Protocol Title: Testing a wearable telemedicine-controllable taVNS device for NeuroCovid Recovery and Rehab

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PROTOCOL TITLE:

Testing a wearable telemedicine-controllable taVNS device for NeuroCovid Recovery and Rehab

PRINCIPAL INVESTIGATOR:

- *Mark S. George, MD*

1.0 Objectives / Specific Aims

Aim 1: **Test a home based taVNS protocol for feasibility and efficacy in NeuroCovid patients.**

We will recruit 30 formerly COVID positive adults (ages 18-70) in order to have 24 completers. We will enroll subjects who had a definite case of COVID (were antigen positive) and are at home and are no longer in the hospital. They must also have a residual neuropsychiatric symptom(s) that started anew after COVID developed (NeuroCovid). We will refer to these subjects as 'initially neurocovid and persisting'. We will also enroll those who were asymptomatic, were tested as COVID positive, and then developed NeuroCovid symptoms shortly after their testing. We call these subjects 'initially asymptomatic with later Neurocovid'. (There are several Covid diseases which occur after the acute illness has passed, particular hypercoagulable states and thrombotic strokes and heart attacks.) Symptoms we will target include anxiety, depression, and other CNS symptoms (e.g., vertigo, anosmia, headaches, fatigue, irritability, cognitive processing, etc.). Subjects will be recruited from MUSC electronic records and local testing centers, with online phone screens, consents and ratings. This study is pioneering in being entirely online and home-based. We will provide telemedicine-based device-use support on demand. There will be two experimental groups – initial active taVNS and initial sham stimulation. Subjects will be randomly assigned to each group for a two-week in-home intervention of two hours per day for six days per week of stimulation (active or sham). After the controlled 2-week period, all participants will continue in a 2-week open label arm. Outcomes will include vital signs recorded through the device, mood ratings and a cognitive battery assessing neuropsychiatric functioning and symptoms. These online ratings will be obtained at baseline, taVNS treatment weeks 1-4, and 2-, 4-, 6-, and 8- weeks after treatment. We will also assess feasibility and tolerability. The device will collect daily subjective patient data as well as heart rate, blood pressure and respiration during the treatments.

Aim 2: **Test whether 2 or 4 weeks of stimulation differ.**

At the end of two weeks, all subjects will receive two more weeks of intervention, with all receiving active stimulation without breaking the blind. This has two purposes. First, all subjects will eventually receive active treatment, aiding IRB approval and recruitment. Second, it will examine two versus four weeks of stimulation.

This work will provide pilot data for a subsequent clinical trial application to test at home taVNS technology for specific NeuroCovid symptoms. Importantly, the data gained on device efficacy and in-home feasibility for NeuroCovid applications can be readily applied to a number of post-COVID disabilities and rehabilitation needs (e.g., COPD and other complications treated through immunomodulatory and respiratory therapy amenable to vagal nerve action). We strongly believe this technology has great potential for treating those currently sick with or disabled by COVID. We simply don't know what is in store one year from now, but it is likely that the aftershocks of this pandemic will be the defining backdrop of the next decade. A strength of this proposal is that it will allow us to pivot in the directions of greatest need in one year with a multitude of potential therapeutic targets and benefits, once initial feasibility and efficacy of the taVNS home therapy protocol has been established. The research team is experienced and are leaders in neuromodulation research and are thus uniquely capable of successfully shepherding this pilot work into a funded clinical trial.

2.0 Background

Unfortunately, Coronavirus disease of 2019 (COVID-19) can enter and directly infect the brain, creating direct neurologic and psychiatric problems. Some have coined the term 'NeuroCovid' to describe this direct CNS infection and damage and differentiate this aspect of the disease from the more widely discussed systemic pulmonary and cardiovascular effects. However, the direct effects of the virus and the subsequent individual immunologic response on the brain and related outcomes are unknown. Thus, we are also just now beginning to understand that after recovery from the acute and immediate infection, many patients are struggling with longer term CNS issues, like fatigue, anosmia, anxiety and depression. Researchers are asking "Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19?[1] Innovative therapeutic approaches, particularly home-based,[2] are desperately needed.

