PROTOCOL TITLE:

Use of novel Sinusonic device for prevention of community acquired upper respiratory infection (URI)

The study will be conducted in compliance with the clinical study protocol, international good clinical practice principles (International Conference on Harmonization [ICH]-Good Clinical Practice [GCP]), and regulatory authority requirements.

PRINCIPAL INVESTIGATOR:

Dr. Ted A. Meyer and Dr. Shaun Nguyen

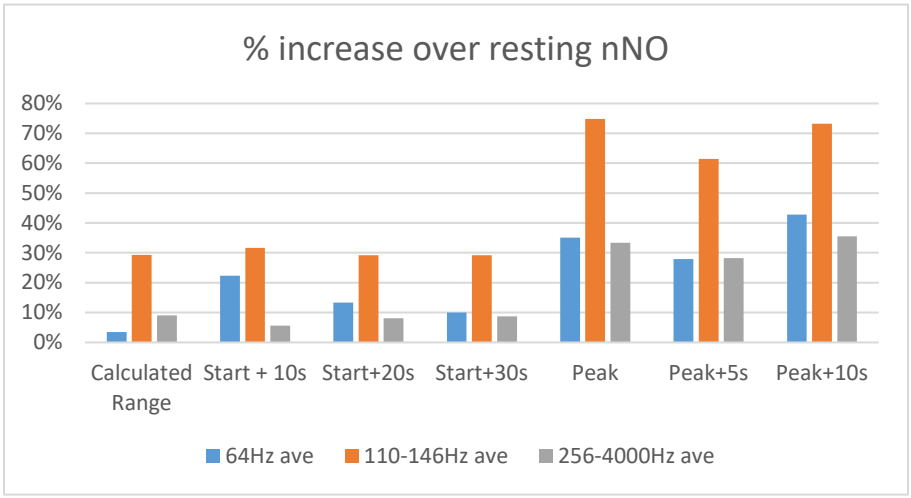
1.0 Objectives / Specific Aims:

Sinusonic is a simple handheld device that uses acoustic vibrations (128Hz) and positive expiratory pressure as patients exhale through their nose. Beneficial effects have been shown in a clinical trial studying chronic rhinitis that showed improvements in nasal blockage/congestion, nasal drainage, nasal/sinus pressure and sense of smell (Soler ZM etal available at https://onlinelibrary.wiley.com/doi/full/10.1002/alr.22537). A small unpublished pilot study demonstrated >70% increases in peak nasal nitric oxide (NO) after one use of Sinusonic. NO is known to stimulate mucociliary clearance and has antiviral properties. Given that Sinusonic improves nasal congestion, nasal drainage and appears to increase NO which has antiviral properties, our hypothesis is that use of Sinusonic will decrease the frequency, severity and duration of community acquired viral URIs.

Aim 1: To determine if Sinusonic decreases the number of URIs experienced during an 8 week fall URI season. Subjects will use an active device (positive expiratory pressure and 128 Hz) or a sham device (no positive expiratory pressure and 1,000 Hz) for 1 min three times a day for 8 weeks. Daily URI symptoms will be recorded electronically.

Aim 2: To determine if Sinusonic decreases the severity and duration of community acquired viral URIs. Subjects will use active or sham device as above. Severity and duration of URIs will be recorded using daily symptom diaries.

2.0 Background



Sinusonic is a simple handheld device that uses acoustic vibrations (128Hz) and positive expiratory pressure as patients exhale through their nose. Beneficial effects have been shown in a clinical trial that showed improvements in nasal blockage/congestion, nasal drainage, nasal/sinus pressure and sense of smell (Soler ZM, etal). Some of these benefits occurred after one use of the device and these benefits continued to increase throughout the 5 week study. In this clinical trial, approximately 80% of patients demonstrated improvement. A small unpublished pilot study demonstrated >70% increases in peak nasal NO after one use of Sinusonic. Our hypothesis is that use of Sinusonic improves nasal congestion, mucociliary clearance and exhaled NO, all of which decrease viral infections.

3.0 Intervention to be studied

Subjects will be screened for likely inclusion during the summer months. Baseline demographics, medical comorbidities, and URI symptoms will be assessed. Informed consent will be completed.

