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Pilot Development and Biomarker Engagement of a Singing Intervention for Chronic Obstructive Pulmonary Disease (COPD)

Protocol # 00160422

NCT # Pending

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RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

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Study Title: Pilot Development and Biomarker Engagement of a Singing Intervention for Chronic Obstructive Pulmonary Disease (COPD)

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I. Purpose, Background and Rationale

A. Aim and Hypotheses

1. COPD, signified as the third leading cause of fatality globally, causes airflow blockage creating hyperinflation of the lungs, distress, and lower well-being. This ailment also causes airflow blockage; this symptom affects around 45% of individuals with COPD. Curated exercises primarily targeting the improvement of lung function and physiological benefits through music-based singing are limited, requiring further exploration.
2. We hypothesize that tailored vocalization activities (i.e., singing) can improve lung function in patients with COPD.
3. Hope involves developing and maintaining agency and pathways to goals according to Snyder's Hope Theory (2002). In COPD, agency promotes motivation and adherence to treatment. COPD requires goal adaptation as the disease progresses. Developing multiple pathways to achieve goals for physical and psychological health is necessary when barriers occur. We hypothesize that promoting hope as a psychological strength will enhance participation in the singing intervention.

B. Background and Significance

1. Study Significance: This study is intended to show if air trapping in functional small airways disease (fSAD) in COPD patients is reduced by a targeted music-based singing intervention.
2. Air trapping in fSAD in COPD is associated with the experience of breathlessness or dyspnea, which is a primary source of patient distress. Air trapping may be mitigated by activities that support slow, controlled, and more complete exhalation. Because singing requires sustained delivery of consistent air pressure for sound production, training in this activity aims to strengthen respiratory musculature to improve airflow control and increase efficient use of each breath. We believe that singing training will be beneficial in strengthening the respiratory musculature and emptying the lungs, possibly reducing the amount of trapped air.
3. Literature Review: Group singing activities for patients with COPD have shown improvements in social and emotional well-being (e.g., Singing for Lung Health,[1, 2, 3, 4] SingStrong,[5, 6] Healing Breath[7]). Systematic reviews of the existing singing interventions for COPD suggest that the interventions lead to improvements in quality of life.[8, 9]. A singing intervention designed with defined features of specific music elements, such as phrase length to facilitate complete

exhalation and pitch jumps to strengthen the diaphragm,[10, 11, 12] may also improve pulmonary pathophysiology by actively reducing air trapping in the regions of small airways disease. We aim to target air trapping directly with a music-based intervention designed to increase patients' ventilation capacity by expelling trapped air, strengthening the diaphragm, and increasing inspiratory capacity and reserve.

C. Rationale

1. A major gap exists in our understanding of whether singing is effective for improving lung function in COPD. Previous interventions based in group singing have been focused on improving social and emotional outcomes, but they do not specifically address the potential physiological benefits of singing as described above. We aim to show specific targeted manipulation of music elements within tailored vocalization activities can successfully improve lung function and reduce dyspnea in patients with COPD, while preserving social and emotional benefits of other more generalized singing interventions. We are focusing on air trapping due to small airways disease as a key symptom that leads to patient experience of dyspnea.[13, 14] Other aspects of COPD pathology and symptoms may be improved by the singing intervention, including a sense of hope through a sense of agency in their own psychological health.
2. The goal of the pilot study is to determine the feasibility of providing a music-based intervention targeting the issue of air trapping, improve functional small airways disease, and improve other symptoms of COPD and further define the details of the intervention.
3. This study will determine participant acceptability of a newly developed music-based intervention hoped to be beneficial for people with COPD. If successful, our proposed singing intervention will improve lung function health through reduced air trapping due to hyperinflation, improve patient experience of dyspnea and foster positive psychological health.

II. Research Plan and Design

A. Study Objectives: The aim of this pilot project is to determine the feasibility of recruitment, intervention delivery practicality, and participants' responses to the singing intervention and repeated CT imaging to document air trapping changes in patients with COPD. Secondarily, we aim to determine the effect size of any intervention-related changes in air trapping and other lung function measures to support sample size estimates for a larger trial. We also aim to further refine the music-based intervention for this targeted population through secondary analysis of intervention mapping details (e.g., intervention components, processes, completion of intervention activities, and pathways of persistence and endurance.

