**Protocol Title:**

**The effect of manual therapy and exercise on age-dependent lung function: a randomised controlled trial.**

**The MELT trial**

Version Number: 2

Date of Protocol: 10 September 2016

SYNOPSIS

Ageing is associated with a range of anatomical and physiological changes. In the case of the musculoskeletal system, ‘normal’ age-dependent changes in the thoracic spine and chest wall start to manifest as early as 40 years of age and include progressive stiffening of the spine, decreasing chest wall compliance, alterations in breathing mechanics and declining lung function.

If an intervention designed to increase chest wall compliance is applied before these age-related changes became irreversible, it is theoretically possible that the intervention could mitigate the changes and deliver improvements in lung function.

The primary aim of this study is to investigate whether manual therapy administered to the spine and chest wall, can mitigate the effects of ageing on these tissues and improve lung function. The secondary aims are to investigate whether different forms of manual therapy are equally effective at achieving this and if improvements continue after intervention has been stopped.

Three hundred and six (306) healthy people between the ages of 50 and 65 years will be randomly allocated to three equal groups. The first group will receive a standardised walking exercise program performed on a treadmill (Ex); the second group will receive a mobilisation protocol administered to the thoracic spine and ribs followed by the same exercise program (MB); and the third group will receive a manipulation protocol administered to the thoracic spine and ribs followed by the same exercise program (MT). Interventions will be administered on six (6) occasions over a 3 week period (weeks 1-3 of the trial). Participants will be required to attend a total of eight (8) times over a period of 9 weeks.

The primary outcome measure is lung function (Forced expiratory volume in the 1st second: FEV1 and forced vital capacity: FVC). Secondary outcome measures include chest expansion (tape measure) and quality of life questionnaire (SF-36). Outcome measurements will be taken at baseline and then again at weeks 3, 6 and 9.

All MT will be administered just prior to exercise.

Collecting outcome measurements after intervention has been stopped will establish whether MT delivers any ongoing improvements in lung function.

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**Summary**

Study title: The effect of manual therapy and exercise on age-dependent lung function: a randomised controlled trial.

Protocol version: 2

Objectives Primary objective: To investigate whether manual therapy administered to the spine and ribs, can mitigate age-dependent changes in lung function

 Secondary objectives: To investigate whether different forms of manual therapy are equally effective at changing lung function and whether these changes continue once intervention has stopped.

Study design Randomised controlled trial

Planned sample size 306

Selection criteria (i) 50-65 years of age

 (ii) Healthy with no history of respiratory disease

 (iii) Currently non-smoking (for preceding 6 months)

 (iv) Able to walk unaided and un-assisted

Study procedure The application of exercise with and without thoracic mobilisation or manipulation to healthy people between the ages of 50 and 65 years.

Statistical considerations

Sample size calculation 306 (3 Groups of 102)

Analysis plan Data will be reported as group means, standard deviations and confidence intervals. Analysis will be performed as an ANCOVA for difference between groups with baseline as a covariate. Statistical significance will be set at p<0.05. Missing data will be accounted for by using an intention-to-treat analysis with data from subjects lost to follow-up imputed using the last observation carried forward method. The Number Needed to Treat will be calculated using Bender’s method for confidence intervals.

Duration of the study 2 years

Funding Osteopathy Australia

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#  BACKGROUND

## Disease Background

Ageing is associated with a range of anatomical and physiological changes. Establishing whether a change is part of ‘normal’ ageing or the early signs of disease is however, often difficult. In the case of the musculoskeletal system, ‘normal’ age-dependent changes in the thoracic spine and chest wall include a reduction in spinal muscle thickness, costal cartilage calcification, osteoporosis and spondylosis.[1-3] These changes start to manifest as early as 40 years of age and lead to progressive stiffening of the spine, decreasing chest wall compliance and declining lung function.[2, 4]

As chest wall compliance is a major determinant of static lung volumes, improving compliance leads to improvements in lung volumes. Changes in lung volume are assessed using functional lung assessments such as forced vital capacity (FVC) and forced expiratory volume in the 1st second (FEV1).