The fall URI season typically runs through September and October (Turner R etal). Towards the end of screening, all subjects will be randomized 2:1 to active use of Sinusonic (128Hz) for 1 minute 3 times daily or an identical "placebo" device that emits a frequency of 1,000 Hz and has the ball valve modified to eliminate positive expiratory pressure. Devices will be shipped to home addresses via overnight mail. On September 1, 2020 all subjects will begin daily use of their assigned device. Subjects will remain blinded as to treatment arm until study completion.

Subjects will be asked to complete a brief daily questionnaire on URI symptoms and whether or not they feel as if they have a "cold". Previously validated questions for viral URI studies are rating 8 items on a likert scale from 0 (no symptoms) to 3 (severe symptoms) (Jackson GG, etal). The 8 symptoms are: sneezing, runny nose, nasal obstruction, sore throat, cough, headache, malaise, and chilliness. A Total Symptom Score (TSS) will be the sum of each symptom to provide a daily score ranging from 0 to 24. Prior studies have defined the common cold as present when:

1) TSS $\geq$ 14 PLUS moderate or severe nasal discharge x 3 days OR patient subjective impression they have a cold OR

2) TSS < 14 AND moderate or severe nasal discharge x 3 days AND subjective impression they have a cold

Answers will be uploaded to secure REDCAP database. The study duration is 8 weeks. At the end of the study, subjects will be asked questions regarding device safety and tolerability.

Our primary outcome will be absolute number of URIs experienced during the 8 week study period. Secondary outcomes will be time to first URI, duration and symptom severity of viral URIs. These metrics will allow us to determine if Sinusonic decreases the frequency of URIs, as well as potentially shortening the duration or decreasing the severity of URIs.

3.1 Device Instructions

Instructions for use:

1. Hold the SinuSonic device at a 45-degree angle
2. Deep breathe in through mouth
3. Hold the SinuSonic to your nose and blow out into the mask of the SinuSonic. The goal here is to hear the "target flutter" sound that is desired during treatment with the SinuSonic
4. You will feel a little resistance to breathe out and a vibration sensation from a speaker in the device
5. Remove the device to "blow the nose" if nasal drainage occurs
6. Return the device to the nose then breathe in and out thru the nose to try and hear the "target flutter" sound
7. Time of use is 1 minute of nasal breathing with the device - as tolerated
8. Goal is to use Sinusonic 3 times per day with uses separated by at least 5 minutes.

3.2 Device Usage and Safety

The SinuSonic consists of a fully-disposable medical grade silicone nosepiece mounted to a resin body. The device is equipped with a flutter valve located at the top of the device which creates gentle, self-guided oscillating expiratory resistance.

The SinuSonic is a legally marketed device used in accordance with its labeling. It is substantially equivalent to many Class I OTC devices with the same intended use and indications for use in clearing mucus to improve air flow, such as the Navage Nose Cleaner.

4.0 Inclusion and Exclusion Criteria/Study Population

Inclusion Criteria

- Adults 18 years or older with no transient symptoms of any URI or allergies at baseline.

Exclusion Criteria

Any transient ENT condition that may impact upper airway to include acute sinusitis or otitis.
Any upper respiratory illness within last 2 weeks
TSS will be measured at baseline as described above and must be <9 for inclusion (Eccles etal).
Topical decongestant use in last week
Current nasal crusting or history of ulceration or perforation
History of severe nose bleeding within last 3 months
Known pregnancy
Immunosuppressed condition or on immune modulating medications such as prednisone or chemotherapy
Allergic sensitivity to silicone or any other component of device
Inability to read and understand English
Inability to perform treatment due to underlying medical condition

After confirming that subjects meet inclusion criteria, they will be entered into study as outlined below. Subjects who have URI symptoms at the beginning of the study will specifically be excluded, as the purpose of the study is prevention of URIs, not treatment of pre-existing URIs.

4.1 COVID19

The purpose of the study is to see if Sinusonic prevents community acquired viral URIs, not to treat existing infections. So patients must be asymptomatic at the beginning of study. As this study is not conducted exclusively on MUSC patients and is being done virtually (to minimize exposure and increase safety during the covid pandemic), we do not have the ability to perform widespread covid testing on hundreds of asymptomatic patients. So it is possible that someone will have undiagnosed covid.

5.0 Number of Subjects

Prior research reports (Turner etal) using identical outcome measures and studying community acquired URIs in the fall season report that approximately 60% of subjects suffered from a viral URI (range 48% to 75% in each arm). We are planning to include 300 subjects (200 active device, 100 sham device). If we conservatively assume that only 50% of sham device subjects get an URI, we will be powered to detect a decrease to 33%.

