PROTOCOL TITLE:

Phonation therapy to improve symptoms and lung physiology in patients referred for pulmonary rehabilitation.

PRINCIPAL INVESTIGATOR:

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

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1.0 Study Summary

Study Title	Phonation therapy to improve symptoms and lung physiology in patients referred for pulmonary rehabilitation.
Study Design	Randomized Controlled Trial
Primary Objective	1) Improvement in patient symptoms (Borg dyspnea score)
Secondary Objective(s)	1) Improvement in time of breath hold. 2) Improvement in lung physiology – FVC, FEV1, NIF 3) Improvement in quality of life
Research Intervention(s)/ Investigational Agent(s)	1) Tonation Breathing Techniques (TBT) Exercises 2) Music Driven Vocal Exercises (MDVE)
IND/IDE #	
Study Population	Patients who are referred to Pulmonary Rehabilitation for symptomatic chronic lung disease
Sample Size	16
Study Duration for individual participants	8-weeks
Study Specific Abbreviations/ Definitions	FVC – forced vital capacity; FEV1 – forced expiratory volume in 1 second; NIF – negative inspiratory force; PR-Pulmonary Rehabilitation; TBT – Tonation Breathing Techniques; MDVE – Music Driven Vocal Exercises; PFT – pulmonary function testing

2.0 Objectives*

The objective of this study is to determine whether breathing and vocalization exercises improve dyspnea in patients who are referred for pulmonary rehabilitation (PR).

The specific aims are to determine the following:

1) Do breathing and vocalization exercises improve subjective pulmonary symptoms and objective pulmonary function in patients referred for PR, compared to no intervention?
    a. Specific outcomes include: subjective: Borg dyspnea score
    b. Specific outcomes include: objective: Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), Peak Flow, Negative Inspiratory Force (NIF), peak flow
2) Do breathing and vocalization exercises improve subjective pulmonary symptoms and objective pulmonary function, compared to calm normal breathing?
    a. Specific outcomes include: subjective: Borg dyspnea score
    b. Specific outcomes include: objective: FEV1, FVC, NIF, peak flow
3) Is there a difference between two different proposed techniques of breathing and vocalization exercise techniques to improve subject pulmonary symptoms and objective pulmonary function?
    a. Specific outcomes include: subjective: Borg dyspnea score
    b. Specific outcomes include: objective: FEV1, FVC, NIF, peak flow

Our hypotheses are that breathing and vocalization techniques are a) feasible; b) can improve subjective and objective pulmonary outcomes; c) there is no significant difference between the two proposed techniques of breathing and vocalization techniques.

3.0 Background*

Music therapy has been successfully prescribed for various diseases such as anxiety, depression, neurological diseases such as epilepsy, Parkinson's disease, and multiple sclerosis. [1,2] Music therapy and psycho-music therapy has also been beneficial in chronic lung disease such as chronic obstructive lung disease and has shown to improve symptoms of dyspnea and depression.[3] Singing is based on respiratory physiology, it consists of four stages of breathing inhalation, suspension, controlled exhalation, and

recovery.[4] The production of voice and phonation is a complex process and involves producing sound as air from the lower respiratory tract passes through the vocal cord this generates a functional connection between the lower respiratory tract and larynx [5]. Singing is distinct from tidal breath, singing generates large lung volumes and therefore requires active exhalation compared to tidal breathing. [6,7] The diaphragm functions differently while singing compared to normal phonation and tidal breathing. During tidal breathing and phonation, the diaphragm is passive, whereas it is continuously contracting during singing. [7,8,9,10]

In the current literature benefit of music therapy in the treatment of chronic lung disease is unclear. A recent metanalysis conducted by Huang et al. showed an improvement in dyspnea and anxiety with the use of passive music(listening) along with mixed music (listening and singing) in COPD patients, The results were statistically significant although the study had a few limitations - methodology of study selection was not clearly defined;, the music was selected by the subjects; and the duration of follow up was short. [11] In another study conducted in Poland in 2017 by Sliwka et al. evaluated the efficacy of pulmonary rehabilitation with music therapy in patient with mild asthma. A greater increase in mean FEV1/FVC, FEF(50), and FEF(75) was observed in music therapy group with pulmonary rehabilitation compared to pulmonary rehabilitation alone, although there was an overall increase in FEV1, FEV1/FVC, (FEF(25), FEF(50), and FEF(75) in both groups.[12] Another large study conducted by Morrison et al. in 2013 followed patients for a 10-month period, 106 subjects with COPD were enrolled into a weekly community singing along with breathing exercises. After 10 months the study showed significant improvement in FEV1% and FVC% along with subject reported improvement quality of life, there was no significant improvement in dyspnea. Despite a longer period of follow up, the authors reported limitation due to no control group.[13] Music therapy for respiratory health remains encouraging but music therapy is not routinely incorporated into pulmonary rehabilitation courses and the type of music therapy that is most effective remains indeterminate.