If an intervention designed to improve chest wall compliance was applied before the age-dependent musculoskeletal changes became irreversible, it is theoretically possible that such an intervention could mitigate these changes and deliver improvements in lung function.

Sandoz (1976) was the first to test this concept when he proposed that altering the “dynamic capabilities” of the thoracic kyphosis would improve lung function.[5] In his seminal work, Sandoz administered a 6 week course of manual therapy (mobilisation or manipulation) to the thoracic spines of 20 women between the ages of 60 and 65. He found both interventions produced clinically meaningful increases in lung function with manipulation producing a greater increase than mobilisation. Interestingly he noted that the maximum improvement in lung function was reached after 3 weeks of intervention for both interventions with no additional improvements achieved during a further 3 weeks of intervention.

This means there may be a functional limit to the effect that manual therapy can have on the reversibility of age-dependent changes.

Others have repeated this experiment on younger people with similar results.[6-8] However, these studies all used small sample sizes and did not address the central issue of the reversibility in lung function that Sandoz was alluding to.

## Rationale for Performing the Study

The hypothesis being tested is: That administering manual therapy to the thoracic spine and ribs of healthy people between the ages of 50 and 65 years produces improvements in lung function.

STUDY OBJECTIVES

## Primary Objective

To investigate whether manual therapy can mitigate normal age-dependent changes in lung function.

## Secondary objectives

To investigate whether different forms of manual therapy are equally effective at changing lung function, and whether the changes continue after intervention has stopped.

#  STUDY Design

## Design

Randomised controlled trial

## Study Groups

Three groups

Group 1: Exercise (Ex)

Group 2: Mobilisation + Ex (MB)

Group 3: Manipulation + Ex (MT)

## number of participants

306 in total: 3 groups of 102

## number of centres

Two Southern Cross University clinics – Lismore and Gold Coast

## duration

Duration: 24 months

Start Date: 22 August 2016

End Date: 22 August 2018

2.6. FUNDING

Osteopathy Australia

#  Participant section

## Inclusion Criteria

* Sex: Male and Female
* Age range: 50-65 years
* Disease status: Healthy
* Currently non-smoking (preceding 6 months)
* Willingness to provide written informed consent.
* Willingness to participate in and comply with the study requirements.
* Able to walk unaided and un-assisted for 10 minutes

## Exclusion Criteria

* Inability to walk unaided and un-assisted
* Contra-indication to thoracic manual therapy
	+ Osteoporosis
	+ Thoracic joint instability
	+ Acute pain on thoracic joint range of motion testing
	+ Below normal chest wall musculature for age and gender
	+ High level of anxiety related to receiving thoracic spinal

mobilisation or manipulation

* Inability to understand English
* People with a cognitive impairment, an intellectual disability or a mental illness

#  STUDY Outline

## 4.0 METHODS

The Study Flow Chart is outlined in 4.1.

Volunteers, who meet the inclusion criteria will be given an information sheet and asked to provide consent. They will then undergo screening for contra-indications to thoracic manual therapy (see 4.4 below). After a volunteer has passed the screening test they will be enrolled in the trial and given a trial specific ID number. Baseline measurements for each participant will then be taken. These include lung function, chest expansion and a quality of life questionnaire.

All outcome measures will be taken by a research assistant. Lung function (Forced expiratory volume in the 1st second: FEV1 and forced vital capacity: FVC) will be assessed using spirometry. Chest expansion will be measured using a tape measure. Quality of life scores will be calculated using the SF-36 Health Survey questionnaire (short form). Spirometry and chest expansion will be assessed with the participant in a standing position.

All exercise (Ex) will be supervised by students enrolled in the Master of Clinical Exercise Physiology degree at Southern Cross University who have experience in the exercise protocol used in the trial. All manual therapy (MB and MT) will be administered by students enrolled as interns in the Masters of Osteopathy degree who have been trained in the relevant manual therapy protocols used in the trial. These students will be supervised by qualified health practitioners at all times.

