PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Inspiratory muscle training protocol for patients with chronic obstructive pulmonary disease (IMTCO-study): a multicentre randomised controlled trial
AUTHORS	Charususin, Noppawan; Gosselink, Rik; Decramer, Marc; McConnell, Alison; Saey, Didier; Maltais, Francois; Derom, Eric; Vermeersch, Stefanie; Helvoort, Hanneke; Heijdra, Yvonne; Klaassen, Mariska; Glöckl, Rainer; Kenn, Klaus; Langer, Daniel

VERSION 1 – REVIEW

REVIEWER	Nicolino Ambrosino University Hospital , Pisa, Italy No competing interest
REVIEW RETURNED	29-Apr-2013

GENERAL COMMENTS	This is a well written protocol by well known researchers in the field which potentially may give important clincial information for the comprehensive management of COPD patients. We need only to know more details on insurance of patients.

REVIEWER	Jean K. Berry, PhD, APN Clinical Associate Professor Emerita University of Illinois at Chicago College of Nursing Chicago, Illinois
REVIEW RETURNED	18-Jun-2013

GENERAL COMMENTS	This is an important study to determine the effectiveness of IMT using a different type of device from the traditional threshold device. I have posed a few questions that you may have already addressed in your detailed study plans. 1. How did you determined your schedule for the IMT training sessions? Since this method of IMT is new (due to the new design of the device), it might be helpful to run a small pilot study testing the loads and schedule of training on patients with COPD. While It should be easier to tolerate this training, working at higher lung

	volumes could be more challenging for these patients. 2. How will you assure the rigor and reliability of measure across the five sites. The initial video with instructions will be helpful, but over time, ilt may be necessary to reaffirm the consistency of procedures and measurements by some method. Standardization of measurements between 5 sites will be challenging. The video will provide initial instructions, but some intermittent coordination of reliability testing/checking of techniques would strengthen the ability to combine results of all sites. 3. Will the number of minutes and the amount of time for rest always be standard for each patient? If a weaker patient required a longer rest period in order to complete the training, how is this handled. Regarding the control group - could 10% of PImax represent an actual training load for weaker patients? The difference in training schedules for intervention vs control groups with only 50% of the time training for control group members adds another variable. 4. How will you handle patients who get respiratly infections/exacerbations. Will they be dropped, put on hold and restarted, or otherwise managed so that you don't lose them? 5. It is not stated if there is a criteria for disease severity, or age range for your subjects. Assuming they are all at least moderate in disease, will any very young or very old subjects be excluded from the sample if they otherwise meet the criteria?

VERSION 1 – AUTHOR RESPONSE

Reviewer: Nicolino Ambrosino
University Hospital, Pisa, Italy
- No competing interest
- This is a well written protocol by well known researchers in the field which potentially may give important clinical information for the comprehensive management of COPD patients. We need only to know more details on insurance of patients.
R: The following statements on insurance of patients have been made in the collaboration agreement that has been approved by all collaborating sites: “In accordance with the Belgian law relating to experiments in humans dated May 7, 2004, KU/UZ Leuven shall assume, even without fault, the responsibility of any damages incurred by a Subject and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance program. All collaborating sites shall have and maintain in full force and effect during the term of this Agreement (and following termination of the Study to cover any claims arising from the Study) adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability, and (iii) other possible damages resulting from the Study at the Institution required by local law, each such insurance coverage in amounts appropriate to the conduct of the services of the Participating Site under this Agreement.” This information has been added to ‘study design’ paragraph in the methods section (page 6; lines 8-16).

Reviewer: Jean K. Berry, PhD, APN
Clinical Associate Professor Emerita
University of Illinois at Chicago College of Nursing, Chicago, Illinois
- This is an important study to determine the effectiveness of IMT using a different type of device from

the traditional threshold device. I have posed a few questions that you may have already addressed in your detailed study plans.

