Inspiratory Muscle Rehabilitation in Children With Obesity (BREATHE Fit)

Funding Sponsor:

Derfner Foundation

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Principal Investigator:	Jason E. Lang, MD, MPH Associate Professor of Pediatrics-Pulmonary and Sleep Medicine Duke University Medical Center Duke Clinical Research Institute [redacted]

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Council for Harmonisation (ICH) E6(R2) guideline for Good Clinical Practice (GCP), and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including 45 CFR 46 (Human Subjects Protection); 21 CFR 50 (Informed Consent), and 21 CFR 56 (Institutional Review Board [IRB]).

All individuals who are responsible for the conduct, management, or oversight of this study have completed Human Subjects Protection and ICH GCP Training.

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Site Principal Investigator Name (Print)

_____ _____

Site Principal Investigator Signature Date

STUDY PRINCIPAL INVESTIGATOR/IND SPONSOR SIGNATURE

The signature below documents the review and approval of this protocol and the attachments (e.g., MOP, package inserts), and provides the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. and international regulations and ICH guidelines.

Jason E. Lang, MD, MPH

Study Principal Investigator Name

Study Principal Investigator Signature

Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
BPM	Beats Per Minute
BMI	Body Mass Index
BPCA	Best Pharmaceutical for Children Act
CI	Confidence Interval
CmH2O	Centimeter of Water
CoC	Certificate of Confidentiality
COVID-19	Coronavirus Disease 2019
CVF	Cardiovascular Fitness
DCC	Data Coordinating Center
DHBS	Duke Healthy Breathing Study
DUHS	Duke University Health System
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FEF25-75	Forced Expiratory Flow at 25% to 75%
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GPS	Global Positioning System
HIPAA	Health Insurance Portability and Accountability Act
HL	Healthy Lifestyles
ICF	International Council for Harmonisation
ICS	Inhaled corticosteroids
IEC	Institutional Ethics Committee
IMR	Inspiratory Muscle Rehabilitation
IRB	Institutional Review Board
ITT	Intention to treat
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene Receptor Antagonist
m	Meter
Max	Maximum
MIP	Maximum Inspiratory Pressure
mm	Millimeter
MVPA	Moderate-Vigorous Physical Activity
BDI	Baseline Dyspnea Index
FWA	Federal-wide Assurance
DMC	Data Monitoring Committee
ACQ	Asthma Control Questionnaire
MOP	Manual of Procedures
NC	North Carolina

NIH	National Institute of Health
O2	Oxygen
PI	Principal Investigator
REB	Research Ethics Board
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions

PROTOCOL HISTORY OF CHANGES		
Version	**Date**	**Summary of Changes**
1.0	DD-MMM-2021	N/A Original protocol

PROTOCOL SYNOPSIS

Protocol Title:	**BREATHE Fit: Inspiratory Muscle Rehabilitation in Children with Obesity to Promote Physical Activity**
Phase:	Pilot
Product:	PrO2 IMR ™ trainer
Objectives:	**Primary:** Demonstrate inspiratory muscle rehabilitation (IMR) as an acceptable add-on intervention in children with obesity. **Secondary:** 1. Demonstrate changes in inspiratory muscle functioning and dyspnea reporting following IMR. 2. Demonstrate changes in daily physical activity following IMR. **Exploratory:** Demonstrate changes in exercise capacity following IMR.
Study Design:	Single-center, randomized, SHAM-controlled, parallel assignment, double masked, interventional study.
Study Population:	**Inclusion Criteria** 1. Documented informed consent from legal guardian and assent from participant as appropriate. 2. Children 8 to 17 years of age with obesity (BMI ≥ 95th percentile for age and sex) being seen at Duke Healthy Lifestyles clinic. 3. Participants (or parent/guardian) must have access to the internet and an approved smart device/computer. 4. Child must have a designated caregiver who expresses a commitment to encourage the participant to complete the study procedures. 5. Participant and legal guardian must speak and read English or Spanish. **Exclusion Criteria** 6. Prior enrollment in an IMR program. 7. Contraindications for IMR including a history of recent lung surgery, recent pulmonary embolism, or history of recurrent spontaneous pneumothorax 8. Progressive neurological or neuromuscular disorders or need for chronic O2 therapy.

	9. Inability to complete baseline measurements in a satisfactory manner according to the judgment of the research coordinator or PI. 10. Current self-reported pregnancy or planning to become pregnant. 11. Body weight greater than 300 pounds. 12. Any condition in the opinion of the PI that would not allow safe conduct of study procedures (including IMR, MIP testing or step-test), such as a physical disability, recent musculoskeletal injury or illness, current and ongoing evaluation for undiagnosed cardiopulmonary or neurologic symptoms, undiagnosed chest pain, pneumothorax in the past 12 months, inner ear surgery in the past 12 months, or undiagnosed syncopal episodes.
Number of Participants:	Up to 30
Number of Sites:	1 site
Duration of Participation:	Planned participation will be approximately 56 days. Total participation may be up to 77 days.
Intervention:	**Intervention:** Inspiratory Muscle Trainer at 75% of the participant's maximal inspiratory pressure (MIP). Target dose: 3 sets of 50 inspiratory breaths 3 times per week. **Sham comparator:** Inspiratory Muscle Trainer at 15% MIP. Target dose: 3 sets of 50 inspiratory breaths 3 times per week.
Estimated start:	**Q1 2022**
Estimated time to complete enrollment	**Q3-4 2022**

SCHEMATIC/DESCRIPTION OF STUDY DESIGN

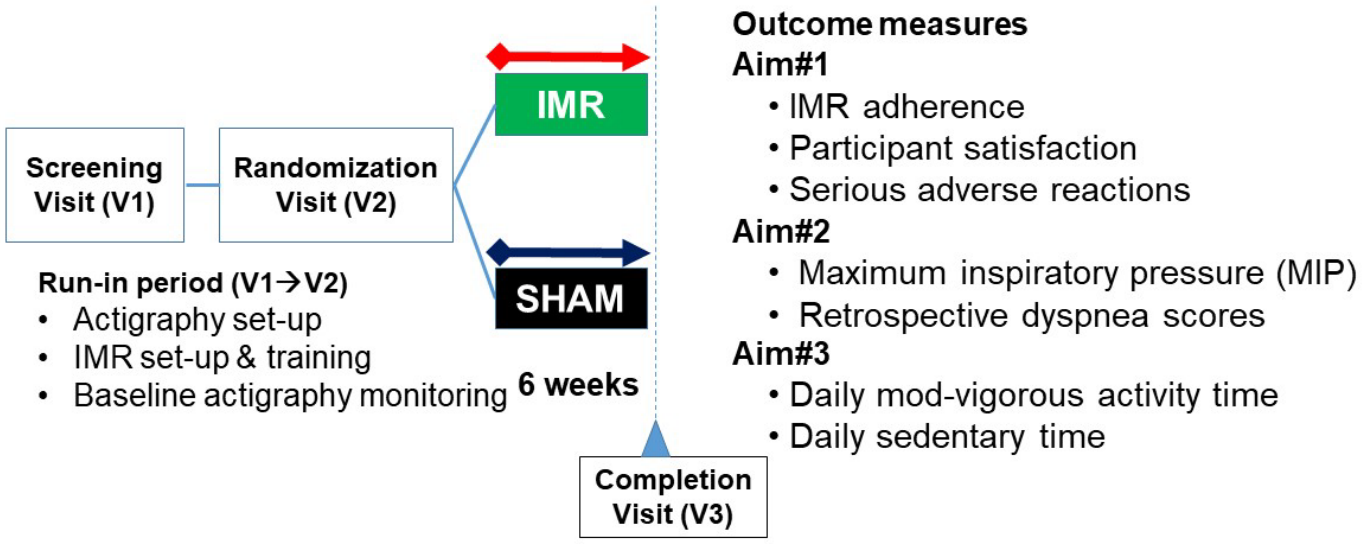

Figure 1 Study schematic. Mechanisms of action of (A) obesity leading to dyspnea and activity avoidance, and (B) IMR facilitating greater activity.