B. Study Type and Design: We will use a single-arm pre-post intervention for the pilot study. We will deliver the intervention over the course of 4 weeks. The online music intervention will be conducted via Zoom. The intervention will be administered by board certified music therapists and mapped through study team members at the University of Kansas – Lawrence (Hanson-Abromeit & Wilson) and the University of Oregon (Brunkan) with support from research assistants. We will assess fSAD with lung CT imaging and pulmonary function using standard clinical evaluation (Pulmonary Function Testing). Air trapping and difficulty breathing reported by the patient will be assessed before and after the intervention to document longitudinal changes and effects of singing on inspiratory and expiratory capacity. Dyspnea will be measured at each intervention session. Materials will be sent by email, mail, or in person as requested by the participant. We will use guided journal entries and semi-structured interviews to assess participant satisfaction.

Intervention mapping will be conducted doing qualitative video coding of participants sessions and development of implementation and fidelity criteria.

C. Sample size, statistical methods, and power calculation

1. No randomization will be used in this pilot study. Feasibility metrics will be generated, including qualitative and quantitative measures of recruitment, participant acceptance, and intervention fidelity. Quantitative recruitment data recorded by the clinic recruitment team will include number of potential participants approached, participants enrolled, participants completing the study, sessions and procedures successfully completed per participant, and the demographic and clinical characteristics of those approached, enrolled, and completing the pilot study. We will calculate the ratio of enrolled to approached participants with a goal of enrolling 10% or greater of those approached. Qualitative analysis of participant diaries and semi-structured interviews will inform participant adherence of responsiveness, exposure, engagement, and enactment.[15] Pulmonary function measures including CT and clinical PFT measures will be assessed to determine adequate effect size for sample size estimation for a larger study. Our in-house quantitative CT (QCT) analysis will be used to quantify fSAD at baseline and follow-up (Pre, Post). Reduction in fSAD will be assessed by one-tailed paired samples t-tests between timepoints (Pre, Post), controlling overall error rate at 0.05. PFT and patient-reported symptoms will be assessed for change over time by one-tailed paired samples t-tests between timepoints (Pre, Post), controlling overall error rate at 0.05.
2. No blinding (masking) is involved: N/A
3. An estimate of 15 participants will be enrolled in this pilot test.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable): All races, ethnicities, and genders 18 years or older with a diagnosis of COPD will be included.

1. Inclusion criteria: Participants 18 years of age or older with a diagnosis of COPD, airflow obstruction and resting hyperinflation of the lung. Participants must be able to hear within normal range with correction if needed. Non-English speakers may participate, and an interpreter will be provided if needed. A short form ICF in the potential participant's preferred language will be used. Participants not able to provide consent due to cognitive impairment may participate with a study partner who can provide surrogate consent.
2. Exclusion criteria: Pregnancy will be excluded for CT imaging safety and radiation safety and disclosure for CT imaging will be clearly communicated with participants during the informed consent process. People with alpha-1 antitrypsin an inherited disorder in younger individuals causing bullous emphysema, similar to COPD, will be excluded.
3. Withdrawal/Termination criteria: Participant becoming pregnant during the study.
4. A study participant may participate in another research study while participating in this research study unless it is another music-based intervention.

E. Specific methods and techniques used throughout the study:

1. Laboratory tests: Pulmonary function tests (PFT) will use standard clinical evaluation and include Forced Expiratory Volume in 1 second, Forced Vital Capacity, Total Lung Capacity, Residual Volume, Maximal Inspiratory Pressure, and Maximal Expiratory Pressure. We plan to use the COPD Assessment Test, Borg Dyspnea Index, Transitional Dyspnea Index, St. George's Respiratory Questionnaire, and the Adult State Hope Scale for patient

reported symptoms. CT imaging of the lungs will capture 1 mm slice thickness for inspiratory and expiratory states at the start of the intervention and follow-ups.