6.0 Setting

Research will be conducted at geographical locations in the Southeast (SC, NC, GA, VA) that have similar fall viral URI seasons. Potential participant screening for all subjects across all aims, as well as informed consent and baseline evaluations, will occur remotely to avoid any risk to research personnel. All baseline and follow-up measures will be collected remotely using REDCap at 4 and 8 weeks.

7.0 Recruitment Methods

We will publicize the study through MUSC and Sinusonic social media targeting geographic regions described above. A number and email will be provided for subjects interested in participating. Only one subject per household can be enrolled.

8.0 Consent Process

Patients who respond to social media recruitment will be contacted by study personnel to determine eligibility. As the goal is to recruit subjects from throughout the southeast, no in person visits will be conducted at MUSC and it will be necessary to obtain remote informed consent.

The remote consent process will include an informed consent discussion with the potential participant and involve the participant signing and returning the informed consent document to the researcher. The informed consent discussion will occur over the phone. The documentation of consent process will include sending the informed consent document to the subject for signature and transmitting it back to the research team to be signed by the researcher before any research procedures begin. The document will be sent using the electronic consent option in REDCap.

A member of the study team will describe in full detail the study and the informed consent form to the potential subject. The study team member will explain:

1. What would be different if the patient participated in the study versus receiving standard of care treatment.
2. The study is voluntary participation, patient may withdraw any time, and PI may take patient off study at any time.
3. The reason for doing the study
4. How many people will be in the study
5. Who is eligible to participate in the study
6. Details regarding the study device.
7. What medical assessments/questionnaires they will have and how often
8. Risks involved in participating in a study
9. What information will be gathered

The prospective participant will be given adequate time to review the informed consent form and ask any questions that they have before the consent is obtained. Participants will electronically be sent a signed copy of the ICF.

9.0 Study Design / Methods

This study is designed as a pilot study.

Data will be collected by the study investigators as well as the subjects themselves throughout the entirety of the study. The data will consist of answers from subjects for questionnaires asked by the clinicians as well as self-reported answers from the subjects.

9.1 Schedule of Events

All subjects (N=300)	Screening	Baseline assessment	Study start	Study endpoint
Date	Up to -30 Days	Day 1	12 Days	60 Days
Informed consent	X			
Inclusion/exclusion criteria	X	Reconfirm TSS<9		
Medical history	X			
Randomization (2:1 active:sham)		X		
Distribution of Sinusonic		X		
Viral URI questionnaire		X	X	X
Safety questions				X

10.0 Data Management

All analyses and graphs will be performed with SPSS 24.0, Sample Power 3.0, and Sigma Plot 10.0 (SPSS, Chicago, IL.). Disease information and demographic variables, such as age, gender, race, and VAS scores will be summarized using frequencies, means, and standard deviation as appropriate. Our primary outcome metric is number of viral URIs as defined above. Secondary outcome metrics include average duration of URIs and severity of symptoms (as measured by TSS) of URIs. Categorical variables will be compared using Chi Square or McNemar's test. Continuous variables will be compared using One-Way ANOVA with repeated measures follow by post-hoc analysis. Data regarding safety and patient satisfaction will be summarized for each time point. A p-value ≤ 0.05 will be considered statistically significant. Due to the exploratory nature of this study, no p-value correction (ie Bonferroni) will be applied.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Safety will be monitored throughout the study based on the monitoring of adverse events, via electronic data collection. The period of observation for collection of non-serious adverse events extends from the time the subject gives informed consent until the completion of the End-of-Study visit or Early Termination Visit. Serious adverse events (SAE) will be reported to the MUSC IRB and to the sponsor from the time of informed consent through 30 days after the last use of the SinuSonic. Adverse event data listings will be reviewed by Principal Investigator and the research team at regular intervals throughout the study.

Safety data listings will be reviewed by Principal Investigator, Co-Investigators, and the research team at regular intervals throughout the study.

Safety will be monitored throughout the study based on monitoring of adverse events, and through collection of symptoms electronically. Collection of symptoms will occur via the Daily URI Symptoms Score questionnaires that are electronically sent to the consented patients.