1. KEY ROLES

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Improved management of obesity is an urgent public health need. Nearly 40% of US children and adolescents have a body mass index that markedly increases their risk for serious metabolic and cardiopulmonary sequelae. Current childhood obesity rates, for the first time in US history, predict a decline in life US expectancy. Importantly, childhood obesity is a key driver of health disparities in the US, with obesity disproportionately affecting African-American, Hispanic-Latino and Native American children. A key contributor to the sequelae of obesity is sedentariness. Thus, best practice in obesity management includes both reducing sedentariness and establishing durable increases in daily physical activity[1,2], however, attrition from planned exercise programs remains high. [3] A key challenge to initiating and sustaining physical activity in children with obesity is the extreme dyspnea (breathlessness) they experience. This is due to the altered thoracic mechanics of obesity which lead to enhanced inspiratory muscle fatigue and dyspnea, with even modest physical activity (Figure 2A). Our group has confirmed that among adolescents, higher body mass index (BMI) associates with lower inspiratory muscle endurance (r= -0.680, p=0.049, n=14), and that this lower endurance correlates with more frequent dyspnea (r= - 0.672, p=0.023, n=12). Treating obesity-related inspiratory muscle impairment and dyspnea is a promising approach to support physical activity in children with obesity, but is yet unproven.

Inspiratory muscle rehabilitation (IMR) is a promising approach to reduce obesity-related dyspnea and boost physical activity. Pulmonary rehabilitation (in its various forms, including IMR) is a treatment cornerstone in adult medicine but is underutilized in pediatrics.[4] In adults, IMR has been studied in healthy athletes[5,6], and numerous lung [7-10] and neuromuscular [11-13] diseases. In adults, IMR consistently improves inspiratory muscle function, reduces dyspnea and improves exercise tolerance.[14-19] Adding IMR to an exercise training regimen in healthy young adults who were obese led to significant improvements in subjective ratings of dyspnea and objectively measured exercise capacity.[20] **IMR has not been sufficiently studied in children with obesity.** However, recently in our pilot work at Duke, children with obesity (and asthma) underwent the 'DHBS' pilot IMR trial (NCT03911206). Children (n=11) were randomized to IMR (3 sets of 50 reps, three times/week), exercise or usual care for 6 weeks. Ten of 11 completed all visits, and 11 reported wanting to continue IMR after the study. IMR improved mean maximum inspiratory pressures (MIP) (+34 cm H2O, p=0.014) and improved exercise capacity measured by 6-minute walk distance (+115 meters) (p=0.136) compared to IMR. Based on these

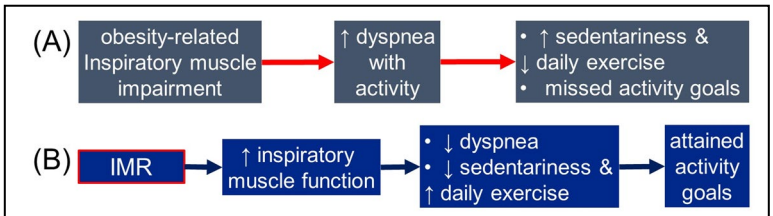


Figure 2 Mechanisms of action of (A) obesity leading to dyspnea and activity avoidance, and (B)

data, we are highly encouraged that IMR will help children with obesity increase their physical activity (**Figure 2B**).

Duke Pediatrics is expertly equipped to advance IMR in Children with Obesity. Duke Pediatrics' Healthy Lifestyles (HL) clinic, led by Co-I Dr. Sarah Armstrong, treats >7000 children ages 8-17 with obesity each year (>35% Black, >20% Hispanic).[21] Treatment includes intensive lifestyle counseling, community-based physical activity, pharmacotherapy, or weight-reduction surgery.[22] As part of routine clinical monitoring, patients in HL complete measures of exercise capacity to assess physical activity gains, and have (as part of consented research) provided wearable accelerometers to track total daily activity (i.e. steps) and time achieving moderate to vigorous physical activity (MVPA).[23,24] Dr. Armstrong has led or facilitated multiple research studies within the obesity clinic, with established protocols and regulatory processes for recruitment, consent, and follow up study visits.[21,25-27] This collaboration between the Pediatric Pulmonary and Healthy Lifestyles clinical research teams focuses on a completely new area of research for the investigators (IMR) and provides a superior environment for studying impactful innovations in pediatric obesity.

Together, we propose **BREATHE Fit**, a randomized SHAM-controlled 6-week trial of inspiratory muscle rehabilitation in children aged 8-17 years with obesity enrolled in the Duke HL. **Primary research question:** *Is IMR an acceptable add-on intervention that promotes greater activity in children with obesity?* The **BREATHE Fit** trial will address the following aims:

Aim 1. Demonstrate the acceptability of IMR in children with obesity. Hypothesis 1a (H1a). More than 80% of participants will be satisfied with active IMR at study completion. H1b. Total IMR adherence will be >80% of planned active IMR repetitions. H1c. Active IMR will not be associated with any serious adverse reactions.

Aim 2. Demonstrate changes in inspiratory muscle functioning and dyspnea reporting following IMR. H2a. IMR will significantly increase inspiratory strength (measured by mean change in MIP). H2b. IMR will reduce patient-reported retrospective dyspnea scores during activities of daily living.

Aim 3. Demonstrate changes in daily physical activity following IMR. H3a. IMR will lead to reduced sedentary time, increased moderate-strenuous time and increased total daily activity measured by a wrist-worn continuous activity tracking monitor.

2.2 Potential Benefits

IMR is very likely to improve inspiratory muscle strength. These benefits in inspiratory muscle strength may reduce dyspnea (breathlessness) with daily activity and with exercise. In addition, IMR may improve exercise capacity and exercise tolerance. Although improvements in these outcomes are not guaranteed, improvements in general health, daily activity and weight loss are a possibility.

Conclusions drawn from this study may benefit children with obesity by adding to the understanding of how IMR affects breathing. All participants will have baseline lung function testing and will have their daily physical activity monitored.

2.3 Compensation

Participants will be fairly compensated for their time and effort. Successful completion of the study (visit 3) will result in a $75 monetary payment (gift cards). In addition, participants will be gifted the Garmin Vivosmart 4 study activity tracker (retail value $100) on visit 1. If participants do not complete the study, they will be asked to return the activity tracker and inspiratory muscle trainer. Participants will receive a $25 gift card with the successful completion of visit 2, and $50 gift card with the successful completion of visit 3.

VISIT #	COMPENSATION
V1	Garmin Vivosmart 4 study activity tracker (retail value $100)
V2	$25 Nike gift card
V3	$50 Nike gift card

2.4 Potential Study Risks

2.4.1 Risks of inspiratory muscle training

The risk of inspiratory muscle training is minimum. Inspiratory muscle training is deep breathing exercises against a resistance. Risks are thought to be generally minimal and similar to daily living or routine exercise. No known systematic reports are known describing risks from IMR. However, patients will be advised that they may experience mild, self-limited dizziness, headache, or dyspnea.

2.4.2 Risks of maximal inspiratory pressure measurement

Inspiratory muscle strength testing is a routine clinical test performed in the outpatient setting. The side-effect profile is expected to be similar to that of inspiratory muscle training.

2.4.3 Risks of stair-step challenge

The stair-step challenge is a generally safe exercise procedure conducted in the outpatient setting. There is a small chance of tripping or falling during the procedure and possible resulting injury. Close supervision and spotting of the participant will take place to reduce the chance of injury.

2.4.4 Potential risk of loss of confidentiality

There is a potential risk of loss of confidentiality. Every effort will be made to protect the participant's confidential medical information, but this cannot be guaranteed.

2.4.5 Unforeseen risks

There may be other risks to the participant from this research that are not known or foreseeable at this time.

3. OBJECTIVES AND OUTCOME MEASURES

Table 1 Objectives an Outcomes Measures			
Primary Objectives	**Outcome Measures**	**Endpoints**	**Analysis**
Demonstrate IMR as an acceptable add-on intervention in children with obesity.	1. completion of study Visit 3 (V3) 2. adherence to active IMR 3. participant satisfaction among active IMR participants	1. prevalence of completer status 2. prevalence of IMR completion (actual / planned reps over intervention period) in active IMR group 3. prevalence of agree or strongly agree to question of satisfaction with active IMR	Simple descriptive statistics: calculation of prevalence
Secondary Objectives	**Outcome Measures**	**Endpoints**	**Analysis**
Demonstrate changes in inspiratory muscle functioning and dyspnea reporting following IMR	1. Maximum inspiratory pressure (MIP) 2. Baseline Dyspnea Index score 3. MRC breathlessness scale	1. change in MIP over intervention period 2. change in dyspnea scores over intervention period	Analysis of covariance (ANCOVA)
Demonstrate changes in daily physical activity following IMR	1. moderate-vigorous physical activity (MVPA) time 2. sedentary physical activity (SPA) time 3. total steps	1. change in average daily MVPA time 2. change in average daily SPA time 3. change in average daily step count	Analysis of covariance (ANCOVA)
Exploratory Objectives	**Outcome Measures**	**Endpoints**	**Analysis**
Demonstrate changes in exercise capacity following IMR	1. heart rate during 3 minute step test	1. heart rate change during 3-minute step test	Analysis of covariance (ANCOVA)

4. STUDY DESIGN

Overall Design

Single-center, randomized, SHAM-controlled, parallel assignment, double masked, interventional study.