2. Study Procedures: Participants will have pulmonary assessments at the KUMC Frontiers CTSI Pulmonary Function Lab at the start of the study and follow-up visits. A six-minute walk test will be included. We will assess fSAD with lung CT imaging. The music intervention will be two times a week for 4 weeks offered virtually via Zoom. Music-based intervention sessions will last approximately 20-40 minutes and be video recorded. The video recording will be used to monitor intervention delivery fidelity. The music-based intervention will consist of an individualized assessment at the start and conclusion of the treatment with six components of singing familiar songs and tailored vocalization exercises based on the participant's PFT and pre-intervention assessment measures. These sessions will incorporate the participant's identified favorite song, music-based activities such as vocal warm-ups, cool-downs, and specialized vocal exercises with adapted melodic phrase lengths (duration of sustained exhalation while vocalizing)that gradually guide participant capacity to fully exhale. Participants will be asked to complete daily, at-home practice sessions for 15-20 minutes. Participants will be asked to share their experience in guided, weekly diaries through surveys administered through REDCap. The surveys will contain open-ended questions and note fields. Participants without access to electronic devices will have in-person sessions at KUMC's Frontiers CTSI.
3. Pulmonary function tests (PFTs), six-minute walk test, and chest CT are all used routinely in standard therapy but are used in this pilot study only for research purposes. No tests will be billed to insurance companies.
4. No body component (blood, CSF, bone marrow, etc.) will be collected in the study: N/A
5. Timeline: We plan to conduct the singing intervention for 4 weeks. A study flow chart is attached.

F. Risk/benefit assessment:

1. Physical risk CT imaging radiation exposure will be minimized by excluding pregnant persons, and by excluding people who have had repeated exposures from other sources (e.g., multiple health-care-related imaging studies).
2. Psychological risk People with COPD experience difficulty breathing which has been shown to increase anxiety or feelings of depression. Asking people to use their voice in a way that mimics singing may be psychologically uncomfortable due to their respiratory challenges, changes in quality of voice, and vulnerability with vocalizing with another person. Our interventionist will be a trained and board certified music therapist who will foster a relationship-based experience to improve comfort, and who will tailor the vocalization experiences to gradually increase in complexity at a level that is achievable by the participant, thus minimizing psychological feelings of discomfort.
3. Social risk There are no known social risks to participating in this study. Study activities will be between study personnel and the participant, and at-home practice can be conducted in a private space as determined by the participant's level of comfort in social exposure (e.g., in front of a partner or alone in a separate room of the house), thus minimizing any perceived social risk.
4. Economic risk There are no known economic risks associated with participating in this study.
5. Potential benefit of participating in the study

a. The participant may benefit through possible improvement in respiratory function (air trapping and dyspnea) and the opportunity to focus their respiratory rehabilitation in a different format (music-based vocal exercises rather than physical activities).
b. Further evidence for singing as a potential treatment to improve pulmonary function.
c. This project will generate preliminary evidence for a larger trial to determine efficacy of this music-based intervention. Respiratory challenges are a growing area of concern to society due to the increased rates of COPD and respiratory-related outcomes of long COVID. An effective, non-invasive, non-pharmacological intervention could benefit society by providing an effective intervention to alleviate these symptoms, their economic impact, and the overall health and well-being of society members. The relationship between the arts and health is recognized by the World Health Organization as critical to their definition of health – physical, social, and mental well-being (https://www.who.int/initiatives/arts-and-health), thus this music-based intervention has the potential to improve human health. In studying a music-based intervention we will contribute to science by furthering our understanding of how and why music may target a health problem and contribute to positive change.

G. Location where study will be performed: KUMC; online via Zoom. Paper records will be kept in locked cabinets. Electronic records will be saved in password protected databases and folders stored on KUMC's Protected network drive.

H. Collaboration (with another institution, if applicable): For this non-federally funded pilot project, the University of Kansas – Lawrence and the University of Oregon will report to their institutional IRBs.

