Royal Papworth Hospital
NHS Foundation Trust

'Measurement of mucus plugging with computer tomography before and following implementation of the AffloVest in adults with bronchiectasis – a feasibility study'

STUDY PROTOCOL – AFFLO Study

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1. Trial Overview

Principal Objective:

The principal objective is to test the feasibility of using computer tomography and the modified Brody score to measure the amount of mucus plugging within the lungs of adults with bronchiectasis at baseline and after six weeks treatment with the AffloVest. The study outcomes will facilitate the design of a future study to test treatment efficacy.

Study Design:

This is a feasibility study using computer tomography to measure the amount of mucus within the lungs of adults with bronchiectasis before and following implementation of the AffloVest. The aims of the study include assessing the feasibility of the study protocol and estimating the size and variability of the treatment effect with the AffloVest to facilitate the design of a future study to test treatment efficacy.

30 adult subjects (male and female) who have a known diagnosis of bronchiectasis and who attend the Cambridge Centre for Lung Infection (CCLI) at the Royal Papworth Hospital will be recruited.

Subjects will be recruited through convenience sampling and must demonstrate stability during a 2-week period prior to enrolment. Stability is defined as no change in medical treatment.

Participants will be asked to use the AffloVest for 30 minutes twice daily (in addition to their standard airway clearance regimen where possible) for six weeks, with clinical review and tests performed at baseline, three and six weeks.

Tests to be performed at baseline, after three and six weeks of treatment with the AffloVest include: computer tomography (CT) at full inspiration and full expiration; spirometry (FEV1 and FVC); and the patient reported outcomes Visual Analogue Scale for ease of sputum clearance (VAS), St George's Respiratory Questionnaire (SGRQ) and Quality of Life–Bronchiectasis (QOL-B).

The CT images will be scored by two independent expert thoracic radiologists using the modified Brody Scoring System which is sensitive and reproducibe.[12] Both radiologists will be blinded to the time point of the CT scans being analysed and if there is disagreement in scores, an average will be taken.

We hypothesize that there will be a reduction in the amount of mucus plugging and an improvement in patient reported outcomes following implementation the AffloVest in adults with bronchiectasis.

Primary Outcome

The primary outcome of this study is to test the feasibility of using computer tomography and the modified Brody score to measure the amount of mucus plugging within the lungs of adults with bronchiectasis at baseline and after six weeks of treatment with the AffloVest. The study outcomes will facilitate the design of a future study to test treatment efficacy.

Secondary Outcome(s)

Secondary outcomes include the full modified Brody score, lung function, quality of life scores and a visual analogue score for ease of sputum expectoration measured at baseline, after 3 weeks of intervention and after 6 weeks of intervention. There will also be a sub-group analysis excluding patients that have a pulmonary exacerbation during the study.

Rationale

Bronchiectasis is a chronic inflammatory suppurative respiratory disease associated with poorer quality of life, increased admissions and increased mortality.[1,2] The disease is characterised by a

clinical syndrome of cough, sputum production and recurrent respiratory infection, with radiological evidence of abnormal and permanent dilation of the bronchi.[1,4] In the United Kingdom, incidence and prevalence rates are increasing with recent reports suggesting a current prevalence of 566 and 485 per 100000 patient years in women and men respectively.[5]

A major strategy in the management of patients with bronchiectasis is to optimise airway clearance and thereby reduce the inflammatory and infective burden in the lung. Several guidelines for airway clearance techniques have been created including the European Respiratory Society Guidelines for the management of adult bronchiectasis[1], and Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient.[5] However, no one technique has consistently been shown more effective than others and all the studies discussed in the guidelines were of poor quality. Furthermore, none of these guidelines evaluated High Frequency Chest Wall Oscillation (HFCWO).

First described in 1966 by Beck, HFCWO uses percussive forces, transmitted to the lungs to mobilise secretions to mimic effects or percussion and vibration without the need of a physiotherapist or caregiver.[7] Traditional HFCWO machines use single waveforms delivered by large volumes of air at high amplitudes to rapidly inflate and deflate an air bladder. Conversely, the AffloVest uses mechanically generated pressure waveforms from 8 dynamic oscillating motors inside a vest. Current evidence for HFCWO has focused on cystic fibrosis (CF) and suggests that it is at least as effective as conventional physiotherapy in clearing secretions with improved patient adherance.[7]

Additionally, studies in asthma and chronic obstructive pulmonary disease (COPD) have shown that HFCWO may be beneficial for hospitalised patients through leading to reduced Borg dyspnoea scores, improved FEV1, increased sputum expectoration and reduced exacerbation frequency.[8,9] Finally, HFCWO has been used by over 50,000 patient's suggesting it is safe and effective intervention in a number of airway diseases and is now recognised as standard of care in individuals with CF in North America.[10]

However, to date, there have been no studies of HFCWO in adult patients with bronchiectasis utilising CT to measure the amount of mucus within the lungs before and after implementation of this intervention. This study aims to assess the feasibility of the protocol and to estimate the size and variability of the treatment effect with the AffloVest to facilitate the design of a future study to test treatment efficacy in adults with bronchiectasis.