4.1 Randomization

Participants (n=30) will be randomized to one of two treatment arms.

- Arm A (n=15): IMR
- Arm B (n=15): Sham

4.2 Blinding/Masking

Treatment assignment will be obtained through the Duke REDCap randomization system. All participant-facing study staff and participants will be blinded to the treatment assignment. Participants may come to feel that they can surmise whether their device is set to the active resistance. Although complete masking may not be possible in all participants, participants will only be informed that they are receiving one of two resistances (low or active). However, all study staff that assess outcomes (and the lead statistician) will remain blinded. Participants will be instructed to not discuss their presumed IMR assignment with study staff.

4.3 Study Interventions

Active IMR or SHAM using the PrO2™ device. Each participant will be provided a PrO2™ device and trained on its use as well as its accompanying PrO2 Fit™ app. The PrO2™ is a flow-resistive device that provides inspiratory resistance via a fixed 2mm orifice and has Bluetooth connectivity to most IOS/Android devices or Mac/Windows computers. The PrO2™ device and app allows for both 100% adherence monitoring and immediate user biofeedback.

Participants will be instructed at Visit 1 and Visit 2 to inspire forcefully through PrO2™ until the device signals that the user has achieved the target resistance (via audible alarm and visible light signal). The research team will implement biofeedback signals at a specific inspiratory resistance to provide precise and individualized training target. Successful IMR repetitions will require that subjects achieve a pressure target that is 75% of their MIP.

SHAM intervention. Participants in the control intervention will also use the same PrO2™ device but at a reduced peak resistance of 15% MIP. The research team will implement biofeedback signals at a specific inspiratory resistance to provide precise and individualized training target. Successful IMR repetitions will require that subjects achieve a pressure target that is 15% of their MIP.

Adherence monitoring. All device repetitions are automatically captured and documented via the Bluetooth connection with the PrO2™ app and end-to-end encrypted and transferred to a HIPAA-compliant cloud server (Amazon Web Services). Study staff will review each participant's adherence each week and will provide encouragement as needed.

4.4 Duration of Participation for Participant

The approximate duration of participation is 56 days. The maximum duration of participation will be 77 days.

4.5 Biological Specimen Testing

No biologic specimens will be taken.

4.6 Safety

See Section 8.

4.7 Events of Special Interest

Not applicable.

4.8 Rationale for Dose (inspiratory load) Selection

We used published IMR regimens to select an initial resistive load (intensity), number of repetitions/sets per day, and weekly session number for our pilot work (**Table 2**). We first completed an IRB-approved pilot study called the Duke Healthy Breathing Study 1(DHBS1) of directly supervised IMR in 10-17 year-olds with asthma. Using a commercially available IMR respiratory training device, participants with asthma completed and tolerated 4 sets of 60 reps of IMR at 60-75% MIP. We solicited feedback from both adolescents and parents regarding tolerability, acceptability, and future interest in IMR as a potential chronic breathing intervention. Nearly 95% of participants were able to complete all repetitions at 60-75% of MIP.

Table 2 Prior Duke IMR Projects

Investigator (year)	Population	IMR characteristics	Results
Lang/Jones (2017) DHBS1 (Duke funded)	14 children and adolescents (10-17 years of age) with persistent asthma	Repetitions: 4 sets of 50 inspirations Intensity: 60-75% MIP Duration: 1 session	No significant AEs 100% acceptability 13 of 14 were interested in a home intervention
Lang/Jones (2018-2020) DHBS2 (Duke funded)	Participants 10-17 years of age with persistent asthma and obesity or sedentariness	Dose: 1 session twice daily, 3 days/wk. Week 1: session= 1 set of 60 reps Week 2: session= 2 sets of 60 reps Week 3-6: session= 3 sets of 60 reps (with automated IMR monitoring) Intensity: 75% MIP Duration: 6 weeks	11 subjects have completed 6-week intervention: 10/11 (91%) completed all visits 11 (100%) reported desire to continue IMR IMR treated participants showed non-significant improvements in inspiratory muscle strength/ endurance, asthma control and exercise tolerance

MIP – maximal inspiratory pressure, IMR – inspiratory muscle rehabilitation, AE – adverse event

This one-time session was well-tolerated in all participants without any significant adverse events. Thirteen of 14 (93%) participants wanted to continue daily IMR after study completion. Based on DHBS1, we initiated the DHBS2 study, an IRB-approved (NCT03911206) randomized, 'usual care'-controlled, parallel-group, 6-

week intervention trial in which we tested the IMR regimen (75% MIP) in 10-17 year-olds with obesity and asthma.

Participants randomized to the IMR treatment completed 3 sets of 60 repetitions at

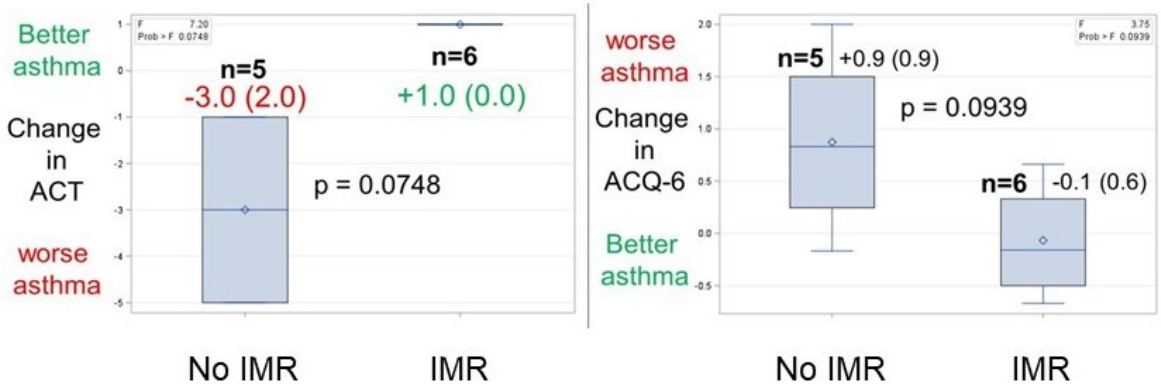


Figure 3 Change in validated asthma symptom scores with IMR. ACT – asthma control test, ACQ6 – asthma control questionnaire 6 item

75% MIP three days per week. Preliminary IMR findings from 11 participants involving changes in respiratory muscle strength and endurance, 6-minute walk distance and asthma symptom scores are encouraging and support the aims of this proposal (See **Figure 3** and **Table 3**). Adherence of IMR (n=6) was 79.2% of prescribed repetitions over 6 weeks, which is superior to published adherence rates (47-57%) for daily asthma controller drugs.

Table 3 Effects of Daily IMR treatment over 6 weeks on Respiratory Outcomes – Preliminary data

Outcome type	**Intervention**			
	IMR (n=6)	**No IMR (n=5)**	**p-value**	**Summary**
Asthma Symptoms: change in ACT, mean (SD) (for ACT, higher score means better asthma)	+1.0 (0)	-3.0 (2)	p=0.075	IMR-treated participants showed a near significant improvement in ACT compared to controls **(Figure 3)**
Asthma Symptoms: change in ACQ-6, Mean (SD) (for ACQ-6, lower score means better asthma)	-0.10 (0.56)	0.90 (0.90)	p=0.094	IMR-treated participants showed a near significant improvement in ACQ-6 compared to control **(Figure 3)**
Inspiratory muscle strength: change in baseline MIP (cm H_20), mean (SD)**	+37.0 (24.1)[1]	+12.5 (16.4)[1]	p=0.128	IMR-treated participants showed near significant greater MIP improvement compared to controls
Inspiratory muscle strength: change in post-exercise MIP (cm H_20), mean (SD)**	+14.6 (10.5)[2]	-19.0 (19.9)[2]	p=0.014	IMR-treated participants showed a significantly greater post-exercise MIP improvement compared to controls
Exercise tolerance: improvement in six-minute walk distance (meters), mean (SD)	119.1 (93.3)	4.0 (112.7)	p=0.136	IMR-treated participants showed non-significant improvement in

				6MW distance compared to controls
**two MIP measures were analyzed at each visit because of acute strengthening. [1] – MIP1 start of visit (before exercise), [2] – MIP2 end of visit (after exercise). ACQ-6 – score ranges from 0 to 6 with lower score meaning better asthma. Minimal important difference =0.4-0.5. ACT – score ranges from 6 to 30 with higher score meaning better asthma. Minimal important difference = 3				

4.9 Study Definition of Enrollment

A participant will be considered *enrolled* in the active study once eligibility criteria are satisfied, informed consent is signed, and the participant receives at least one dose of a study intervention (i.e. one training session).