I. Single IRB Review for a Multi-site study (if applicable):

1. **For which sites will KUMC serve as the IRB of record?** KUMC will serve as the IRB of record for KUMC and KU-L. Funding for the study will be administered internally by KUMC. KUMC-Lawrence and the University of Oregon will submit to their IRBs separately.
2. *** Indicate which study activities will occur at each site. If all study procedures will be identical across study sites, state this.** Recruitment, consent, CT imaging, PFT will take place at KUMC only. The intervention sessions will be conducted virtually over Zoom. Investigators at KU-Lawrence and the University of Oregon will interact with participants over Zoom while delivering the intervention and monitoring implementation fidelity. Data analysis will be conducted at all three sites.
3. *** Describe how you will assess the capacity of each site to perform the research (e.g., expertise, staffing, space, equipment, etc.) If applicable, include site evaluation tools in your IRB submission.** We will verify that interventionists at each site have access to minimum broadband requirements for Zoom and will request KUMC accounts for access to KUMC computing resources (shared network drive, REDCap) as needed. The lead investigator at KUMC will ensure that all participating sites use the KUMC IRB-approved version of the protocol, consent, recruitment materials and other study documents. All study documents will be approved through KUMC IRB first and will then be approved secondarily through the other institutional IRBs.

4. *** Describe how the lead investigators will communicate with and disseminate new information to other sites (e.g., training meetings, regularly scheduled conference calls, notifications, etc.)** The study team will meet virtually through regular conference calls to ensure study goals are met.
5. The lead investigator will assess protocol compliance, unanticipated problems and adverse events at other sites by communicating with the other site PIs biweekly throughout the study. Site PIs will report any problems to the lead PI at those meetings.
6. Name the member of the KUMC study team who will be the point of contact to coordinate oversight and communication with the sites. Rebecca Lepping; Jasmine Taylor

J. Community-Based Participatory Research (if applicable)

1. Participants and the nature of their involvement: N/A
2. Cultural issues: N/A
3. Origin of the research question: N/A
4. Risks and Benefits: N/A
5. Study Description and Process: N/A
6. Return of results: N/A
7. Sustainability: N/A

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s): Imaging Research Assistant, Study Coordinator, Interventionist.
2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: Principal Investigator, Co-Investigator, Study Coordinator
    b. Obtaining informed consent: Principal Investigator, Co-Investigator, Study Coordinator
    c. Providing on-going information to the study sponsor and the IRB: Principal Investigator, Co-Investigator, Study Coordinator
    d. Maintaining participant's research records: Principal Investigator, Co-Investigator, Study Coordinator, Interventionist
    e. Completing physical examination: Principal Investigator, Co-Investigator, Study Coordinator, Interventionist
    f. Taking vital signs, height, weight: Principal Investigator, Co-Investigator, Study Coordinator
    g. Drawing / collecting laboratory specimens: Principal Investigator, Co-Investigator, Study Coordinator

h. Performing / conducting tests, procedures, interventions, questionnaires: Principal Investigator, Co-Investigator, Study Coordinator, Interventionist
i. Completing study data forms: Principal Investigator, Co-Investigator, Study Coordinator, Interventionist
j. Managing study database: Principal Investigator, Co-Investigator, Study Coordinator, Interventionist, Imaging Research Assistant

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

1. Elements of the plan include:
    a. Persons/groups who will review the data (study team; independent safety monitor, data monitoring committee or formal DSMB) Study team, Dr. Castro, Dr. Stewart.
    b. **Data/events that will be reviewed** Worsening of pulmonary symptoms or vocal measures.
    c. **Frequency of review** Monthly during the pilot study
    d. *** Types of analyses to be performed**
    e. Safety-related triggers that would cause the PI to stop or alter the study 4 or more participants experiencing worsening of symptoms during the intervention.
2. Adverse events, such as worsening of vocal assessment scores, will be examined on a case-by-case basis by the study team and Primary Physician Monitor (Dr. Castro).
3. If a participant experiences an adverse event or other problem we will discontinue study participation for that participant.

III. Subject Participation

A. Recruitment:

1. Patients at the KUMC COPD Outpatient Clinic meeting criteria for the study will be invited to participate.
2. Recruitment will be conducted by Dr. Nancy Stewart, the study team pulmonology expert and Director of the KUMC Outpatient COPD Clinic.
3. The advertising flyer is attached and will be posted in the KUMC Outpatient COPD Clinic waiting room and distributed to KUMC Pulmonology Division for referrals.
4. No recruitment letter or introductory statement will be used: N/A

B. Screening Interview/questionnaire: The screening questionnaire and interview script is attached. Dr. Stewart will provide the Study Coordinator with the name and contact information for interested potential participants. The Study Coordinator will conduct the interviews. Interested potential participants will consent to participate in the screening process verbally at the beginning of the interview.

