSA. If they are determined to be high-risk by the self-administered questionnaire, they will be given the following options: 1) complete a full, overnight in-office sleep study, 2) complete a discounted in-home sleep study, or 3) discontinue use of the device and return it for a full refund. The response of these subjects will be monitored to see how they respond and whether they continue to use the device or seek medical attention to evaluate their risk of sleep apnea.

This is a non-significant risk study, and the only 'extra' requirements for this study are the completion of the pre-study and post-study questionnaires by the patient.

Data Collection

- Attachment A is the list of questions to gather personal information about the subject, including age, gender, weight, height and contact information. This will allow for the calculation of Body Mass Index (BMI), a well-known risk factor in both snoring and obstructive sleep apnea. This attachment also contains the Inclusion/Exclusion criteria, where potential subjects will be asked to review and certify that they meet the requirements of the trial (they will also see this information later in the process at the Informed Consent).
- Attachment B is the Visual-Analog Scale (VAS) asking potential subjects how much their snoring is bothering them and their partner (if applicable). The VAS method is commonly used and has been validated for patient satisfaction (Brokelman et al, 2012).
- Attachment C is the Snoring Severity Scale (SSS). This validated, three-question survey has been shown to accurately assess the severity of snoring and the risk for obstructive sleep apnea (Morris L et al, 2008)
- Attachment D is the Stop-Bang Assessment, which is the most frequent assessment used to determine the risk of sleep apnea. This 8-question survey has been validated as a risk assessment for moderate to severe sleep apnea (Nagappa et al, 2015).

The pre-questionnaire will consist of Attachments A, B, and C to establish a baseline. The post-questionnaire will consist of Attachments B, C, and D, also allowing the study to evaluate the response of subjects at high risk of OSA.

Data Analysis and Monitoring

The primary endpoints, a VAS assessment of snoring and the Snoring Severity Scale will be analyzed using a two-sample *t*-test comparing the pre-study and post-study questionnaire results. The ANCOVA method may also be used to evaluate the impact of different variables, like age, weight, gender, or others, on the study results. There are no potential serious risks to patients, and no stopping criteria that need to be analyzed during the study.

In determining sample size, it was estimated that the device would produce a 15% improvement in snoring, as measured on the VAS. With a level of significance of $p < 0.05$ and a power of 80%, approximately 350 subjects will need to complete the study to generate statistically significant data. Assuming a 30% dropout rate for non-compliance with the study or the discovery of moderate to severe sleep apnea, 500 subjects will be enrolled in the study to ensure the study is adequately powered.

Data Storage and Confidentiality

Data will be collected via a password-protected website and confidential email forms. The results will be securely stored in password-protected cloud storage and then downloaded onto a personal computer to be compiled in Excel. Once transferred to Excel, the data will also be placed into a password-protected file. This data will be available to the study coordinator alone, as the principal investigator is blinded (a precaution since he has a financial interest in the device). Subject identifiers will be necessary, but only the study coordinator will have access to the data with subject identifiers. These identifiers will be removed before any data or statistical analysis is conducted. The principal investigator will be provided the subject identifier and data for any patient that has an unexpected serious reaction to use of the device for analysis and response as well as notification of regulatory bodies and the investigational review board.

Transition from Research Participation

As this research study only asks patients to use the product as they would normally, subjects will continue with their use according to the device instructions, and are free to stop use at any time following the post-study survey after 10 days of application.

Statistical Analysis

A two-sample *t*-test will be used to compare the results from the pre-trial and post-trial questionnaires. Statistical significance will be set at a 95% confidence level ($p < 0.05$).

Risk/Benefit Assessment

Definition of Significant Risk (SR)/Non-significant Risk (NSR) Study

Under 21 CFR 812.3(m), an SR device means an investigational device that: i) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; ii) Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; iii) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or iv) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device study is one that does not meet the definition for an SR device study

Risk Category

The risk the research presents is minimal. The chance of harm or discomfort is not higher than subjects may experience in daily life. There are many over-the-counter mouthguards and intraoral devices on the market, with a safety profile that has been established for nearly 40 years. The probability and magnitude of potential harm is well within the routine dental examination of healthy persons.

In addition, this device has been used on the market (for a different application) for several years, and more than 100,000 users have demonstrated the low risk of this device. Should any complications occur, use of the device can immediately be discontinued.

There is a risk that the patient has undiagnosed OSA, but this risk is lowered by participating in the study and taking a survey to indicate the level of the risk. No additional risk is incurred by a patient with OSA.

Potential Risks

One potential risk is overheating the moldable material when fitting. The device is placed in boiling water to make it pliable and then molded to the individual user. These 'boil and bite' mouthguards have been on the market for more than 40 years, and this device has no higher risk than these OTC products currently on the market. The product instructions are clear about instructing patients to ensure that the mouthpiece is at a suitable temperature prior to application.

A silicon strap on the device keeps the tongue from falling back, preserving the airway. It might be possible for this strap to break free and be swallowed. This is an unlikely risk, as it is held in place by two different attachment points, so even if one side of the strap were to break free, there would no longer be any stress on the other side of the strap, which makes it highly unlikely that both sides of the strap would break at the same time. During the 510k approval process for the Zypah Boil and Bite, the FDA was presented with data showing the forces necessary to break the silicon strap. With more than 100,000 users of the product per year, there has not been a single reported or known incident where both sides of the strap have come off. However, even if the silicon strap were to break free, the silicon is inert and should not cause any health concerns if swallowed.