The objectives of our study are to a) determine whether breathing and phonation exercises improve symptoms and lung function in patient with chronic lung disease referred to pulmonary rehabilitation and b) compare two approaches to music therapy (Tonation Breathing Technique (TBT) and Music Driven Vocal Exercises (MDVE)) for feasibility and efficacy in incorporating into pulmonary rehabilitation.

We propose a pilot study to obtain preliminary data and assess feasibility of instituting music therapy into pulmonary rehabilitation. Once we establish feasibility, we will propose a larger study to compare the two approaches to music therapy as well determine the long-term effects of music therapy added to pulmonary rehabilitation.

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4.0 Study Endpoints*

1) Specific outcomes include: subjective: Borg dyspnea score
2) Specific outcomes include: objective: FEV1, FVC, NIF, peak flows (all obtained from spirometry)

No specific safety outcomes are proposed, as no significant risks are associated with the proposed intervention.

5.0 Study Intervention/Investigational Agent

Tonation and Breathing Techniques (TBT): consist of a combination of organic inhalation and controlled exhalation with tonation. This will be guided by a trained facilitator, and the entire exercise will take 20 minutes.

1. Guided relaxed breathing: the subjects are asked to be conscious of any tensing of muscles all along the respiratory system and guided to relax them.
2. Mindful breathing: the subjects are next asked to observe their breathing and its effects at different points in their body.
3. Patterned tonation: the subjects are asked to hold a tone at any frequency comfortable to them, followed by a slightly lower frequency, a slightly higher frequency and then again at their original frequency.
4. Nasal tonation: The subjects are asked to close one nostril, inhale gently through the other nostril, followed by slow exhalation with tonation. This is done for 5 repetitions. The process is repeated for the other nostril.
5. Pursed lip tonation: The subjects are asked to inhale gently through their nostrils, purse their lips (in the motion of sucking a straw or blowing a balloon) and then exhale through their mouth with tonation. This is done for 5 repetitions.

Music Driven Vocal Exercises (MDVE): The following Music Therapy procedure will be implemented by a trained facilitator, utilizing an accompanying instrument (ie, guitar or Autoharp) and moving stepwise up and down within a scale of 8 whole steps. The total length of the procedure is 20-25 minutes.

1. Subjects will be taught the following vocal exercises that they will sing 10x each in the following order
   a. Ha-Ha-Ha (Do-Re-Do)
   b. Hee-Hee-Hee-Hee-Hee (Do-Re-Do-Ti-Do)
   c. Hoo-oo-oo-oo-oo-oo-oo-oo-oo (Do Re Mi Fa Sol Fa Mi Re Do)

2. Subjects will be taught the following melodic exercises that they will sing 10X and then speak 5X. The first session will consist of the first 3 phrases, each subsequent session will add the next phrase on the list.
   a. Whose Hands Hold Hearts Harps and Hangers (Do-Re-Do-Fa-Re-Do-Ti-Do)
   b. Peter Piper Picked a Peck of Pickled Peppers (Do-Re-Do-Ti-Do-Re-Do-Re-Mi-Re-Do-Do)
   c. Awkward Alice Ate Apples At an Airport (Do-Mi-Sol-Mi-Mi-Fa-Mi-Re-Mi-Mi-Do)
   d. Granny Grills Grits for Gorillas (Do-La-Ti-Do-Do-Re-Mi-Do)
   e. Zealous Zebras in Zoot Suits (Do-Re-Mi-Re-Fa-Do-Do)

f. William and Gabby Grow White Grapes in Gorgeous Wintry Gardens (Do-Mi-Re-La-La-Ti-Re-Do-Ti-Do-Re-Re-Do-Mi-Do)