Exercise (Ex) consists of a standardised 10 minute walking program performed on a treadmill. Joint mobilisation (MB) consists of a pre-determined series of manoeuvers designed to increase mobility in the thoracic spine and rib cage (Grade III-IV mobilisation – Maitland [9]). Joint manipulation (MT) consists of two separate manipulations (Grade V mobilisation - Maitland [9]). Each manipulation involves the delivery of a high-velocity low-amplitude (HVLA) thrust directed at the inter-vertebral, costo-vertebral and costo-transverse joints. The first manipulation will be delivered at the level of the upper/middle thoracic spine while the second will be at the level of the middle/lower thoracic spine. Two different manipulation techniques are available under the trial’s manipulation protocol. The choice of technique will be made by the treating clinician based on biomechanical factors e.g. size of patient relative to size of practitioner. All MT intervention will be administered as non-specific, multi-joint (group) techniques. Administering manipulation in this way reduces the total number of manipulations required to manage the thoracic spine within a single intervention session as each manipulation has the potential to affect several thoracic vertebrae and their associated ribs simultaneously.

In the MB and MT groups, exercise will be performed immediately after manual therapy intervention is administered.

All intervention sessions will last between 15 and 20 minutes.

## Study Flow Chart

Diagram of the study design

 Recruitment of potential participants

 

Consent

Screening for contra-indications to thoracic manual therapy



 Enrolment

 

Baseline measurements (week 0)



Randomisation

 Group 1 Group 2 Group 3

 Exercise Mobilisation Manipulation

 (Ex) (MB) (MT)

 6 x Ex 6 x MB 6 x MT

 Outcome Outcome Outcome

 measurements measurements measurements

 (3, 6, 9 weeks) (3, 6, 9 weeks) (3, 6, 9 weeks)

## Investigation plan

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Interventions** | Visit 1Baseline (week 1) | Visit 2-5weeks 1-3 | Visit 6week 3 | Visit 7week 6 | Visit 8week 9 |
| Informed Consent | ✓ |  |  |  |  |
| Medical history | ✓ |  |  |  |  |
| Inclusion / Exclusion criteria | ✓ |  |  |  |  |
| Screening for contraindications to thoracic manual therapy  | ✓ |  |  |  |  |
| Physical examination (height, weight) | ✓ |  |  |  | ✓ |
| Spirometry | ✓ |  | ✓ | ✓ | ✓ |
| Chest wall movement measurements | ✓ |  | ✓ | ✓ | ✓ |
| Quality of Life questionnaires (SF-36) | ✓ |  | ✓ | ✓ | ✓ |
| Adverse Event Assessment |  | ✓ | ✓ | ✓ | ✓ |
| Intervention (Ex / MB / MT) | ✓ | ✓ | ✓ |  |  |

## Study Procedure Risks

The risks of harm or discomfort to participants in this study primarily relate to the application of manual therapy. Adverse events (AEs) associated with manual therapy have been classified into three groups: mild, moderate and severe.[10] The majority of AEs associated with manual therapy are mild and self-limiting. They include muscle soreness and local discomfort in and around the treated region, do not require further medical attention and resolve within 48 hours [10]. Moderate AEs have also been reported following certain types of manual therapy such as joint manipulation. Moderate AEs have been estimated to occur at a rate of 1 in 40,000 manipulations.[11] Reports of major or catastrophic AEs resulting from spinal manipulation appear in the literature. The majority of these reports relate to neck (cervical) manipulation.[10, 11] As this trial only involves manipulation of the thoracic spine and ribs and does not include neck (cervical) manipulation any estimation of risk of a severe AE should not be based on the incidence of AEs associated with neck (cervical) manipulation.