The period of observation for collection of non-serious adverse events extends from the time the subject gives informed consent until completion of the End-of-study visit or Early Termination Visit. Serious adverse events (SAE) will be reported to the IRB and to the sponsor from the time of informed consent through 30 days after the last use of the SinuSonic. Adverse event data listings will be reviewed by the principal investigator, co-investigators, and the research team at regular intervals throughout the study.

All AEs, regardless of seriousness or relationship to SinuSonic use, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be reported to the Healthy Humming, LLC. All AEs which follow the IRB qualifications will also be reported to the IRB within 24 hours of site knowledge of the event.

The Investigator will take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last timepoint per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by Healthy Humming, LLC.

In the case of occurrence of an SAE, the Investigator will immediately (within 24 hours) report the event to Healthy Humming, LLC and to the IRB, as applicable.

12. Withdrawal

At any point during the study, a subject may withdraw from the study. The subject may refuse to take part in or stop taking part in this study at any time. The subject will be instructed to call the investigator in charge of this study if they decide to do this. Their decision not to take part in the study will not affect their current or future medical care or any benefits to which they are entitled. If they wish to withdraw, they will be provided contact details for the study team to initiate their withdrawal.

Early termination from the study is also subject to the PI's discretion. Subject will no longer be in the study and data will no longer be collected. The reasons for this withdrawal could be due to study non-compliance or if the subject no longer meets eligibility requirements. A member of the study team will notify the study participant if they will no longer be participating in the study.

13.0 Risks to Subjects

There are risks to subjects using the SinuSonic device. Subjects may experience a degree of discomfort, nosebleeds or crusting due to use of the device. Prior studies have reported: Mild discomfort in 2.5-5% of patients; Bleeding in 0% of patients; Crusting in 0% of patients (Soler ZM etal).

There is a risk of a loss of confidentiality of your personal information as a result of participation in this study.

14.0 Potential Benefits to Subjects or Others

This study is for research purposes only. Participants may benefit from decreased infections with potentially milder symptoms or shorter duration, but we do not know if this will occur. Information learned from the study may help other people in the future.

15.0 Sharing of Results with Subjects

Information about the subjects (including identifiable private information) may have all of their identifiers removed and used for future research studies.

Records of the subjects' participation in this study will be held confidential except as disclosure is required by law or as described in the ICF.

16.0 Payment

For participating in this study, participants will be given a free device, but no payment will be given.

17.0 Devices

Dispensing and storage of SinuSonic devices will be done by the study sponsor.

18.0 Data safety monitoring and reporting

Patients will initially be screened over the phone and informed consent obtained. This will occur during the summer months so we have a group of 300 subjects who pass this initial screen. Towards the end of the screening period, we will re-contact patients to confirm their interest in participation. As described above, we will also ask symptom scores to ensure TSS<9 and patient does not have an active URI at the start of the study.

If patients still wish to participate and still meet inclusion criteria, they will be randomized and devices shipped out within a week.

Safety will be monitored throughout the study based upon self reporting of symptoms. Subjects will be advised to seek medical care if at any time their symptoms become severe. Review of the daily reports will occur weekly to ensure the condition of each patient is adequately monitored for possible signs of URI or COVID19.

The period of observation for collection of non-serious adverse events extends from the time the subject gives informed consent until completion of the End-of-study visit or Early Termination Visit. Serious adverse events (SAE) will be reported from the time of informed consent through 30 days after the last use of the SinuSonic. Adverse event data listings will be reviewed at regular intervals throughout the study. In addition, investigators will be alerted of Adverse Events of interest via automated emails programmed in the EDC system. Patient compliance will be assessed via weekly phone calls from study coordinator.

References

Soler ZM, Nguyen SA, Salvador C, Lackland T, Desiato VM, Storck K, Schlosser RJ. Safety and efficacy of a novel device combining acoustic vibration with oscillating expiratory pressure for the treatment of nasal congestion. Int Forum Allergy Rhinol2020;00:1-9.

Turner RB, Fuls JL, Rodgers ND, etal. A randomized trial of the efficacy of hand disinfection for prevention of rhinovirus infection. Clinical Infectious Disease 2012;54(10):1422-6.

Eccles R, Winther B, Johnston SL, etal. Efficacy and safety of iota-carrageenan nasal spray vs placebo in early treatment of the common cold in adults: the ICICC trial. Respiratory Research 2015;16:121.