6.0 Procedures Involved*

Patients who are referred for pulmonary rehabilitation for chronic lung disease and/or post-COVID19 therapy, who have had pulmonary function testing already will be approached. Pulmonary rehabilitation is an 8-week program (meeting 3 times per week for the 8 weeks). Pulmonary rehabilitation (PR) is standard of care for patients with chronic lung diseases and or post-COVID-19 therapy. Eligible study participants will be called prior to their introductory PR session to explain the research project, and those who are interested will be given full information and offer time to ask questions. We find this necessary for logistics, given many of our patients rely on scheduled transportation to/from PR and this will allow those who are interested in obtaining more information and to consent to the study to arrange for appropriate transportation. Informed consent will be done in person on an individual basis at their introductory PR session, with 1:1 discussion with the study staff and the patient.

As this is a pilot study to determine feasibility, and preliminary data (as no data are currently available for this patient population), we propose 16 participants in total, 4 in each arm of the study. Randomization will occur by random number generator (1-4 for each arm proposed).

Once informed consent is obtained, patients will be randomized to 4 arms of the study. Randomization will be performed using a random number generator.

1) Comparing TBT to normal breathing:
    a. Of the 8 weeks of PR, first 4 weeks will be sessions of normal breathing exercises for 20 minutes, then subsequent 4 weeks will be with TBT intervention for 20 minutes.
    b. Of the 8 weeks of PR, first 4 weeks will be with TBT intervention for 20 minutes, then next 4 weeks will be of sessions of normal breathing exercises for 20 minutes.
2) Comparing MDVE to normal breathing:
    a. Of the 8 weeks of PR, first 4 weeks will be sessions of normal breathing exercises for 20 minutes, then subsequent 4 weeks will be with WT intervention for 20 minutes.
    b. Of the 8 weeks of PR, first 4 weeks will be with MDVE intervention for 20 minutes, then next 4 weeks will be of sessions of normal breathing exercises for 20 minutes.

These interventions would be performed after usual PR time, when patients would be normally discharged home. Therefore, no additional monitoring is expected.

Pulmonary function testing is standard for all patients who receive PR – testing before and after PR is routine clinical course. We propose an additional PFT study at 4 weeks, as part of the research protocol (covered by the Department of Medicine funding)

In summary, the interventions for research purposes will include:

1) 20-minute sessions after PR for intervention (TBT or MDVE) or normal breathing for twice a week for the 8 weeks they are participating in PR.
2) PFT at end of week 4

Proposed subjective outcomes are routinely asked of PR patients, but will be collected at baseline, at 4 weeks (mid-way), and at 8 weeks (end) of PR.
Proposed objective outcomes:

1) For FEV1, FVC – these are routinely collected at baseline and at end of PR. We propose an additional PFT study at 4 weeks, covered by the DOM Faculty Development Fund.
2) For peak flow and NIF – these are procedures that ask for patient to breathe maximally for inspiration and expiration. They are not routine measures collected but are routine bedside measurements for pulmonary patients that can be collected for any person without any additional risk or cost.

Data will be obtained as following:

1) Routinely obtained information will be collected from EPIC into a REDCap database. This includes:
    a. Patient demographics – name, MRN, DOB, sex, gender, race, ethnicity, height, weight, BMI,
    b. Pulmonary history: reason for PR referral (routine collection); date of symptom onset; date of diagnosis of lung pathology; prior PFT findings – FEV1, FVC, peak flow, NIF.
    c. PR questionnaire info: Borg dyspnea score at baseline and each visit (routine collection)

There are no plans for long-term follow-up.

7.0 Data and Specimen Banking*

Data will be obtained as following:

Routinely obtained information will be collected from EPIC into a REDCap database. This includes:

7.1 Patient demographics – name, MRN, DOB, sex, gender, race, ethnicity, height, weight, BMI,

7.2 Pulmonary history: reason for PR referral (routine collection); date of symptom onset; date of diagnosis of lung pathology; prior PFT findings – FEV1, FVC, peak flow, NIF.

7.3 PR questionnaire info: Borg dyspnea score at baseline and each visit (routine collection)

Informed consent forms will be signed and scanned into patient charts (in the media manager). Physical consent forms will be retained in the PI's office, in a locked cabinet in the locked room for the required amount of time.

8.0 Sharing of Results with Subjects*

As this is a pilot project, no significant findings are expected from the study. For an individual, the results of repeat PFT testing done for research will be available to the patient in EPIC through MyChart.