4.10 Study Definition of Completion

Participant study completion will be defined as a participant who has been enrolled and completes Visit 3.

5. STUDY POPULATION

5.1. Selection of the Study Population

Children 8 to 17 years of age with obesity (BMI ≥ 95th percentile for age and sex) being seen for a visit at the Duke HL clinic, and meeting study inclusion and exclusion criteria will be enrolled. Both males and females are eligible, as are participants of any race or ethnicity. Participants (or parent/guardian) must have access to the internet and an approved device/computer (see below).

5.2. Inclusion/Exclusion Criteria

Inclusion Criteria	1. Documented informed consent from legal guardian and assent from participant as appropriate. 2. Children 8 to 17 years of age with obesity (BMI ≥ 95th percentile for age and sex) being seen at Duke Healthy Lifestyles clinic. 3. Participants (or parent/guardian) must have access to the internet and an approved smart device/computer. 4. Child must have a designated caregiver who expresses a commitment to encourage the participant to complete the study procedures. 5. Participant and legal guardian must speak and read English or Spanish.
Exclusion Criteria	1. Prior enrollment in an IMR program. 2. Contraindications for IMR including a history of recent lung surgery, recent pulmonary embolism, or history of recurrent spontaneous pneumothorax 3. Progressive neurological or neuromuscular disorders or need for chronic O2 therapy. 4. Inability to complete baseline measurements in a satisfactory manner according to the judgment of the research coordinator or PI. 5. Body weight greater than 300 pounds. 6. Any condition in the opinion of the PI that would not allow safe conduct of study procedures (including IMR, MIP testing or step-test), such as a physical disability, recent musculoskeletal injury or illness, current and ongoing evaluation for undiagnosed cardiopulmonary or neurologic symptoms, undiagnosed chest pain, pneumothorax in the past 12 months, inner ear surgery in the past 12 months, or undiagnosed syncopal episodes.

5.3. Screen Failures

Participants who sign informed consent but are not enrolled in the active study are considered screen failures and will be recorded in the Screen Failures area of the electronic data capture (EDC). Participants who do not initially satisfy eligibility requirements may be rescreened up to 2 additional times. Re-consent is not required for rescreened participants unless a revised version of the consent that requires re-consent is made available.

5.4. Treatment Assignment Procedures

5.4.1 Randomization procedures

Treatment assignment will be 1:1 (IMR or sham intervention), and will be obtained through the Duke REDCap randomization system using the randomization schedule as

designed by the unblinded statistician. All study staff and participants will be blinded to the treatment assignment with the exception of one un-blinded clinical research coordinator. Participants may be able to tell whether their device is set to the active resistance. Although complete masking may not be possible in all participants, participants will only be informed that they are receiving one of two resistances (low or active). However, all study staff that assess outcomes (and the lead statistician) will remain blinded. Participants will be instructed to not discuss their presumed IMR assignment with study staff.

5.5. Participant Discontinuation/Withdrawal

5.5.1 Participant decides to withdraw consent

A participant may voluntarily withdraw consent to participate in the study at any time. Participants are not obligated to state the reason for withdrawal. Participant withdrawal should not affect the participant's medical care outside of this study. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator. No additional study procedures or data should be collected after consent has been withdrawn.

5.5.2 Participant decides to withdraw from study intervention/product

Participants may also withdraw from receiving the study intervention/product for any reason but continue to be followed for safety. Participants are not obligated to state the reason for withdrawal.

5.5.3 Study investigator/sponsor decides to withdraw participant

The study investigators or sponsor may decide to take the participant out of this study at any time without consent if:

- Participant's condition changes and the study is no longer in his/her best interest;
- Participant non-compliance with the study protocol;
- The entire study is stopped by the sponsor.

5.5.4 Individual stopping of dosing criteria:

The study investigators will stop treatment of study intervention and the participant will not receive additional doses of study intervention if:

- Participant has a clinically significant severe AE or SAE related to the study intervention;
- Participant becomes pregnant;
- Participant newly meets criteria for study exclusion;
- In the opinion of the investigator, the participant is at significant risk.

If the intervention is discontinued for safety concerns, participants must be followed for safety until 7 days after the last study training session. Participants who are discontinued from study intervention due to an AE, whether serious or non-serious, must be followed by the investigator until the AE is resolved or considered stable.

If any of the above occurs, the participant will be informed, and the investigator will discuss other options.

5.5.5 Handling of withdrawals

The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator. Reasons for withdrawal may include:

a. Participant withdraws consent and requests no further follow-up;
b. Participant does not withdraw consent but withdraws from study intervention;
c. Study PI/Sponsor decision.

Unless there is complete withdrawal of consent from the participant, every effort will be made to continue follow-up visits.

5.5.6 Replacements

Females who become pregnant during the study will not receive further study intervention. In cases of early withdrawal, an additional participant may be enrolled.

6. STUDY PROCEDURES

Procedures will occur as in **Table 4**.

Table 4 Study Procedures

	Screen visit	Randomization visit	Completion visit
Visit number	V1	V2	V3
Timeline in days (target)	-10-14[a]	0	42 (40-56)
Consent/assent	x		
Height/Weight/BMI[#]	x		x
Eligibility assessment	x	x[5]	
Study instructions	x	x	
Actigraphy training[1]	x	x	
PrO2 device/app training		x	
Retrospective Dyspnea scoring[##]		x	x
Dyspnea scoring with exercise[2]		x	x
Randomization		x	
Maximal inspiratory pressure (MIP)[###]		x	x
Stair Step Test		x	x
Adverse event monitoring		x	x
Follow-up actigraphy[3]			x
Patient satisfaction questionnaire			x
phone check-ins[4]	will occur on day (+/- 2) 7, 14, 21, 28, and 35 to assess any problems, encourage adherence and give appreciation for efforts		

1 – worn at least 7 full days (max of 14) prior to randomization
2 – Modified Borg Dyspnea scale and Dalhousie Dyspnea
3 – worn at least 7 full days (max of 14) during week prior to V3; the follow-up actigraphy should occur during the last 14 days.
4 – communication will be made by (IRB approved) mode of participant's choosing including voice call or direct messaging.
5 – assess for eligibility for randomization (tracker adherence, no new exclusions prior to randomization)
a – a date range of 10-14 days prior to randomization is preferred but can be extended up to -28 days. A randomization visit can be scheduled beyond 28 days only at the discretion of the PI.
- should be taken from clinic visit data; may be performed as a research procedure only if needed
- Baseline Dyspnea index (BDI) and MRC Breathlessness Scale
- MIP will be collected before and after the Stair step test

6.1 Screening

The investigator will screen participants in accordance with the eligibility criteria detailed previously. Research staff will document applicable informed consent for all participants who satisfy eligibility criteria, and will follow all site policies, procedures and criteria for control of COVID-19. Participants must satisfy all Inclusion/Exclusion criteria to be enrolled in the active study. Information will be recorded from the clinical medical record or from interview of the participant. The investigator will not exercise selectivity so that bias is prevented.

Informed consent and collection of demographic information will be performed at screening. The following screening assessments must be done to confirm study eligibility: medical history (past medical/surgical history, medications, and smoking/drug history), review of concomitant medications, height/weight/physical exam, and confirm satisfaction of all eligibility criteria (inclusion and exclusion) for the study. Assessments not recorded per standard of care, must be conducted as a study specific procedure.

6.2 Summary of Procedures

6.2.1 Visit 1 (goal timing: day -10 to -14 prior to randomization)

General Visit Description: Eligibility criteria will be confirmed at Visit 1 or via phone call before their visit to the Healthy lifestyle's clinic, if the researcher believes the participant meets eligibility criteria. Research staff will document informed consent from the parent/ guardian in eligible participants. Participants above the age of 12 years will also provide assent. Eligible participants will receive a Breathe Fit study packet with study handouts and study materials.

Equipment/Supplies needed: Body weight scale, stadiometer, eligibility checklist (printed or electronic), participant informational handouts (for activity tracker accompanying smart device(s) to link with activity tracker).