C. Informed consent process and timing of obtaining of consent:

1 The Study Coordinator will give subjects detailed and comprehensive information about the study and obtain their written consent.

2 Informed consent will be conducted over Zoom with a passcode protected link. The study coordinator will walk through the entire consent form and then participants will have the opportunity to ask questions and be given time to consider before signing. Signatures will be obtained virtually using the DocuSign secure process.
3 Participants' ability to provide their own consent will be assessed by Dr. Stewart in the COPD clinic. Any participants who wish to have a study partner with them will be accommodated.

D. Alternatives to Participation: Participants may choose to have standard pulmonary rehabilitation instead of participating in this study.

E. Costs to Subjects: No tests will be billed to insurance.

F. How new information will be conveyed to the study subject and how it will be documented: Enrolled participants will be contacted by the study team and reconsented if necessary.

G. Payment, including a prorated plan for payment: Participants will receive $25 for completing the baseline CT and PFT; $25 for each week (4) of participation in the intervention; and $25 for completing the follow-up CT and PFT for a maximum of $150 per participant. Participants who withdraw from the study will receive payment for portions completed. Participants who are withdrawn from the study for safety or other reasons will receive the full $150.

H. Payment for a research-related injury: No payments will be given for a research-related injury.

IV. Data Collection and Protection

A. Data Management and Security:

1. Approved study personnel (PI, Co-Is, Study Coordinator, Research Assistants) will have access to study data.
2. Participant data will be kept in locked cabinets at KUMC, or virtually on KUMC's Protected (P:) drive. Zoom intervention session recordings will also be saved to KUMC's P: drive.
3. During the study, participants and their data will be initially identifiable. Data will be deidentified as soon as possible for analysis and identified by participant study ID.
4. Dr. Lepping and the study team will have access to the linking information during the study.
5. Participants will be assigned a study ID at enrollment which will be associated with all data.
6. Participant data will be kept in locked cabinets at KUMC, or virtually on KUMC's Protected (P:) drive. Zoom intervention session recordings will also be saved to KUMC's P: drive.
7. Study team members and participants will connect to a KUMC Zoom link that is set up to store recorded data on KUMC's network (P:) drive.
8. KU-L and UO study team members will have access to participants' identity through the Zoom intervention. Zoom recordings and intervention data will be saved on KUMC's P: drive. We will utilize additional zoom recording functions that are only available by cloud recording. These are auto-transcript and separate audio tracks for individual zoom meeting participants, which will improve the quality of voice analysis. Thus, initial

recording will be done using HIPPA-compliant cloud recording under Dr. Choi's KUMC zoom account that only he can access. Then the recording files will be transferred to the protected (P) drive directory for storing and analysis.

9. KU-L and UO study team members will have KUMC accounts for accessing the shared drive and computing resources behind KUMC's firewall. We will retain these video recordings for 7 years after publication and then destroyed using current standards of destroying digital videos.

B. Sample / Specimen Collection: No samples or will be collected: N/A

C. Tissue Banking Considerations: N/A

D. Procedures to protect subject confidentiality: Zoom intervention sessions will be performed by study team members in a private space. Participants will be advised to join the intervention sessions in a private location.

E. Quality Assurance / Monitoring

1. Intervention sessions will be recorded and monitored by the intervention team for consistency, fidelity and intervention mapping. Imaging, PFT, and other digital source data will be verified to be correctly labelled with the participant's study ID, to be complete, and to be of high quality by the study team.
2. There are no plans to have ongoing third-party monitoring: N/A