1. How did you determine your schedule for the IMT training sessions? Since this method of IMT is new (due to the new design of the device), it might be helpful to run a small pilot study testing the loads and schedule of training on patients with COPD. While it should be easier to tolerate this training, working at higher lung volumes could be more challenging for these patients.
R: The training load in this study will be adjusted according to data from a previously performed pilot study about a home-based, high intensity IMT programs in COPD patients with inspiratory muscle weakness (page 17 reference 28: Langer D, et al (2013)). In this pilot study we used the same methods as described in the manuscript to increase training loads. Patients in the pilot study were very compliant with this protocol and achieved meaningful improvements in inspiratory muscle function. They also tolerated significantly higher training intensities than patients training with previously used threshold loading devices. The program was effective despite of shorter training durations in comparison to previously established protocols. Based on these data we assume that the IMT training protocol in this study should also lead to clinically relevant improvements in inspiratory muscle function. This information has been added to 'intervention' paragraph in the methods section (page 7; lines 7-9).

2. How will you assure the rigor and reliability of measure across the five sites? The initial video with instructions will be helpful, but over time, it may be necessary to reaffirm the consistency of procedures and measurements by some method. Standardization of measurements between 5 sites will be challenging. The video will provide initial instructions, but some intermittent coordination of reliability testing/checking of techniques would strengthen the ability to combine results of all sites.
R: According to suggestions of the reviewer, this information has been added to 'study design' paragraph in the method section (page 5; lines 13-19). Besides a manual of procedures and an instructional video we will also pay visits to every site to instruct the responsible parties on-site about the correct performance of the interventions and measurements. Collaborators from participating centers will also be invited to the University Hospital Leuven to follow an instructional session on the performance of all measurements and interventions. To further improve the consistency between centres, the five sites will regularly receive a newsletter to update them on the progress of the study and to share eventual technical problems between centers. Staff from all participating centres will be able to contact the coordinating center in Leuven by e-mail or telephone in case they should have any questions concerning the study. We will furthermore centralize data management so that all data will be collected, entered, and quality-controlled in the coordinating center in Leuven in order to detect possible flaws in the collected data and to make collaborating centers aware of these shortcomings.

3. Will the number of minutes and the amount of time for rest always be standard for each patient? If a weaker patient required a longer rest period in order to complete the training, how is this handled? Regarding the control group - could 10% of PImax represent an actual training load for weaker patients? The difference in training schedules for intervention vs control groups with only 50% of the time training for control group members adds another variable.
R: Each cycle or session will be separated by at least one minute resting period until the patient recovers from the exhaustion. Patients are also allowed to take short breaks during each cycle and will be given the opportunity to split up their 30 breaths sessions in to two or three blocks of breathing if needed. Resting periods will be given as needed as long as patients are able to complete the full volume of training that is prescribed. This information has been added to 'intervention' paragraph in the methods section (page 9; line 13-14).
A training load of 10% PImax is used in the endurance exercise training (sham) group. Based on previous meta-analyses in patients with COPD it has been concluded that training loads below 30% of PImax do not have significant effects on patients' inspiratory muscle function.
Total training duration in sham and intervention group will be identical. Total daily training time for

both groups will be 21 minutes, consisting of 6 cycles of 30 breaths (two cycles, three times daily in the intervention group or three cycles, two times daily in the control group).

4. How will you handle patients who get respiratory infections/exacerbations? Will they be dropped, put on hold and restarted, or otherwise managed so that you don't lose them?
R: According to suggestions of the reviewer, this information has been added to 'intervention' paragraph in the method section (page 9; lines 16-20). When patients experience acute exacerbations or respiratory infections leading to hospitalizations during the training period, they will temporarily interrupt their participation in the rehabilitation and IMT program. Based on guidance from the treating pulmonologist they will however return to the program as quickly as possible. Periods of infections, exacerbations, and hospitalizations will be registered and their stay in the program will be prolonged in order to complete 12 weeks of IMT training program. Patients will not be dropped or restarted if they are able to continue their program. Only patients who withdraw their consent or who are unable to return to the rehab program after their exacerbation or hospitalization period will be considered drop-outs.

5. It is not stated if there is a criteria for disease severity or age range for your subjects. Assuming they are all at least moderate in disease, will any very young or very old subjects be excluded from the sample if they otherwise meet the criteria?
R: This study is focused on COPD patients who are eligible for participation in an outpatient pulmonary rehabilitation program. Therefore, all patients -independent of severity or age- with spirometry-proven and inspiratory muscle weakness will be eligible to participate in this study. Most patients who are eligible for participation in these programs will however be diagnosed with moderate to severe airflow obstruction (FEV1 < 50% predicted).