Luckily, a new neuromodulation technique (Transcutaneous Auricular Vagus Nerve Stimulation – taVNS) can directly stimulate the brain and has important anti-inflammatory and other neuromodulatory functions that likely can aid with NeuroCovid recovery. taVNS may help with the acute illness, and more importantly for the proposed work, with the long-term recovery from NeuroCovid. taVNS is a new, non-invasive neuromodulation approach combining: 1) convenience (e.g. ear clip) and potential for at home delivery; 2) tolerability, even extending to testing in neonates; and 3) direct mono-synaptic modulation of deep brain nuclei that regulate parasympathetic function. taVNS offers the ability to directly treat the brain, reducing neuroinflammation and potentially improving and facilitating recovery from a variety of COVID disorders. With the rapid clinical testing supported through this proposal, taVNS may help with the long-term recovery from COVID or NeuroCovid.

Preclinical and clinical trials show that implanted vagus nerve stimulation (VNS) may be an effective anti-inflammatory treatment and may improve outcomes in disorders with inflammation. VNS prevents septic shock and can stop anaphylactic shock. VNS activates the cholinergic anti-inflammatory pathway and targets different immune, proinflammatory, and other signaling pathways, as well as modulating heart rate and blood pressure. Cervical VNS is FDA approved to treat chronic depression and also helps with anxiety but is invasive and expensive ($30k per device). taVNS is a home-based, less expensive, non-invasive alternative.

3.0 Intervention to be studied

We will be using the Soterix Medical Handheld home based taVNS device. Our group has been using taVNS in a variety of clinical laboratory, office or ICU based studies, most of them monitored through this IRB. [3-10] This is the first MUSC protocol using home based taVNS.

The Soterix device is a research device that is FDA cleared in terms of safety but is not FDA approved for any indication. More information can be found here. *https://soterixmedical.com/research/tavns*

This IRB and most others have found that taVNS is a minimal risk device and does not require an FDA IDE.

We have attached the device specifications from the manufacturer.

- Cervical VNS is FDA approved for medication resistant epilepsy as well as medication resistant depression (Livanova). FDA pivotal trials are underway for paired cervical VNS with rehab for stroke (microtransponder). Noninvasive

cervical VNS is FDA approved for treating cluster headache (electrocore). To date there are no FDA approved indications for taVNS.

- We will use the device twice daily, six days/week for an initial 2-week double blind phase followed by an additional two weeks active open phase. Thus, subjects will get 24 or 48 actual sessions over 4 weeks. Those randomized to active during the first two weeks will get twice as much overall taVNS as those who get sham during the first two weeks *(25Hz, 500us pulse width, 60s ON, 30s OFF, 1 hr. duration per session).*Subjects will be given a training video to watch and will then have an online training session with the MUSC RA. They will be instructed how to administer the device. For the first 3 sessions at least, the RA will be online watching them do this. They will prepare a checklist of how well the subject is doing the treatment. The patient can then only administer the treatment alone if they are checked off. Treatments will be monitored online for as long as it takes for the participant to be checked off.
- Active stimulation will be in the proper location in the ear. Sham stimulation will be in the same location but there will be a small ramp up of the device, delivering stimulation for 20 seconds, and then it will be programmed to turn off, until the end of the session when it will turn on again for 20 secs.

4.0 Study Endpoints

Outcomes will include vital signs, mood ratings and a cognitive battery assessing neuropsychiatric functioning and symptoms, and will be obtained at baseline, 2, 3, 4, 5, 6, 8 and 12 weeks after treatment. We will also assess feasibility and tolerability.

Primary Outcome:

As this is a pilot and exploratory study, the outcomes are largely descriptive. In terms of feasibility we will assess dropout rates and compliance and subjective ratings of the device and the online only study. In terms of safety we will assess changes in blood pressure and any syncope or other adverse events. We will also examine changes in neuropsychiatric symptoms for patients presenting with different NeuroCovid symptoms.

Secondary Outcome:

See above.