Schedule of Events

Day -21 to Day -1

- Informed consent and review of inclusion & exclusion criteria

Day 1 – Start of intervention

- CT scan; FEV1 and FVC; PROs (VAS for ease of sputum clearance, SGRQ & QOL-B).
- Participants will be shown how to use the AffloVest and will complete a skills checklist for home use.
- 3 weeks of AffloVest for 30 minutes twice a day (10 minutes each of percussion, vibrations and drainage at an intensity tolerable by each individual participant) in addition to their standard airway clearance regimen (where possible).

Day 21 – Midpoint of intervention

- CT scan; FEV1 and FVC; PROs (VAS for ease of sputum clearance, SGRQ & QOL-B); adherence check.
- 3 further weeks of AffloVest for 30 minutes twice a day (10 minutes each of percussion, vibrations and drainage at an intensity tolerable by each individual participant) in addition to their standard airway clearance regimen (where possible).

Day 42 – End of intervention

- CT scan; FEV1 and FVC; PROs (VAS for ease of sputum clearance, SGRQ & QOL-B), adherence check.

2. Patient Recruitment Criteria

Study Population

Participant number: n = 30

Population group: Adults (males and females) with bronchiectasis who attend the Cambridge Centre for Lung Infection, Royal Papworth Hospital NHS Foundation Trust

Time in study: A total of 63 days from enrolment

Inclusion

- Adult male and females ≥18 years
- Current diagnosis of bronchiectasis (see above definition)
- Productive of sputum on a daily basis
- Clinical stability over a 2-week period prior to enrolment (see above definition)

Exclusion

- Cystic fibrosis
- Severe obstructive airways disease (defined as FEV1 < 25%)
- Predominant lung disease is not bronchiectasis in the opinion of the investigator (e.g. asthma; COPD; pulmonary fibrosis)
- Bronchiectasis in only 1 lobe
- Currently treated non-tuberculous mycobacterial lung disease
- Acute congestive cardiac failure
- Contra-indication or unable to perform HRCT imaging, including pregnancy
- Contra-indication to using AffloVest including lung malignancy, recent rib fractures, radiological evidence of lung cavitation, and recent significant haemoptysis (in the opinion of the investigator)
- History of poor adherence to physiotherapy treatment
- Cognitive or memory problems affecting ability to follow instructions or give informed consent

Recruitment

The planned recruitment target is 30 participants. No strategies for promoting or boosting recruitment are deemed necessary, other than 'in-house' referral from respiratory physicians and physiotherapists working at the Cambridge Centre of Lung Infection, Royal Papworth Hospital.

Section 3. Sample Size and Data analysis

Sample Size:

N = 30.

There are currently no data on which to base an estimation of treatment effect following implementation of high frequency chest wall oscillation, nor what the minimal clinically significant change in CT parameters might be. Thus feasibility data are required to guide the design and power calculation of a future larger study to test treatment efficacy. In these circumstances, we have suggested a sample size of 30 patients, as we anticipate that this will allow sufficiently precise estimation of the size and variability of the treatment effect. Furthermore, if we encounter a drop out rate of 15%, a cohort size of 30 would generate 95% confidence intervals 2.2% and 27.8%.

Statistical Analysis:

To analyse the primary outcome, the CTs will be reviewed by two independent radiologists blinded to the time point for each scan and quantified using the "mucus component" of the modified Brody scoring system. If there is discrepancy on the score for an individual participant at one time point, the two scores will be averaged. After the modified Brody score for each patient is determined we will calculate summary statistics including group mean, standard deviation, standard error and confidence intervals at baseline and after 6 weeks of treatment. Other feasibility measures such as participant dropout rate will also be calculated.

Secondary outcome summary statistics including the full modified Brody score, FEV1, FVC, SGRQ, QOL-B, VAS score and adherence to treatment will be calculated at baseline, after 3 weeks of treatment and after 6 weeks of treatment. Any participants who suffer an exacerbation of their bronchiectasis during the trial will continue in the study and will be included in the analysis of the primary endpoint. However, an additional sub-group analysis will be undertaken excluding this population as a secondary outcome.