The manual therapy protocol (MTP) that will be used in this trial is similar to the one used in two previous trials on people of a similar age with chronic obstructive pulmonary disease (COPD).[12, 13] There were no severe or moderate AEs reported in either of those trials. Mild AEs resulting from manual therapy were reported at a rate of 15% (18 out of 112) in the trial on people with moderate COPD and an average age of 56.1 years[12] while mild AEs were reported at a rate of less than 1% (2 out of 403) in the trial on people with moderate to severe COPD and an average age of 65.5 years.[13] Furthermore, in a case series of 6 elderly patients with an average age of 79.1 years, moderate to severe COPD and low levels of daily activity, no major or moderate AEs were reported following 72 thoracic HVLA spinal manipulations while mild AEs were reported at a rate of 29% (21 out of 72).[14]

These trials included pre-trial screening for contra-indications to manual therapy. The current trial will include the same pre-trial screening. As the participants in this trial are healthy with no history of or current respiratory disease, it is reasonable to assume they will have a lower level of risk of harm or discomfort following manual therapy compared to people with COPD. With reports of only minor AEs following previous applications of this type of manual therapy we submit that the potential benefit to lung function is adequately balanced against the level of risk of harm or discomfort to participants that may arise as a result of administering manual therapy.

## Recruitment and Screening

Recruitment will be by way of one or more of the following:

(i) In response to advertisements seeking volunteers for the trial in the local print media and on public noticeboards.

(ii) In response to interviews on local radio.

(iii) By word of mouth.

Potential participants will be directed in the first instance to contact Principal Investigator 2 (SG) by email or telephone. She will perform an initial check for basic inclusion and exclusion criteria e.g. age, history of respiratory disease, abdominal surgery etc.

Volunteers are under no obligation to progress to full participation.

Once a volunteer has successfully completed the initial check a potential participant will then be screened for contraindications to thoracic manual therapy. This process, conducted by either Principal Investigator 1 (RE) or 2 (SG), involves a physical assessment of the thoracic spine, rib cage and associated musculature and a discussion about the risks associated with administering thoracic manual therapy.

The trial will use the same criteria for contra-indication to manual therapy as the previous studies [12-14]: osteoporosis, thoracic joint instability, acute pain on thoracic joint range of motion testing, below normal chest wall musculature for age and gender or a high level of anxiety related to having thoracic manual therapy administered.

## Informed Consent Process

Obtaining informed consent takes place before the pre-trial screening for contra-indications to manual therapy. No specific tools will be used to determine a participant's capacity to decide whether or not to participate in the project. All potential participants will be supplied with a Patient Information Statement and Consent Form (PICF) explaining the trial's processes and procedures and what is expected from them during the trial. All potential participants will then be given the opportunity, either by telephone, email or in person, to ask questions about their participation in the trial. In the event there is any doubt on the part of the investigators about a person's capacity to understand the information that has been supplied to them or to decide whether or not to participate in the trial, a decision will be made to exclude that person from the trial.

The consent form will be signed and dated by the participant and a representative from the trial.

## Enrolment Procedure

After a participant has provided written informed consent and met all of the inclusion criteria (including screening for contra-indications to manual therapy) they will be enrolled in the trial. The participant will then receive a trial-specific identification number which will be used on all study documents related to that participant for the duration of the trial.

## Randomisation Procedure

Participants who have passed the screening test, provided written consent and completed baseline measurements will be sorted according to gender and then randomly allocated to one of the three study groups (Ex, MB or MT) using a computer generated random sequence created by an administrative officer at Macquarie University not otherwise involved in the trial.

#  SAFETY

## Adverse Event Reporting

In this trial all adverse events will be recorded. An adverse event is any untoward medical occurrence in a participant which may or may not be related to the trial’s treatment. It includes any unfavorable or unintended sign, symptom or condition that is directly or indirectly related to the application of Ex or manual therapy.

## Serious Adverse Event Reporting

A serious adverse event is any untoward medical occurrence that results in the following: death, is life-threatening, requires inpatient hospitalisation, persistent or significant disability/incapacity or a condition that requires medical or surgical intervention.