5.0 Inclusion and Exclusion Criteria/ Study Population

Study Population:

Our study population will include adult NeuroCovid patients, who qualify for the study regardless of race or sex. COVID patients will be outpatients. We have the following racial distribution of patients: 66% Black or African American, 30% Caucasian and 2% other; Ethnicity: 2% Hispanic, 98% non-Hispanic. For sex we expect the following: 60% males and 40% females as early data suggest that for some reason males do worse with COVID. We will enroll all patients who qualify regardless of sex, if they or their caregivers consent to the study. We will not include children in this study

Inclusion Criteria:

We will enroll subjects who were COVID positive, had some identifiable time of illness, and are home and afebrile. They then must also have some residual new

neuropsychiatric symptom that started after COVID developed. We will also enroll those who were asymptomatic, were tested as COVID positive, and then developed NeuroCovid symptoms. Inclusion symptoms include new onset anxiety, depression, and other CNS symptoms (e.g., vertigo, anosmia, headaches, fatigue, irritability, cognitive processing).

Exclusion Criteria:

Damage to left or right ear or anatomy that does not allow taVNS; unstable hemodynamic effects that make a novel clinical intervention unsafe; ischemic or hemorrhagic stroke after developing COVID, patient unable to give consent, or follow instructions, not able to read or write or speak English; no home WiFi.

6.0 Number of Subjects

We will recruit 30 COVID positive adults in order to have 24 completers.

7.0 Setting

Subjects will be in their home for this trial. MUSC study staff will use an electronic tele-consenting (Doxy.me) and rating platform to communicate with the subjects.

8.0 Recruitment Methods

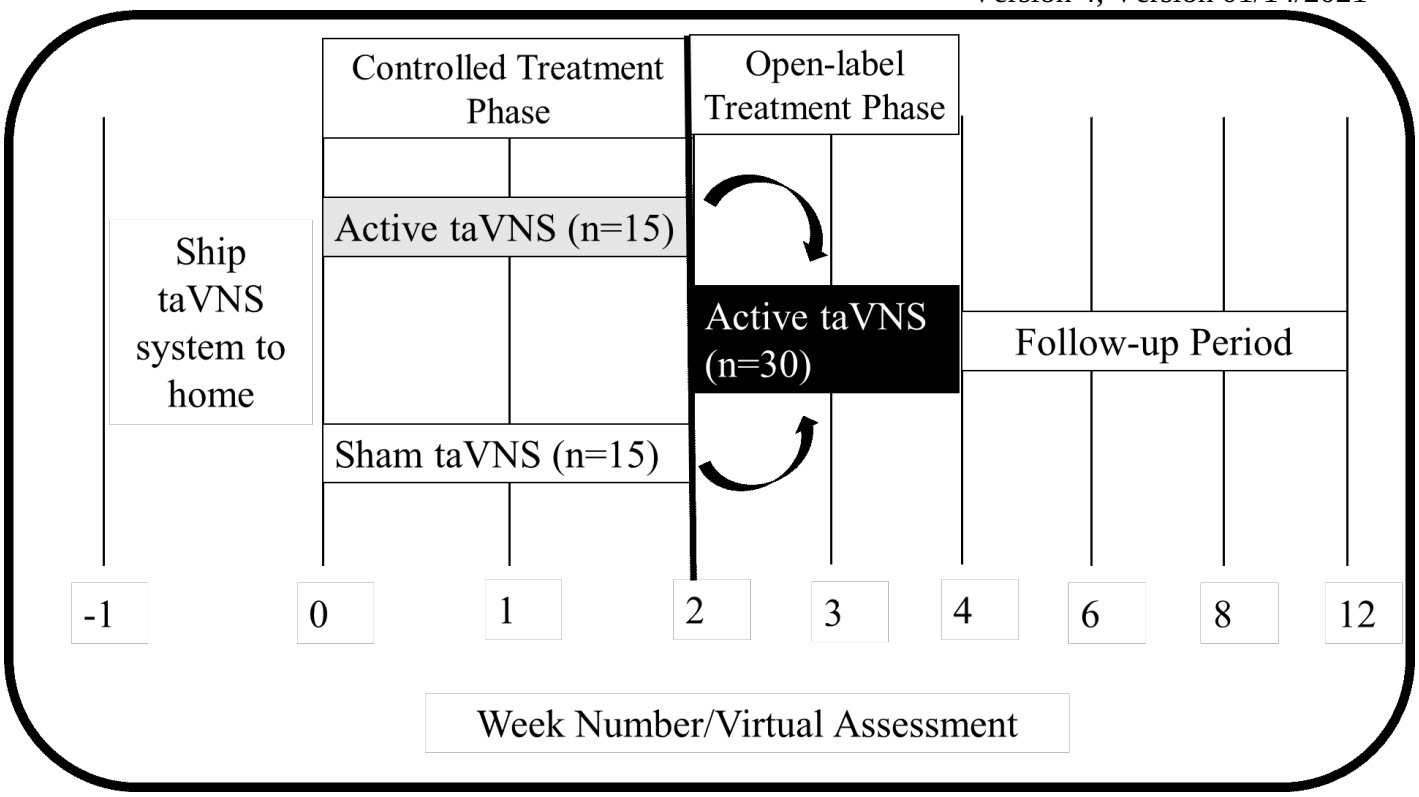
We will screen for formerly COVID positive people in our electronic medical record (Epic) who have given permission to be contacted for research. Through our electronic medical record, we will contact MUSC COVID positive patients at least 14 days after their last test, and ask if they have residual symptoms. Subjects will sign consents and complete assessments online. We will then serially administer a broad ranging and comprehensive online battery assessing neuropsychiatric functioning and symptoms. MUSC will ship the device to subjects and they will be educated on the device use. We will provide telemedicine-based device-use support on demand if they have questions.