Anticipated duration: Goal is 30-45 minutes.

Visit 1 Procedures:

1. Confirm eligibility (eligibility checklist).
2. Obtain consent and assent (if child is <12 years old). The consenting process will include instruction about general study details (visits, durations, compensation) and participants will be given a study packet of instructions.
3. Obtain participant demographics, including height, weight, and BMI data (these data should be taken from the electronic health record if already collected). If not obtained during routine care, these data will be collected by research staff.
4. Questionnaires (printed or electronic).
5. Actigraphy training (participants will be given a Vivosmart 4 activity tracker in the correct size and taught on its proper fit and use).
6. Following consent, if all V1 procedures are not able to be completed (due to participant time constraints or family preference), an optional V1a (continuation visit) may be scheduled by phone or in-person home or by follow-up clinic visit.
7. Plan day -7 phone check-in (see phone check-in section below).

6.2.2 Visit 2 (Day 0)

General Visit Description: Visit 2 will be Day 0, will re-confirm eligibility prior to randomization, will include randomization if eligible and will start the intervention and observation period. Participants must not newly meet any exclusion criteria and must continue to meet all inclusion criteria. Inclusion criteria for randomization will include collection of at least 7 days of valid actigraphy data (confirmed at Visit 2).

Equipment/Supplies needed: Activity tracker (from participant), accompanying smart device(s), printed questionnaires, participant informational handouts, PrO2 trainer, Stair Step Test equipment.

Anticipated duration: 60 minutes.

Visit 2 Procedures:

1. Assessment of baseline actigraphy (participants must have worn the Vivosmart 4 activity tracker for at least 7 full days (max of 14) prior to randomization. If not,

the date of Visit 2 may be extended for an additional 4-14 days for a continuation Visit 2).

2. Questionnaires and eligibility assessment (eligibility checklist, questionnaires can be printed or electronic) (see questionnaires section).
3. Interval history and event monitoring.
4. Measure Maximal inspiratory pressure (MIP) before and after step test (see MIP section).
5. Stair Step Test (see stair step section).
6. Retrospective dyspnea scoring that assesses dyspnea from daily activities (Baseline Dyspnea Index (BDI), the MRC Breathlessness scale), and during the step-test (Modified Borg Dyspnea scale and Dalhousie Dyspnea/Perceived Exertion Scale).
7. Randomization (see the randomization procedure section).
8. Study instruction refresher and questions/answers.
9. PrO2 Fit app and device IMR training.
10. Refresher Training (question and answers) on the use of Vivosmart 4 activity tracker.
11. Discuss plan for phone call visits and future study visit. Plan next phone call check-in visit (Day 7).

6.2.3 Continuation visit

In the event that during the initiation of Visit 1, 2, or 3, the participant is not able to complete the visit (but remains eligible for study participation), a continuation visit (e.g. 1b, 2b) can be scheduled to finish protocol-defined procedures. The continuation visit will be scheduled at the earliest possible date but no later than 14 days from the previous visit. The continuation visits beyond 14 days out of this window must be approved by the study PI.

6.2.4 Home visit

Conducting all or part of a planned visit is allowed but will only be conducted as a last option, is requested by the participant and legal guardian, and meets all home visit requirements. The home visit must be approved in advance by the PI and deemed to be an appropriate setting (adequate space available, approved by participant's legal guardian, safe environment). Home visits will occur only when two or more IRB-approved study staff members are present and occurring during normal business hours.

6.2.5 Phone check-ins (days -7, 7, 14, 21, 28, and 35)

During phone check-ins, communication will be made by a (IRB approved) mode of participant's choosing including voice-only or zoom call. Research staff will ask if there are any problems, concerns or questions about the study or intervention. Study staff will encourage adherence, and give appreciation for the participant's efforts.

6.2.3 Visit 3 (Day 42) Final In-person visit

General Visit Description: Visit 3 will be on approximately day 42, final assessment of the study. This visit is preferred as an in-person study visit, but may be conducted as an in-home visit if needed (as with Visit 2). Day 42 (+/- 5 days) will be the goal day for study Visit 3. With PI approval, Visit 3 may be conducted up to 14 days away from Day 42, if necessary.

Equipment/Supplies needed: Scale, stadiometer, activity tracker (from participant), accompanying smart device(s), printed questionnaires (or tablet-based REDCap questionnaires), PrO2 trainer (from participant), Stair Step Test equipment, assignment and thank you letter.

Anticipated duration: 60 minutes.

Visit 3 Procedures:

1. Reassessment of participant height, weight, and BMI.
2. Dyspnea scoring assessing daily activities [Baseline Dyspnea Index (BDI), the MRC Breathlessness scale].
3. Dyspnea scoring during the step-test (Modified Borg Dyspnea scale and Dalhousie Dyspnea and Perceived Exertion Scale).
4. Adverse effect monitoring.
5. Measure Maximal inspiratory pressure (MIP) before and after step test.
6. Stair Step Test.
7. Follow up actigraphy (participants must have worn the Vivosmart 4 activity tracker for at least 7 full days (max of 10) during week prior to Visit 3).
8. Patient satisfaction questionnaire.
9. Close out procedures:
    i. Assignment envelope;
    ii. Close out letter (i.e. thank you letter).

6.3 Early Study Termination Visit

No clinic visit will be planned following termination (withdrawal of consent or PI termination). Participants who stop the study intervention early due to a safety concern will still be followed according to the protocol.

6.4 Actigraphy/Physical Activity Assessment

Actigraphy is non-invasive method used to assess cycles of activity and rest over several days to weeks. Actigraphy will be measured using Vivosmart 4 activity tracker, a wrist-band based device that tracks and displays participant fitness activity progress, including steps, floors climbed, calories burned, intensity minutes, oxygen saturation, and heart rate.

Participants will be asked to wear the tracker with the proper fitting (as directed in Visit 1) for at least 7 full days (7 full 24 hour blocks) (max of 14) prior to Visit 2 and at least 7 full days (max of 14) during the week prior to Visit 3.

Participants will be given the safety and product information handout and user's manual from the company that comes with the device. This will include information on battery life and handling, and device precautions.

https://www.garmin.com/en-US/p/605739/pn/010-01995-13#specs

6.5 Maximal Inspiratory Pressure (MIP) Measurement

Each participant will be asked to perform five MIP maneuvers, with a goal of matching the highest two within 10 cmH2O. MIP will be recorded using the PrO2 Fit device. The patient

will be seated for the test. The study staff member will first demonstrate the correct maneuver. The participant will be instructed to exhale slowly and completely, seal lips firmly around the MIP mouthpiece, and then "breathe in as hard as you can, like you are trying to suck up a thick milkshake." The study staff member will note the largest negative pressure sustained on the pressure reading. The participant will be allowed to rest for about 30-45 seconds and then repeat the maneuver 5 times. This procedure will be completed before and again after the 3-minute step test. The change in best MIP value (post minus pre) will be computed.

6.6 Questionnaires/Data Forms

6.6.1 Baseline medical history form

The baseline medical history form will ascertain general demographics, medical evaluation (for eligibility), degree of dyspnea at rest and related to daily activity, and other general respiratory symptoms. This will be completed by the research staff using a combination of adjudicating the electronic health record and direct enquiry from the participant or guardian.

6.6.2 Questionnaire during exercise: Modified Borg dyspnea scale

Ten-unit scale used to denote degree of dyspnea with exercise[28,29] will be assessed at the 1-, 2- and 3-minute marks during the 3-minute step test, and again at post-1, post-2 and post-3.

Patient Instructions for Borg Dyspnea Scale
"This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you right now?"