Jackson GG, Dowling HF, Spiesman IG, etal. Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a clinical entity. Arch Intern Med 1958;101:267-78.

APPENDIX

SCREENING CRITERIA (all must be no):

QUESTIONS	YES	NO
Have you had sinusitis, otitis or laryngitis or any other upper respiratory illness in the last 2 weeks?		
Have you used topical nasal decongestant spray in the last week?		
Do you currently have nasal crusting or history of ulcers or perforation?		
Have you had severe nasal bleeding in the last 3 months?		
Are you pregnant?		
Are you allergic or sensitive to silicone?		
Do you have any underlying medical condition that would prevent your ability to perform treatment?		
Are you immunosuppressed or on immunosuppressant medications, such as prednisone or chemotherapy agents?		

Baseline medical history and exam

SinuSonic Study

PI: Meyer TA

Subject ID#: _____ Subjects Initials: _____

DEMOGRAPHIC AND CLINICAL VARIABLES (If not previously collected):

Age at enrollment (years): | | |

Gender: Male Female

What is/was your profession (current/retired)?_____

Do you have significant daily contact with young children (age under 12 years)? Yes / No

Do you fly frequently, ie more than twice per month? Yes / No

LANGUAGE, ETHNICITY, RACE, MARITAL STATUS

Please mark one of the following categories which describes your native language:

- ☐ American English
- ☐ Other: please specify _____

Please mark one of the following categories which describes your ethnicity:

- ☐ Not Hispanic or Latino
- ☐ Hispanic or Latino

Please mark one or more of the following categories which describes your race:

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Other

SMOKING HISTORY

1. Do you **currently** smoke tobacco products? **Yes** **No** **(If No please go to question 2)**

How many tobacco products do you use in a day? _____ Singles Packs

Have you been tested for COVID19? **Yes** **No**

If yes, were you positive? **Yes** **No**

CURRENT MEDICATION USAGE

- ☐ Nasal steroid sprays (Flonase, Nasonex, etc) ☐Yes ☐No
- ☐ Nasal antihistamine spray (Astelin, etc) ☐Yes ☐No
- ☐ Oral antihistamines (Allegra, Claritin, Benedryl, etc) ☐Yes ☐No
- ☐ Oral decongestant (Sudafed, etc) ☐Yes ☐No
- ☐ Mucolytic (Mucinex, etc) ☐Yes ☐No
- ☐ Luekotriene (Singulair, etc) ☐Yes ☐No

COMORBID MEDICAL CONDITIONS: Check box and provide details if present

- ☐ Obstructive Sleep Apnea: ☐Currently being treated ☐History / No current treatment
- ☐ Allergic rhinitis:_____
- ☐ Previous allergy testing (blood test or skin prick): ☐Yes ☐No
- ☐ Immunotherapy shots for allergies: ☐Yes ☐No ☐Currently
- ☐ Non-allergic rhinitis ☐Yes ☐No
- ☐ Asthma ☐Yes ☐No
- ☐ Chronic rhinosinusitis ☐Yes ☐No
- ☐ Nasal polyps ☐Yes ☐No
- ☐ Prior ear/sinus surgery ☐Yes ☐No
- ☐ Migraine headache history: ☐Resolved/past diagnosis ☐Present/medicated ☐Present/not medicated

_____

- ☐ Height (ft/in):_____
- ☐ Weight (lbs):_____

DAILY URI SYMPTOM SCORE
To be completed each evening

PLEASE RATE HOW BOTHERSOME YOUR SYMPTOMS
HAVE BEEN OVER THE PAST DAY

	Not at all	Mild	Moderate	Severe
Lost sense of smell/taste	0	1	2	3
Sneezing	0	1	2	3
Runny nose or thick nasal discharge	0	1	2	3
Nasal obstruction or congestion	0	1	2	3
Sore throat	0	1	2	3
Cough	0	1	2	3
Headache	0	1	2	3
Malaise (feeling unwell or exhausted)	0	1	2	3
Chilliness	0	1	2	3
TOTAL SYMPTOM SCORE (TSS) of last 8 items				

Do you feel like you have a cold today? Yes/No

How many times did you use Sinusonic in the last 24 hours? _____

Week 8 patient satisfaction/safety

How much pain did you experience using device? None Mild Moderate Severe

Bleeding after using device? None Mild Moderate Severe

Would you use device again? Yes No

Would you recommend device to others? Yes No