Please see the attached flyer.

9.0 Consent Process

Subjects will sign consents and complete assessments online. Subjects will be consented by Drs. George or Badran via a tele-consenting platform.

10.0 Study Design / Methods



- Please see the study timeline above. Potential subjects will be phone screened and if appropriate scheduled for a consent meeting and then baseline assessments. They will then be given the video showing how to use the device. MUSC research assistants will then ship a device (and urine pregnancy test) to subjects. They will then have a training session online with MUSC RA's. Then, for each session initially they will do this online with MUSC RA's watching and rating and assisting if needed. They will complete a checklist of how well the subject administers the device. After three sessions if the subject is competent, they will self administer the device after that if they wish. All subjects can ask to have the RA online during any and all treatments if they wish. All sessions are immediately put into the database and the MUSC RA will daily monitor this and make sure the subject has correctly performed the session with no adverse events. If a subject misses a session the RA will call and talk about this. There will be immediate questions before and after each session, as well as the weekly online battery. There are also weekly online assessments and at 4,6,8 and 12 weeks after study start.

Procedures performed to lessen the probability or magnitude of risks.

We are excluding subjects with strokes or who are hemodynamically unstable. All sessions will be seated or even reclined if there are problems. Initial sessions are done with the MUSC RA and Soterix staff online. All session data and heart rate are sent immediately to the database and will be checked daily by research staff.

How all drugs and devices will be used in the research (e.g. dose, dosage form, etc.)

The device is taVNS applied to the left or right ear at two times the amplitude for perceptual threshold. This intensity of taVNS has been

used in MUSC IRB 1 monitored studies in Parkinson's Disease, Stroke Patients, Newborns and healthy volunteers. The dose for each session is *25Hz, 500us pulse width, 60s ON, 30s OFF, 1 hr. duration.*

Subjects will receive two treatment sessions/day, 6 days per week, for two weeks (randomized), for 24 treatments in the double-blind phase. All subjects will then receive an additional two weeks – 24 more treatments. For those initially randomized to active VNS, they will thus receive up to 48 hours of VNS therapy. For those initially randomized to sham, they will still receive 24 sessions, or 24 hours of treatment. While this may seem like a lot, remember that cervical VNS is implanted and then stimulates on and off for many years. Thus, this dose is minimal compared to the large and safe database of VNS for epilepsy or depression.

The source records, including medical or educational records that will be used to collect data about subjects.

We will collect demographic and clinical data from the Epic Database. We will perform phone screens and then online consent and ratings. All ratings will be done online with data going into Redcap with secure access. All data collected from the device will also go to the secure online MUSC Redcap database.

Describe data collection procedures (e.g. chart review, subject interview, etc.). Provide a description of all assessment instruments to be used. (Upload in eIRB all surveys, scripts, etc.) Include what data will be collected.