V.Data Analysis and Reporting

A. Statistical and Data Analysis: Analysis will be performed at the end of data collection. No interim analysis is planned. Feasibility metrics will be generated, including qualitative and quantitative measures of recruitment, participant acceptance, and intervention fidelity. Quantitative recruitment data recorded by the clinic recruitment team will include number of potential participants approached, participants enrolled, participants completing the study, sessions and procedures successfully completed per participant, and the demographic and clinical characteristics of those approached, enrolled, and completing the pilot study. We will calculate the ratio of enrolled to approached participants with a goal of enrolling 10% or greater of those approached. Qualitative analysis of participant diaries and semi-structured interviews will inform participant adherence of responsiveness, exposure, engagement, and enactment.[40] Pulmonary function measures including CT and clinical PFT measures will be assessed to determine adequate effect size for sample size estimation for a larger study. Our in-house quantitative CT (QCT) analysis will be used to quantify fSAD at baseline and follow-up (Pre, Post). Reduction in fSAD will be assessed by one-tailed paired samples t-tests between timepoints (Pre, Post), controlling overall error rate at 0.05. PFT and patient-reported symptoms will be assessed for change over time by one-tailed paired samples t-tests between timepoints (Pre, Post), controlling overall error rate at 0.05. We will conduct descriptive statistics of pre/post changes in patient reported symptoms collected through COPD Assessment Test, Borg Dyspnea Index, Transitional Dyspnea Index**,** St. George's Respiratory Questionnaire, and the Adult State Hope Scale.

Intervention mapping will consist of qualitative analysis of intervention details to identify patterns in the music-based activities, including qualities of the music stimuli and participant

responses to music-based experiences. The qualitative analysis will be conducted by study team members at KU-Lawrence. Investigators from KUMC will send the Zoom recordings in a secure fashion through the Secure File Transfer service to KU-Lawrence investigators for analysis. The study team members at KU-Lawrence will code for patterns and themes using standard qualitative processes.

B. Outcome: We expect this pilot study to generate data to support further development of a music-based intervention to improve lung function for people with COPD. Several outcomes are identified that will be evidence of a successful pilot study: ***Recruitment Capability*****:** Can participants who will benefit from the intervention be identified and recruited into the study? Do participants remain in the study, and participate in all study activities (pre/post interviews, pulmonary assessments and lung CT imaging, and all intervention sessions)? Why/why not?; ***Data Collection***: Are data collection procedures and outcome measures appropriate and sensitive to change? Clinical outcomes: within session and pre/post intervention's 4-week implementation changes in sung and spoken phrase length expansion paired with quality of tone and variation in pitches, personal plethysmograph and reported level of perceived dyspnea, pulmonary function test, lung CT Imaging.; ***Effectiveness***: Do we see evidence of the potential of this intervention to improve respiratory function in one or more of our outcome measures?: ***Practicality:*** Can the intervention be implemented in an online format? Are the materials, time, and available resources adequate for delivery of the intervention (e.g., sound and web-camera quality for real-time assessment, playback for at-home practice and implementation evaluation). ; ***Adaptability***: As a tailored music-based intervention, is the intervention flexible enough to support participants with different stages of COPD? Implementation: Can the interventionist implement the intervention with fidelity?; ***Participant Social Validity, Acceptability, and Integration*****:** Do participants find the intervention to be appropriate, reasonable, fair, and potentially effective? Do participants find the intervention acceptable? Do they believe they will continue to use it on their own? Would they continue with the weekly intervention, if available? Do participants integrate the intervention into their daily life?

C. Study results to participants: PFT and chest CT results will be given to participants after the final study visit.

D. Publication Plan: Results will be used as preliminary data for a larger grant application as well as disseminated via conference presentation and journal manuscript.

VI. Bibliography / References / Literature Cited

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APPENDIX I: VULNERABLE POPULATIONS

I. People with COPD are at a higher risk of developing dementia and cognitive impairment. In order to develop an intervention that is also likely to be beneficial to this group of patients, we are not excluding participants with cognitive impairment at this stage of intervention development.

II. **Cognitively or Decisionally impaired individuals**: Participants' ability to provide their own consent will be assessed by Dr. Stewart in the COPD clinic. A surrogate decision-maker (spouse or legally authorized representative) would provide consent and act as a study partner to assist during the intervention. Any participants who wish to have a study partner with them who are otherwise deemed able to provide their own consent will be accommodated.

III. **Children**: N/A

IV. **Pregnant women:** N/A

V. **Prisoners:** N/A

VI. Students and/or Employees:

A. Students: N/A

B. KUMC employees: N/A

C. Public or private school students: N/A