9.0 Study Timelines*

An individual participants time in the study will be approximately 8 weeks.

Time 0 – Informed Consent signed.

Weeks 1-8 – normal Pulmonary Rehabilitation 3 times a week, with phonation intervention (TBT or MDVE) or silent breathing time.

On last session of week 4 and week 8: PFT's, NIF, VC, peak flows will be measured. Borg dyspnea scale will be collected.

We hope to collect 16 participants for this study by November 2022, and have primary analysis completed by December 2022 for submission to American Thoracic Society 2023 presentation.

10.0 Inclusion and Exclusion Criteria*

Inclusion:

1) Age 18 years and older
2) English-speaking and reading patient
3) Able to consent for study
4) Referred for pulmonary rehabilitation for chronic lung disease (including long COVID19 syndrome, COPD, ILD, PH)
5) Baseline Borg dyspnea score as moderate (score 3) or higher.
6) Has baseline pulmonary function testing available in electronic medical record.

Exclusion:

1) Cannot commit to staying an extra 30 min after Pulmonary Rehabilitation sessions for the study.

11.0 Vulnerable Populations*

This study does not include vulnerable populations.

12.0 Local Number of Subjects

Plan to recruit 16 participants for this study.
Anticipate needing to screen 40 participants for this study.

13.0 Recruitment Methods

Patients who are scheduled to start Pulmonary Rehabilitation will be called by one of the consenting investigators. The study will be described and any questions will be answered. The consent form will be sent to the patient to review in full. On the first day of Pulmonary Rehabilitation (PR), the patient will meet with a study investigator in a private room, and any further questions will be answered, and if patient is agreeable, will sign the consent form.

Source of participants will be all referred for Pulmonary Rehabilitation (patients are within the practice of the PI).

We will request partial HIPAA waiver to access patients' charts who are scheduled for Pulmonary Rehabilitation and assess inclusion and exclusion criteria and study eligibility. This will allow us to call patients and talk to them about their participation in this study, and answer questions prior to obtaining full informed consent.

A payment of $10 by MetroHealth gift card will be given to the patient upon completion of 4 weeks of the research study / PR. An additional $20 will be added to the participant's MetroHealth gift card on the last day of PR after completion of the study surveys and testing. This will be funded through the Pulmonary/CC Fellow MH Foundation fund.

14.0 Withdrawal of Subjects*

Participants of the study who miss 3 sessions of study intervention in the first 4 weeks of the PR will be notified that their enrollment in the study is at risk. Participants who miss 4 sessions will be withdrawn from the study. They will be given written notification that their enrollment in the study is cancelled, and this will be put in the patient's electronic medical record, in the media manager.

Subjects will not have sufficient data collected to analyze, so the data will not be analyzed, and the participant will not count towards the expected enrollment number.

15.0 Risks to Subjects*

There are no foreseeable risks or hazards to the proposed interventions. There may be a discomfort in the phonation exercises, if persons have not done this before, but the participant is only asked to do what is tolerated. There is an inconvenience to the patient that they have to stay an extra 30 min after their usual PR session for the study intervention. They will be compensated $30 total ($10 at the beginning of the study, $20 at the end of the study).

There are risks of loss of confidentiality in this study, as in any other study that identifies participants. No sensitive data will be collected, and the data will be stored in the secure REDCap system. Only de-identified data will be downloaded from REDCap for analysis purposes. This de-identified data will be stored in the PI's secure G: drive folder for research.

16.0 Potential Benefits to Subjects*

Individual participants may experience improved symptoms of dyspnea and pulmonary function. They may also enjoy the interaction with a trained music therapist.

Overall, the data from this study would inform a larger study that could show a novel way of improving pulmonary rehabilitation, and innovative ways to improve dyspnea symptoms and pulmonary function in patients with chronic respiratory illness.

17.0 Data Management* and Confidentiality

Descriptive analyses will be performed first on each of 4 categories. Chi-squared tests and ANOVA testing will be performed, although with low sample size, significance is not expected in these analyses. No power analysis will be performed, as this will be a pilot study.