See above. We have uploaded all database questionnaires.

12.0 Data Management

All data will be stored in the Redcap database. The blind will be kept by the MUSC RA, but they will be blinded as well. Soterix will set the active or sham control from the company after being instructed by the MUSC RA about the randomization code number for that patient, but MUSC will have the unblind in terms of emergency.

Information about the participant (including their identifiable private information and/or any identifiable biospecimens) may have all of their identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from them or their legally authorized representative.

In rare cases, the device manufacturer, Soterix, may need access to minimal PHI (such as name, phone number and address) in the event there is a device malfunction. Well-trained MUSC staff will make every attempt to resolve any issues before putting Soterix in direct contact with the participant.

At a high-level analysis, we will compare the group changes in neuropsychiatric questionnaires in active versus sham taVNS using repeated measures ANOVA from baseline to immediately after last treatment and then as well over the 3-month follow-up.

Power analysis on primary outcome: As there is no real data yet on taVNS effects on NeuroCOVID patients, it is difficult to perform a formal power analysis. The repeated measures design in 15 active and 15 sham patients will allow us to detect differences with a large or moderate effect size to be used for calculating power and sample size for subsequent trials.

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

Dr. George or his designee, should he be unavailable, will be responsible for reporting all unanticipated problems or AEs to the IRB. The PI or some study team member will be present for each patient and record AE's real time. Soterix will be responsible for reporting any unanticipated device-related AE's to FDA. All screening data will be kept in a file on Redcap. Screening data collected from participants who do not qualify for the study will be securely destroyed.

Dr. Mark George, who is a board certified neurologist and psychiatrist, and Dr. Badran will oversee the device testing and technical use of the Soterix system.

An independent Safety Monitoring Committee (SMC) will be formed to advise the study investigators. The SMC will review and evaluate accumulated study data to ensure safety. They also will make recommendations concerning continuation, modification, or termination of any of the taVNS studies. It will be composed of several prominent COVID experts and Dr. Jeff Borckardt, MUSC associate professor and assistant provost who has extensive VNS, TMS, and tDCS experience.

The SMC will be notified immediately of any and all SAE's. We will report to the IRB the number of treatments held for HR or redness, discomfort.

Drs. George or Badran will obtain informed consent, during which participants or their guardians are fully advised on the research procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse their infant's participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the principal investigator. The legal guardians of all subjects will be required to have legal ability to consent.

Regarding confidentiality, subjects are informed that the information they provide, as well as participation in the study, will be kept strictly confidential, with access limited to the research staff. The identity of subjects in databases will be protected with alphanumeric codes. All data will be kept in locked file cabinets or on secure servers designed for use and access by Brain Stimulation Lab members only.

14.0 Withdrawal of Subjects

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent, including stopping participation for safety reasons.*

  taVNS has been a very safe procedure and we do not anticipate subject withdrawal due to taVNS side effects. We will be monitoring each session and if a patient is extremely hemodynamically sensitive to the device we might consider terminating. Severely worsening of symptoms would be another reason (for example, worsening of headaches). VNS is antidepressant, antinociceptive, anti-inflammatory and anxiolytic so we do not anticipate worsening in these areas.

- *Describe any procedures for orderly termination of subjects by investigator.*

Any termination would involve online video conversations with subjects and follow the patterns used for in person documentation of the reasons and ensuring that patients have understanding and medical follow-up.

- *Describe procedures that will be followed when subjects voluntarily withdraw from the research, including partial withdrawal from procedures with continued data collection.*

  As with all research, a subject can withdraw from research at any time. We will honor this and make sure the patient is safe and has good options and care and will ship the device back to MUSC.

15.0 Risks to Subjects

Ear Stimulation:

Ear stimulation is safe, however there are some risks associated with stimulating the ear: There may be local discomfort. This will likely be temporary. In extreme cases burns might occur. We will video monitor any potential burns and will stop stimulation and advise subjects to apply vitamin E cream. Tissue surrounding the ear may be sensitive, sore or feel slight numbness. Hopefully this will be temporary and will go away after stimulation is turned off.

Potential Headache, Dizziness, and Facial Pain:

Ear stimulation might cause headaches or face pain, which should resolve shortly after treatment.