## Data Safety and Monitoring Board

The data safety monitoring board (DSMB) appointee for the trial is the Manager, Technical & Laboratory Services in the School of Health & Human Sciences at Southern Cross University.

## Early Termination

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as unacceptable side effects or the treatment was shown not to be effective or the treatment was shown to work and not need further testing. In the event of the trial being terminated due to unacceptable side effects Investigators 1 & 2 (RE & SG) will be responsible for managing all aspects of the early termination including informing participants, correspondence with the HREC and compiling a final study report.

#  BLINDING AND UNBLINDING

All assessors associated with collecting data from the outcome measurements will be blinded to a participant’s group. Students overseeing the exercise intervention will also be blinded to a participant’s group. Practitioners providing manual therapy intervention will obviously not be blinded to group allocation. All participants will be blinded to outcome measurements until the end of the trial.

#  STATISTICAL CONSIDERATIONS

Sample size calculation

Minimum clinically important difference in lung volume (FVC) = 200 ml

Standard deviation = 480ml (obtained from previous studies)

Power = 0.8 (80%)

Alpha = 0.05

Minimum sample size for two sample t-test = 92 per group

Minimum cohort size (i.e. 3 groups) is 3 x 92 = 276

Assuming a drop-out rate = 10%

Minimum cohort size = 306 (3 Groups @ 102)

Statistical analysis plan

Data will be reported as group means, standard deviations and confidence intervals. Analysis will be performed as an ANCOVA for difference between groups with baseline as a covariate. Statistical significance will be set at p<0.05. Missing data will be accounted for by using an intention-to-treat (ITT) analysis with data from subjects lost to follow-up imputed using the last observation carried forward method. The Number Needed to Treat (NNT) will be calculated using Bender’s method for confidence intervals.

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#  STORAGE AND ARCHIVING OF STUDY DOCUMENTS

Information will be stored in paper copy form and as encrypted computer files. All paper copy forms will be stored in a locked filing cabinet in the university clinics during the active phases of the trial. Once the trial has been completed (post week 9), all data will be entered on to a University laptop computer, stored as encrypted files and backed up on an external hard drive that will be stored in the university office of Investigator 2 (SG). Once the trial has been completed, all paper copy forms will be stored in a locked filing cabinet in the university office of Investigator 1 (RE).

Information will be stored for a minimum of 5 years after the last publication that relies on the data from this trial.

Should Investigator 1 (RE) cease to be employed at Macquarie University, all information collected as part of this trial will be stored in a locked filing cabinet in the university office of Investigator 2 (SG) at Southern Cross University.

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#  APPENDICES

Appendix 1: Advertisement in local media

Appendix 1

**The Manual Therapy, Exercise and Lung Function Trial**

**(The MELT Trial)**

**CALL FOR VOLUNTEERS**

Project title: The effect of manual therapy and exercise on age-dependent lung function: a randomised controlled trial.

Ageing is associated with a range of changes that include the respiratory system. These changes start to manifest as early as 40 years of age and lead to progressive stiffening of the spine, decreasing chest wall flexibility and falling lung function.

The main aim of this study is to investigate whether administering an intervention (manual therapy) that reduces stiffness in the spine and makes the chest more flexible can improve lung function. The secondary aims are to investigate whether different forms of manual therapy are equally effective at achieving this and whether any improvements are ongoing.

We are looking for volunteers between the ages of 50 and 65 years interested in participating in a trial that will investigate the effect of manual therapy on lung function.

To participate in this trial, volunteers must:

* Be between 50 – 65 years of age
* Be currently non-smoking (minimum 6 months)
* Have no history of respiratory disease
* Not be contra-indicated for thoracic manual therapy
* Not have had thoracic manual therapy in the past 3 weeks
* Be able to walk unaided on a treadmill for 10 minutes

If you are interested in participating in this trial or would like further information please contact:

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