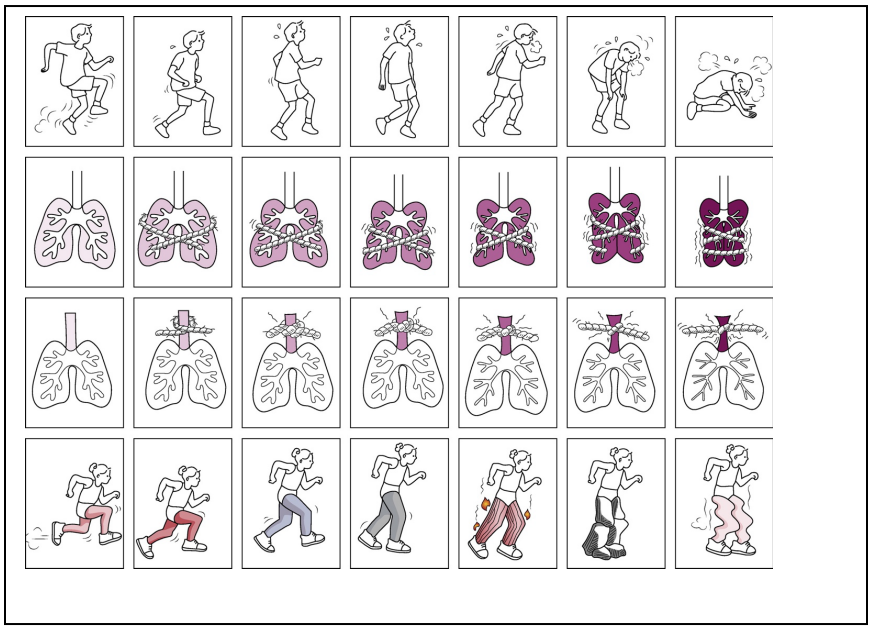
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very Slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very Severe
8	
9	Very, very severe (almost maximal)
10	Maximal

6.6.3 Questionnaire during Exercise: Dalhousie rating with exercise

This will be assessed at the 1-, 2- and 3-minute marks during the 3-minute step test.
The purpose of this test is to assess breathing and leg and body fatigue during exercise. Participants will be told that there is no right or wrong answer. The pictures in the Dalhousie questionnaire[30] will be shown to the

participant and asked to rate their experience from no difficulty at all, to the most difficulty you can imagine. (**Figure 4**)

Research staff will say, “You might feel this difficulty breathing in your chest or in your throat. Another scale simply asks you to tell us how hard it is to breathe—from nothing at all, to the hardest breathing imaginable. With the final set of pictures, tell us how your legs feel—from nothing at all, to the hardest imaginable.”



6.6.4 Retrospective questionnaire assessing dyspnea during daily activity: Baseline Dyspnea Index (BDI).

The BDI [31] is a retrospective questionnaire assessing perceived dyspnea during activities of daily living 'on a typical day' over the past two weeks and will be assessed at Visits 2 and 3.

Baseline Dyspnea Index Questionnaire

I. Functional impairment

_____ **Grade 4**	No impairment	Able to carry out usual activities and occupation without shortness of breath.
_____ **Grade 3**	Slight Impairment	Distinct impairment in at least one activity but no activities completely abandoned. Reduction, in activity at work or in usual activities, that seems slight or not clearly caused by shortness of breath.
_____ **Grade 2**	Moderate Impairment	Patient has changed jobs and/or has abandoned at least one usual activity due to shortness of breath.
_____ **Grade 1**	Severe Impairment.	Patient unable to work or has given up most or all usual activities due to shortness of breath.
_____ **Grade 0**	Very Severe Impairment.	Unable to work and has given up most or all usual activities due to shortness of breath.
_____ **W**	Amount Uncertain	Patient is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
_____ **X**	Unknown	Information unavailable regarding impairment.
_____ **Y**	Impaired for Reasons Other than Shortness of Breath.	For example, musculoskeletal problem or chest pain. Usual activities refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, shopping, etc.

II. Magnitude of Task

_____ **Grade 4**	Extraordinary	Becomes short of breath only with extraordinary activity such as carrying very heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary tasks.
_____ **Grade 3**	Major	Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on the level.
_____ **Grade 2**	Moderate	Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing fewer than three flights of stairs, or carrying a light load on the level.
_____ **Grade 1**	Light	Becomes short of breath with light activities such as walking on the level, washing, or standing.
_____ **Grade 0**	No Task	Becomes short of breath at rest, while sitting, or lying down.
_____ **W**	Amount Uncertain	Patient's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
_____ **X**	Unknown	Information unavailable regarding imitation of magnitude of task.
_____ **Y**	Impaired for Reasons Other than Shortness of Breath.	For example, musculoskeletal problem or chest pain.

III. Magnitude of Effort

_____ **Grade 4**	Extraordinary	Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.
_____ **Grade 3**	Major	Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.
_____ **Grade 2**	Moderate	Becomes short of breath with moderate effort. tasks performed with occasional pauses and requiring longer to complete than the average person
_____ **Grade 1**	Light	Becomes short of breath with little effort tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.
_____ **Grade 0**	No effort	Becomes short of breath at rest, while sitting, or lying down.
_____ **W**	Amount Uncertain	Patient's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
_____ **X**	Unknown	Information unavailable regarding limitation of effort.
_____ **Y**	Impaired for Reasons Other than Shortness of Breath.	For example, musculoskeletal problems or chest pain.

6.6.5 Retrospective questionnaire assessing dyspnea during daily activity: MRC Breathlessness scale.

The MRC breathlessness questionnaire is a retrospective questionnaire assessing perceived dyspnea during activities of daily living 'on a typical day' over the past two weeks and will be assessed at Visits 2 and 3. The score ranges from 0 to 5 with higher score representing worse dyspnea.[31,32]

The MRC Breathlessness scale	
Grade	**Degree of breathlessness related to activities**
0	No breathlessness even with strenuous exercise
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yards or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

6.7 Stair-step Challenge.

The Stair-step Test is a recognized clinical procedure used to measure cardiovascular fitness in adults aged 18 and up. The Bench Stepping Test has been adapted for children aged 5-18 for the purposes of this study. It has been validated in other clinical studies designed to measure the effectiveness of exercise and/or dietary interventions to improve cardiovascular fitness and other clinical measures related to obesity.[33,34]

6.7.1 Preparation for administration of Stair-step Test

1. Ensure that all of the necessary materials are present. Study materials include a stable step, 8 risers, metronome, timer, pulse oximeter, and chair.
2. Step Setup
    a. For ages 8-9: Have child set one foot on the floor and one foot on the step and measure with protractor. Protractor should read between 20 and 30 degrees. Add/remove risers as necessary.
    b. For ages 10-17: Set step on two risers (8 inches).
    c. If patient is ≥ 6'0", have them place one foot on the floor and one on the riser and measure with protractor. Add/remove a riser until protractor reads between 20 and 30 degrees.
    d. Patients over 300 lbs. do not complete the step test
3. Set metronome to beat at 96 beats per minute.
4. Set timer for 3 minutes.
5. Train the subject to complete the Step Test.
    a. In time with the metronome, the subject will step one foot onto the step (1st beat), step the second foot up (2nd step), step down with one food (3rd beat), and step down with other food (4th beat).
    b. Allow a short rest before beginning test.

6.7.2 Administering the Step Test

- Measure baseline (at time 0) heart rate with pulse-oximetry before child begins step test.
- Have child step up and down step at 96 bpm for 3 minutes.
- Assess dyspnea scores at minutes 1, 2 and 3, and post-1, post-2 and post-3.

- After 3 minutes, end the stepping and check child's heart rate on pulse-oximetry (post-1).
- Direct child to sit in chair for one minute, then check heart rate again (post-2).
- Direct child to remain in chair for another minute, then check heart rate (post-3).

6.7.3 Recording heart rate and pulse oximetry

a. Heart rate at baseline, post-1, post-2 and post-3.
b. Pulse oximetry at baseline, post-1, post-2 and post-3.

6.11 Specimen Preparation, Handling, Storage and Shipping

No biological specimens will be collected.

7. STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Intervention Information

7.1.1 Dose of inspiratory muscle training

Arm A: The ***intervention group*** will be required to achieve a pressure target that is ***75% of their MIP*** for each repetition. Participants will perform 3 sets of 50 inspiratory breaths 3 times per week.

Arm B: The ***sham group*** will be required to achieve a pressure target that is ***15% of their MIP*** for each repetition. Participants will perform 3 sets of 50 inspiratory breaths 3 times per week.

7.1.2 Formulation, packaging, and labeling

The PrO2™ is a flow-resistive device that provides inspiratory resistance via a fixed 2mm orifice and has Bluetooth connectivity to most IOS/Android devices or Mac/Windows computers. The PrO2™ device and app allows for both 100% adherence monitoring and immediate user biofeedback.

7.1.3 Product use and directions

Participants will be instructed to inspire forcefully through PrO2™ until the device signals that the user has achieved the target resistance (via audible alarm and visible light signal). The research team can implement biofeedback signals at a specific inspiratory resistance, which allows for a precise and individualized training target.