Safety in case of pregnancy

This protocol will exclude pregnant women. The risks of using taVNS with pregnant women are currently unknown. If in the screening and consent a patient is a woman of childbearing age, we will send them by mail a urine pregnancy test. They will need to complete this and show the negative result to the RA on doxy.me.

Potential decrease in heart rate:

Ear stimulation may slow heart rate. In rare cases (less than 1%) decreased blood pressure or fainting may occur. We expect no significant changes in heart rate or blood pressure, or fainting may occur. For the initial sessions all subjects will be stimulating while they are seated, never standing. We expect no significant changes in heart rate or blood pressure, but if this occurs, the study team will evaluate the situation and either decide that the patient should be dropped from the study, or do all sessions laying on a couch, or with lower doses.

Unknown Risks:

There is always the possibility of other risks for a relatively new technology. The Study team will let the participant know if they learn anything that might make the participant change their mind about participating in the study.

Loss of Confidentiality:

There is a risk of a loss of confidentiality of personal information. Subjects are informed that the information they provide, as well as participation in the study, will be kept strictly confidential, with access limited to the research staff. The identity of subjects in databases will be protected with alphanumeric codes. All data will be kept in locked file cabinets or on secure servers designed for use and access by Brain Stimulation Lab members only.

Potential Randomization Risk:

The treatment a subject receives may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

Questionnaire Risk:

There are no anticipated risks to the participant. However, the participant may feel that some of the questions we ask are stressful or upsetting. If they do not wish to answer a question, they may skip it and go to the next question, or they may stop immediately. Also, being assessed for study entry, including the possibility that they may not meet criteria for entering the study may be distressing. If they become upset or distressed as a result of their participation in the research project, the research team will be able to arrange for a one on one meeting with our team psychiatrist.

Our commitment to patients is to take all reasonable steps to help them find treatments for worsening psychiatric symptoms. If the subject's psychiatric conditions worsen (specifically suicidality or suicide ideation), we will provide the National Suicide Prevention Hotline call or text number (1-800-273-8255) to the subject or advise the subject to go to the nearest Emergency Department or call 911.

16.0 Potential Benefits to Subjects or Others

A strength of this proposal is that it will allow us to pivot in the directions of greatest need in one year with a multitude of potential therapeutic targets and benefits, once initial feasibility and efficacy of the taVNS home therapy protocol has been established. The research team is experienced and are leaders in neuromodulation research and are thus uniquely capable of successfully shepherding this pilot work into a funded clinical trial. Invasive cervical VNS is FDA approved for epilepsy and depression. Noninvasive cervical VNS is FDA approved for cluster headaches. We have seen anxiolytic and antidepressant effects of taVNS. There is legitimate prospect of benefit for NeuroCovid symptoms although this is still experimental. All subjects will get the active open treatment for weeks 2-4.

17.0 Sharing of Results with Subjects

There is no plan to inform subjects of the results of the study, but they can always contact the research staff and ask. If there are significant new findings during the course of the study, they will be notified.

18.0 Devices

Soterix, the device company, will ship the device to the RA's at MUSC. The MUSC RA will then ship the device to the subject (along with a urine pregnancy test if that is indicated.) The subject is in charge of storing the device while it is at their house. The subject will be informed on how to manage and care for the device prior to receiving the device through a video. The study team will then hold training sessions with the subject. At the end of the 4 weeks the subject will need to ship the device back to MUSC with pre-paid packaging and a label. If the device is damaged at home, we will ship another device and have them ship the damaged unit back. Because the device can be remotely controlled, we will inform patients that the device becomes a 'brick' after the 4th week and has no resale value and cannot be used further.

Importantly, the device is programmed remotely, and subjects cannot administer more than the indicated dose. That is, they cannot stimulate for more than the two one-hour sessions each day. If a subject falls asleep with the device on it will turn itself off automatically.

We are asking for a Non-significant risk determination of this device. IRB 1 has consistently given NSR status for all prior taVNS studies at MUSC, including studies in stroke patients (Badran), brain damaged newborns learning to feed (Jenkins), Parkinson's Disease (Hinson, Badran) and healthy volunteers (Badran).

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