Baseline data, including patient demographics, baseline pulmonary function test results, baseline Borg dyspnea score will be saved into a REDCap database. This database will only be accessible by study investigators. De-identified database will be downloaded for analysis, and this will be stored on the PI's G: drive research folder. Study records will be stored according to the MHS Record Retention Policy VII-4, which is minimum 4 years after study completion.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

N/A

19.0 Provisions to Protect the Privacy Interests of Subjects

Consent will be obtained from participants. Data will be collected into a secure REDCap database, that will be accessible only by study investigators.

We have one consultant working with us, Dr. Uma Ranjan, CEO of Clisonics. She developed the TBT therapy approach. She will not have access to the REDCap database. Individual-level data will not be shared with her – only the final summaries of the data. No data will leave MetroHealth's campus/intranet.

20.0 Compensation for Research-Related Injury

We do not anticipate any research-related injuries. This proposed project is a minimal risk study. No compensation will be provided

21.0 Economic Burden to Subjects

No costs are anticipated for the patients. The study intervention would require an additional 25-30 min of time to be spent at Pulmonary Rehabilitation, which they would already be scheduled for. Pulmonary function test for research purpose will be funded by grants secured by the investigators.

22.0 Consent Process

Consent will be obtained by one of the designated study investigators. Patients eligible for the study will be identified through EPIC review, and the patient will be called by a designated study investigator to introduce the idea of the study and determine if the patient is interested. If so, then the informed consent form will be mailed/emailed to the patient. There will be at least 1 week between patient receiving the consent form and the patient's first day of PR.

On the first day of PR, the patient will be met by a designated study investigator to give informed consent. A private room in the PR area will be used to discuss the study. All patient questions will be answered at this time. If patient is agreeable and understands the study and expectations, they will sign the consent. The patient will be given a $10 MetroHealth gift card at that time.

Upon completion of PR and participation in the study, the participant will receive another $20 uploaded to their existing MetroHealth gift card on the last day of PR.

23.0 Process to Document Consent in Writing

Consent forms will be signed by participants. They will be given a copy of the ICF. The signed form will be scanned into Media Manager of the patient's electronic medical record. The physical copy will be stored in the PI's office, in a locked cabinet. The paper forms will be kept for 4 years after the study completion. Completed consent will be noted in the REDCap database.

24.0 Setting

The study will primarily be conducted in the Pulmonary Rehabilitation center, in Hamann 3rd floor H&V clinic on MetroHealth main campus. There are rooms

that are secure and private in the area that can be used for recruitment and consent process.

Data analysis will be conducted on MH computers on-site, in the PI's office in BG3-38. Data will be saved on secure intranet folders, and only available to the research investigators. Signed paper consent forms will be the only paperwork for this study, and will be stored in a locked cabinet in a locked office of BG3-38 (PI's office).

No community advisory board will be involved in this study.

No research will be conducted outside the organization.

25.0 Resources Available

Patients are enrolled in pulmonary rehabilitation each week – approximately 16 new patients per month. They are enrolled for an 8-week period. Based on prior research studies on the same patient population, we anticipate about 50% enrollment. This is a pilot project proposal, so we propose to recruit 10 subjects initially.

PI proposed about 2.5% of FTE to the research study. Fellows will have dedicated research time to enroll subjects and collect data. Music therapy consultants will spend about 30 min/patient session (2 sessions per week x 8 weeks x 16 participants = 128 hours) on the study. They have graciously offered to provide the music therapy intervention pro bono for this pilot study. Baseline and post-rehab PFT's are clinically routine. The research spirometry proposed at 4 weeks requires funding. Investigators have been awarded a DOM Faculty Development Grant to support this expense ($150 per spirometry x 16 participants = $2400). Additional funding is also provided by Arts in Health operating budget. Patient incentive MetroHealth gift cards will be funded by the MH Pulmonary/Critical Care Fellows Fund through the MH Foundation.

The study will be conducted in the Pulmonary Rehabilitation center, in Hamann 3rd floor in the H&V clinic. There are dedicated rooms for education that will be used for the intervention sessions. No additional equipment will be needed.

No medical or psychological support is anticipated as needed during these sessions. There is always a physician-on-call for pulmonary rehabilitation while patients are present. If the physician-on-call is notified about a patient who is enrolled in the current study and develops any complications during the intervention, the physician-on-call will notify the PI.

All study investigators and persons assisting with the research will be given the full study protocol. We will have regular meetings to determine study progress, review study procedures, and address any issues related to the proposed study.

26.0 Multi-Site Research*

N/A