At Visit 1: Participants will download the PrO2™ Fit App from the Apple App Store or Google Play. They will be shown how to set up their own PrO2 Fit account and how to connect with their PrO2™ trainer. Research staff will review the planned dosing to start after visit 2. They will be instructed to try to avoid inferring what treatment assignment they have been given, and to not share any impressions they have developed on treatment assignment. The proper use of the trainer will be taught, including safe storage, cleaning and maintenance. Participants will be taught to create an air-tight seal over the mouthpiece after maximal exhalation. The participant will be instructed to breathe in forcefully until the device alarms then continue to maximal inspiration. At Visit 1, participants will be taught on the device while the alarm is set for 15% of their MIP. They will complete a set of 50 repetitions supervised so their technique is assessed and re-direction can occur if needed.

At Visit 2: participants will have refresher training on the use of the PrO2™ Fit app and will repeat their supervised single set of 50 repetitions while supervised to ensure they have the proper technique and the device is working properly.

Research staff will encourage participant and guardian to discuss a plan to optimize adherence to the IMR intervention. This may include picking particular days of the week (e.g. MWF, TuThS) and particular activities to link with IMR (e.g. in mornings before school, evenings before homework, etc.). Guardians will be asked to commit to helping the participant remember their intervention days.

7.2 Accountability Procedures for the Study Product(s)

The PrO2™ devices will be purchased and provided by PrO2 Health Inc.

8. ASSESSMENT OF SAFETY

8.1 Adverse Event

All adverse events during the study period will be collected.

An **adverse event (AE)** is any untoward medical occurrence in humans, whether or not considered study drug-related, which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator is considered an AE.

An **unexpected Adverse Event** is defined as any adverse event, the nature, specificity, or severity of which is not consistent with the applicable product information (e.g., package insert/approved label) or investigational plan.

A **suspected adverse reaction (SAR)** is any adverse event for which there is a reasonable possibility that the study intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study intervention caused the event. An **adverse reaction** is any AE caused by the study intervention.

8.2 Guidelines for Assessing Association of an Adverse Event

A **serious adverse event** (SAE) or **serious suspected adverse reaction** or **serious adverse reaction** as determined by the investigator or the sponsor is an adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death
- Life-threatening AE ("life-threatening" means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital abnormality or birth defect
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.3 Guidelines for Assessing Intensity of an Adverse Event

The investigator/delegate (defined as a clinician licensed to make a diagnosis) should use the following definitions when assessing intensity of an adverse event:

- **Mild -** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required.
- **Moderate** - Participant experiences enough symptoms or findings to require intervention.
- **Severe -** Participant experiences symptoms or findings that require significant intervention.

8.4 Guidelines for Assessing Causality

The investigator/delegate (defined as a clinician licensed to make a diagnosis) will use the following question when assessing causality of an AE to study intervention: Is there a reasonable possibility that the intervention caused the event? "Reasonable possibility" means that there is evidence to suggest a causal relationship between the study

intervention and the AE. An affirmative answer designates the event as a suspected adverse reaction. The investigator/delegate (defined as a clinician licensed to make a diagnosis) must document their assessment of severity and causality in the participant records in a timely manner and submit safety reports as required by their IRB/REB/IEC.

8.5 Collection Period and Reporting Procedures

Adverse event information will be gained from direct monitoring of the study participants as well as from clinician observation and self-reporting by the study participants. The investigator/delegate (defined as a clinician licensed to make a diagnosis) must document their assessment of intensity and causality in the participant records in a timely manner and submit safety reports as required by their IRB.

8.5.1 Adverse Events and Serious Adverse Events

Adverse events (AEs) and SAEs will be reported from the time of consent through the end of study participation.

Participants who have study intervention stopped due to a safety concern will be followed for an additional 7 days from the time the intervention was stopped.

Adverse events (AEs) will be followed until resolution, even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Adverse events (AEs) will be entered in the data system within 7 days of identification. Serious adverse events (SAEs) will be entered in the data system within 24 hours of identification.

Any SAE entered in the EDC system will generate an automatic email notification to the DCC, BPCA medical monitor, and the sponsor. The BPCA medical monitor will review all SAEs at the time they are reported. The investigator/delegate (defined as a clinician licensed to make a diagnosis) must document their assessment of severity and causality in the participant records in a timely manner and submit safety reports as required by their Institutional Review Board (IRB)/ Research Ethics Board (REB)/ Institutional Ethics Committee (IEC).

8.5.2 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Serious, unexpected, suspected adverse reactions related to terbutaline sulfate will be reported from the time of first study procedure through the end of study participation. SUSARs can be elicited at any time during the defined study period. SUSARs will be entered in the data system within 24 hours of site awareness.

8.6 Event of Special Interest

Not applicable.

8.7 Safety Interim Analysis

No interim analysis is planned.

9. STUDY HALTING/TERMINATION

9.1 Study or Site Halting/Termination Criteria

This study may be terminated at any time by the study PI or sponsor. Reasons for termination include but are not limited to, if in their judgment, there are no further benefits to be achieved from the study, or, if the treatment presents an unreasonable and significant risk to participants. If the study is terminated, notifications will be made to the regulatory authorities, investigators, or study participants, as appropriate, in accordance with all applicable regulations governing the study and site/investigator.

9.2 Halting Rules

No halting rules are planned.

Individual participant stopping criteria are outlined in the section above titled Study Investigator/Sponsor Decides to Withdraw Participant

10. STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

Primary Specific Aims: Compare measures of satisfaction, adherence and safety between patients randomized to IMR as compared to sham to demonstrate IMR as an acceptable add-on intervention that promotes greater activity in children with obesity with no safety concerns. More satisfaction and adherence are expected in the IMR group compared to sham.

- Hypothesis 1: More than 80% of participants will be satisfied with active IMR at study completion.
- Hypothesis 2: Total active IMR adherence will be >80% of planned IMR repetitions.
- Hypothesis 3: Active IMR will not be associated with any serious adverse reactions.

Secondary Aim: Compare inspiratory strength (measured by mean change in MIP) in IMR versus sham participants to demonstrate changes in inspiratory muscle functioning and dyspnea following IMR. Also, to demonstrate changes in daily physical activity following IMR versus sham participants.

- Hypothesis 1: IMR will significantly increase inspiratory strength (measured by mean change in MIP) with more improvements in IMR compared to participants receiving sham.
- Hypothesis 2: IMR will reduce patient-reported dyspnea scores from activities of daily living and during the step test.
- Hypothesis 3: IMR will lead to reduced sedentary time, increased moderate-strenuous time and increased total daily activity measured by a wrist-worn continuous activity tracking monitor.

Exploratory Aim: Demonstrate changes in exercise capacity following IMR versus sham participants.

- Hypothesis 1: IMR will reduce the peak heart rate increase induced by the step test in IMR compared to sham participants.

10.2 Objectives and Endpoints

Aim 1:

- Satisfaction with active IMR (yes/no) as an intervention rated at study completion measured as a percentage of study completers.
- Active IMR adherence measured as a percentage of planned IMR repetitions (completer status).
- Serious adverse events (yes/no) measured as a percentage of participants receiving at least one active IMR intervention.

Aim 2:

- Change in maximum inspiratory pressure as measured by maximal inspiration in centimeters of water.
- Change in dyspnea as measured retrospectively of activities of daily living.
- Change in sedentary time measured by mean daily sedentary time assessed by the Vivosmart 4 activity tracker.

- Change in moderate-strenuous physical activity time measured by the mean daily MVPA time assessed by the Vivosmart 4 activity tracker.
- Change in total daily activity measured by mean daily step count and mean daily calorie expenditure.

Aim 3:

- Change in heart rate during step test.

10.3 Analysis Population

All participants who are randomized and receive at least one IMR intervention will be included in the modified intention-to-treat (MITT) population.

10.4 Timing of Analyses

The final analysis will be performed when the last recruited patient has completed Visit 3 and after the finalization and approval of the statistical analysis plan document. The final analysis will be performed on blinded data transferred to the lead statistician following data cleaning conducted by a study research coordinator. Data cleaning will include checking for missing data/extreme values and outliers.

10.5 Missing Data

Missing at random will be judged based on tabulating missing Visit 3 primary outcome values by intervention group and demographic characteristics. If there is a substantial amount of missing data and missingness is considered to be not random, sensitivity analyses utilizing worst-case/baseline scenarios or imputation will be used for descriptive and inferential assessments to address attrition bias.

10.6 Multiple Testing

Adjustment for multiple testing will not be performed given the exploratory nature of this study.

10.7 General Summary of Study Data

Statistical analyses will be overseen by Dr. Cindy Green, a faculty member within the Department of Biostatistics & Bioinformatics at Duke. She will serve as the unblinded statistician and oversee the lead statistician.