The device does not advance or adjust the position of the jaw, so there is no risk of TMJ issues or bite changes. The top and bottom halves of the device are locked together, preventing any jaw advancement.

One potential concern is the ability of the mouthpiece to pull out fillings or crowns. However, the device is made of a soft material with limited retentive abilities. With more than 100,000 users of the product, no known incidence of a filling, crown, or tooth being pulled out by the device has been reported. In addition, the device is made of the same material used safely for more than 40 years with mouthguards and other intraoral devices.

Mouth or tooth soreness can also result from the use of any intraoral device. If a patient experiences any significant soreness, it is likely the result of an improper molding of the device to the teeth. The device can be re-molded up to three times to make sure a correct fit is generated. If the patient is unable to generate a correct fit and the tooth soreness persists, they are instructed to contact customer service and discontinue use. This risk is identical to that of other OTC mouthguards.

Protection against Risks

To minimize the risk of contacting the mouth with a hot mold, the instructions for use have multiple bolded, red warnings about the boiling water. The risk of the silicon strap breaking free is mitigated by the design of the device, which makes it highly unlikely that it would break free of both attachment points, as well as by the inert silicon composition. The material that the device utilizes minimizes the risk of pulling out any dental fillings or crowns, and the ability to re-mold the device if there are any sore spots reduces the risk of mouth or tooth soreness. If there is any lingering mouth soreness, it should be temporary and cease when use of the device is discontinued.

Alternatives to Participation

Participants have many other options to choose in trying to reduce or eliminate snoring. Nose strips, which attempt to increase the amount of air that can pass through the nasal passage, are available over-the-counter. Other intraoral devices designed to combat snoring are available as either over-the-counter or prescription devices. Simple lifestyle changes, including losing weight, avoiding alcohol

consumption prior to sleeping, and sleep position can also be effective for some patients with habitual snoring.

If the more serious condition of severe obstructive sleep apnea is suspected, patients are encouraged to go through a sleep study to conclusively diagnose sleep apnea. Sleep apnea can be treated with a CPAP machine, or with various other intraoral devices under the care of a sleep specialist or dentist.

Subject Identification, Recruitment, and Consent

Method of Subject Identification and Recruitment

Subjects will self-identify as habitual snorers and be recruited to the study when they visit the Zypah website using the buttons shown above. Once the potential subject expresses their potential interest in the study by pressing the button, they will be taken to a separate page where they will receive the following notice.

“This clinical study is intended for patients 18 years or older who live in the United States. If you have any of the following conditions, you cannot participate in the study:

- Missing teeth (as the device won't be properly fitted)
- Any severe breathing or respiratory disorder, such as chronic asthma, emphysema, COPD, or a similar condition
- Poor dental health, such as severe gum disease, loose teeth, an abscess, mouth sores, or bleeding gums
- A dental implant placed within the last three months
- Diagnosed with a Temporomandibular joint condition (TMJ)
- Actively experiencing any mouth or jaw pain, including clenching of the teeth, grinding, or any other physical injury to the jaw or teeth
- Full dentures
- Braces
- Diagnosis of sleep apnea

If you do not have any of these conditions, you may participate in the study. As a participant, you will be provided with a free dental mouthpiece that you wear when sleeping to hopefully reduce or eliminate your snoring. To participate in the study, you will also be required to fill out a pre-study and post-study survey that will take about 5 and 10 minutes respectively. If you would like to participate in the study, you will be asked to pay \$90 for the device, which will be refunded to you once you complete the surveys, fill out the pre-study survey and sign an informed consent, which provides you with all the details of the study. If you would like to participate, please click NEXT.”

Process of Consent

Consent will be obtained through online forms. The respondent will read through and initial at the primary sections throughout the informed consent, ensuring they have reviewed the document, before providing an electronic signature after reviewing the Informed Consent in its entirety.

There will be no coercion or undue influence, as these subjects are not being reimbursed for participating in the study (other than receiving the study materials free of cost) and are free to decline to participate at any point in the enrollment process.

Subject Capacity

All subjects will have the capacity to give informed consent.

Subject Comprehension

Comprehension will be addressed by having the prospective subject read and initial at the conclusion of each segment of the informed consent, ensuring they have read and comprehend the material. If they do have questions about the language or meaning of the document, they will be able to contact the sponsor directly to ask any questions they might have.

Consent Documentation

Consent will be required before the subject can go forward with the ordering process of the study, ensuring that no subjects will be able to enter the study or receive the product without having read and agreed to the informed consent. This will be documented and stored using the same system described in the Data Storage section.

Costs to the Subject

The subject will not incur any costs as the result of participating in the study. The subject will pay for the device upon enrollment, at a cost of \$90, which will be refunded immediately after the completion of the follow-up survey. Should the subject not complete the follow-up, the cost of the device would not be refunded, encouraging compliance with the study protocol. Should the subject have any costs related to complications of the device, that are not covered by insurance, they will be paid by the Sponsor.

Payment for Participation

No payments will be given for participation, other than providing the study device at no cost (should the subject complete the trial).