Patient disposition, demographics, baseline measurements, outcomes and adverse events will be summarized overall and by intervention group. We will use standard summary statistics to describe the distribution of outcome measures outlined in each aim by intervention group including mean, standard deviation (SD), median, 25^{th} and 75^{th} percentiles (Q1-Q3) and range for continuous variables and frequency counts with percentages for non-missing data. We will assess distribution and normality assumptions, identify outliers, evaluate missing data and check for unusual patterns. We will use SAS version 9.4 or higher (SAS Institute, Inc., Cary NC) for all analyses, and a two-sided p-value <0.05 will be considered statistically significant. Data derivations, calculations and analysis programs will be archived to allow future replication of our results.

10.8 Subject Disposition

Some withdrawal from the study is expected for various reasons. A CONSORT diagram will be used to describe the number of patients that reached the various stages of the trial and the number of participants that dropped out and for what reasons.

10.9 Protocol Deviations

Protocol deviations are expected to be minimal and will be summarized in tables by randomized intervention group.

10.10 Efficacy Analyses

Aim 1: We will use exact 95% confidence intervals and Fisher's exact test to report and compare the expected satisfaction, adherence and SAE percentages within the IMR compared to the sham group.

Aim 2: We will use analysis of covariance (ANCOVA) to estimate and test the difference in mean 6-week change between treatment groups (IMR versus Sham) for each outcome adjusting for the baseline value of the outcome variable. Given the small sample size, sex (male/female), age, and BMI will each be evaluated in separate ANCOVA models. We will report adjusted (least squares) means with 95% confidence intervals (CI) for each group, as well as the estimated between-group difference in means with 95% CI and p-value for testing the null hypothesis of no difference between group means. The model assumptions will be verified for each outcome, and model fit will be assessed using residual plots.

10.11 Sample Size Considerations

For pilot studies, determining the sample size based on power calculations is problematic and often not recommended[35,36] due to problems of type II error and the inability for a small study to reject the null hypothesis. Pilot sample sizes between 10-16 per intervention arm[37-39] are justified. Our plan of 15 participants in each IMR arm is feasible given past HL recruitment success and will result in reasonably good power estimates as shown in (**Table 5**).

Table 5 Statistical power based on effect size

	Attrition			
	0%	**6.7%**	**13.3%**	**20%**
Effect size	**N=30**	**N=28**	**N=26**	**N=24**
Cohen's d=0.75	0.509	0.480	0.451	0.420
Cohen's d=0.85	0.613	0.581	0.548	0.512
Cohen's d=0.95	0.709	0.677	0.642	0.604
Cohen's d=1.05	0.793	0.762	0.729	0.691
Cohen's d=1.15	**0.860**	**0.834**	**0.803**	0.768
Cohen's d=1.25	**0.910**	**0.889**	**0.864**	**0.833**

11. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

11.1 Informed Consent Process

Informed consent is a process that is initiated prior to the participant agreeing to participate in the study and continuing throughout the individual's study participation.

11.2 Permission from Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study specific procedures or intervention.

Extensive discussion of risks and possible benefits of participation in this study will be provided to the participant. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participant will provide consent prior to being enrolled in the study. The participant may withdraw consent at any time throughout the course of the study. A copy of the executed informed consent document will be given to the participants for his/her records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor, or designee will provide the investigator, in writing, any new information that bears significantly on the participant's risk to participating in the study. This new information will be communicated by the investigator to participants who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented, if necessary. Site staff may employ IRB-approved recruitment efforts prior to the participant consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be executed. By providing informed consent, the participant agrees to complete all evaluations required by the trial, unless the participant withdraws voluntarily or is involuntarily withdrawn from the trial for any reason. Participants may be asked to authorize exchange of information between the study staff and their primary care provider and/or other significant medical providers.

11.3 Documentation of Consent

Consent must be documented using forms and processes determined by the Duke University Health System (DUHS) IRB.

Prior to enrollment of participants into this trial, the protocol, the applicable informed consent template, and any materials or advertisements presented to participants will be reviewed and approved by the DUHS IRB. The consent templates approved by DUHS IRB will then be provided to sites and revised as necessary to comply with local regulations and institutional requirements. Sites are required to submit all changes to the templates to the BPCA DCC, which ensures compliance with US and international regulations and sponsor (NIH) policies, prior to submission and approval to the IRB/REB/IEC of record for each site. Notification of the IRB/REB/IEC 's approval, its composition, and the institution's federal-wide assurance number (FWA) will be provided to the BPCA DCC.

Should amendments to the protocol and consent documents be required, the amendments will be written by the sponsor, approved by the DUHS IRB, and provided to the site investigator for submission to the site's IRB/REB/IEC of record.

Participants may be compensated for their participation in this study. Compensation will be in accordance with the local IRB/REB/IEC's policies and procedures and requires IRB/REB/IEC approval, and must be documented in the consent forms.

For non-English speakers, a fully translated consent or an oral presentation accompanied by a short form may be used to obtain informed consent. The fully translated consent and the short form must be approved by the site's IRB of record and executed according to local requirements.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the executed informed consent document will be given to the participant for their records.

Site staff may employ IRB/REB/IEC-approved recruitment efforts prior to the participant consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, informed consent or waiver of informed consent must be obtained. The informed consent process will be conducted and the form fully executed e.g., signed and dated, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor, or designee will provide the investigator, in writing, with any new information that bears significantly on the participants' risk to receive the investigational product. This new information will be communicated by the site investigator to participants who consent to participate in the trial in accordance with IRB/REB/IEC requirements. The informed consent document will be updated, and participants will be re-consented, if necessary.

11.4 Confidentiality and Privacy

All research activities will be conducted in as private a setting as possible.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The PI will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined in the informed consent document (if approved by the IRB).

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/REB/IEC, and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/REB/IEC, Institutional policies, or sponsor requirements. Both the site PI and the Institution at which the study is contracted to be conducted, will hold responsibility to maintain custody of all study records until the sponsor permits their destruction.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the BPCA-DCC. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the BPCA-DCC research staff will be secured and password protected.

To further protect the privacy of study participants, this study is covered by a Certificate of Confidentiality (CoC) from the NIH. The CoC limits the ability of courts and other agencies from forcing the study team to share participant information or body fluids during a legal or legislative action without the participant's permission.

12. DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state and federal laws, and the International Council for Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB/REB/IEC of any safety issues related to the study and the study intervention, including reports of serious adverse events, and all IND safety reports, as required by their IRB/REB/IEC.

12.1 Data Handling

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the eCRFs to record and maintain data for each participant enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF should be consistent with the data collection form/source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the data collection forms and eCRFs.

12.2 Data Management Responsibilities

All data collection forms and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality by a licensed clinician, and reviewed by the site principal investigator or designee. Data collection, management and quality review is the responsibility of the clinical trial staff at the site under the supervision of the principal investigator. During the study, the investigator must maintain complete, current and accurate documentation for the study.

The unblinded and lead statistician will be responsible for the statistical analyses, and reporting of the final study results.

12.3 Data Capture Methods

Clinical data (including AEs) will be entered into a 21 CFR Part 11-compliant web-based data capture system (REDCap). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the data collection forms/source documents.

12.4 Types of Data

Data for this study will include safety, efficacy, and outcome measures.

12.5 Timing/Reports

No interim analysis is planned, so the final report will serve as a summary of the study.

12.6 Study Records Retention

Study records and source documents will be kept until the child is 21 years of age. The research data collected in this study will be kept indefinitely.

The disposition date related to FDA application will be posted on the PTN website for the Investigator’s reference.

12.7 Protocol Deviations

A protocol deviation is any noncompliance/unplanned excursion from approved investigational plan (e.g., protocol, MOP), or ICH GCP guidelines. The noncompliance may be on the part of the participant, investigator, or site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. For this study, certain procedures obtained out of window will not be considered protocol deviations in order to facilitate retention of participants for later study assessments but will be tracked and reported to the sponsor.

Each investigator must adhere to the investigational plan as detailed in the study protocol and/or associated study materials (e.g. MOPs, Forms Instructions, User Guides etc.). Each investigator will be responsible for the training of delegated staff and enrolling only those participants who have satisfied all protocol eligibility criteria.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor, via the BPCA DCC's Electronic Data Capture (EDC) system.

All deviations from the protocol must be reported in the study records/data system. Protocol deviations must be submitted to the local IRB/REB/IEC per their guidelines. The site investigator and study staff are responsible for knowing and adhering to their IRB/REB/IEC requirements.

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