Finally, we will also carry out paired t-tests to assess change in CT, lung function and symptom parameters following implementation of the AffloVest. However, this is not the primary aim of this feasibility study and the study may be significantly underpowered to properly address this point. In any case, data generated by the study will inform the design of a larger trial to fully investigate efficacy. A p-value of 0.05 will be interpreted as statistically significant unless otherwise stated.

4. Consent Process and Visit Schedule

Visits

- Subjects will be approached about the study by the CCLI Research team, physiotherapy team or CCLI consultant team at an outpatient appointment, during a day case / inpatient visit or via postal invitation (if known to the service and deemed appropriate for the study). Once seen, and if deemed to be eligible for the study, they will be consented and enrolled.
- Each participant will be assigned a study number; the study numbers will be allocated sequentially starting at 10.
- Participants will then be arranged to undergo first visit testing with treatment and follow up according to the schedule below.
- Visits will be scheduled and performed according to table 1.
- Trial specific procedures *versus* routine procedures are detailed in table 2. The trial specific procedures will only be performed after written informed consent has been obtained.

Table 1 Visit Schedule

Visit Number	Screening	Visit 1	Visit 2	Visit 3
Time interval of Visit	Day -21 to day -1	Day 1	Day 21	Day 42
Informed consent	**X**			
Review of inclusion & exclusion criteria	**X**	**X**		
Medical history and examination		**X**	**X**	**X**
Size for AffloVest	**X**			
Fit AffloVest, teach how to use it, check tolerance of settings		**X**		
AffloVest skills checklist of participant competency		**X**	**X**	**X**
AffloVest adherence tracking			**X**	**X**
Spirometry (FEV_1 and FVC)		**X**	**X**	**X**
Pregnancy test if appropriate (urine dipstick)		**X**	**X**	**X**
Patient reported outcomes (VAS, SGRQ & QOL-B)		**X**	**X**	**X**
CT scan		**X**	**X**	**X**

Informed Consent Procedure

- Subjects will receive written and verbal information about the trial.
- Written informed consent will be obtained by a member of the trial team using the Patient Information and Consent Form (PICF). Consent will only be obtained after a suitable time has elapsed during which the subject has had ample time to read the information sheet, consider

the trial and ask any questions. The Investigator or appropriate delegate will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. The signed PICF will be scanned and uploaded electronically onto the hospital's secure electronic medical records.

- The ultimate responsibility for obtaining written informed consent lies with the Investigator but this responsibility may be delegated to a suitably trained and experienced person.
- Prior to the subject's participation in the study, the written informed consent form will be signed and personally dated by the subject and by the clinician who conducted the informed consent discussion. Each box at the end of each statement on the consent form will be signed by the subject.
- Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment.
- A copy of the informed consent document will be given to the participant. One copy will be filed in the participant's hospital case notes and uploaded on the password locked hospital electronic medical records.
- The Principle Investigator or research delegate will ensure that the subject does not have any trial specific procedures prior to giving informed consent.
- If a participant withdraws their consent a line will be drawn diagonally through the consent form and labelled 'consent withdrawn' and signed and dated by a member of staff and uploaded into the electronic medical record.

5. Follow-up Visits, Travel Expenses and Other Costs

Follow up Visits:

The follow up visits will be in accordance with the visit schedule outlined in table 1. Participants will be seen at each visit by one of the principal investigators.

If the participants choose to consent to it, the study organisers may contact participants after the study has completed to request feedback regarding the longer-term experience of using the AffloVest.

Travel Expenses:

Reasonable travel expenses will be reimbursed for each study visit.

Study Costs:

- 30 HFCWO AffloVests (provided by International Biophysics)
- 90 inspiratory and expiratory CT scans (3 per participant) with reporting by two independent
- radiologists – £437 each (Total = £39,330)
- 90 FEV_1 measurements (3 per participant) – £45 per time point per patient (Total = £4,050)
- Pregnancy test – covered by Royal Papworth Hospital where applicable
- Physiotherapist time (£177 per patient) – £5,310
- CI time – £1,962
- R&D overheads (20%) - £10,130
- Total – £60,782
- Total costs (Travel and Study Costs): £65,28230

6. Data Collection, Auditing and Retention of Documents

Data Collection Form Completion

- The Investigator will ensure the accuracy, completeness, legibility and timeliness of the data recorded and in all required reports to e.g. the Sponsor, Funder, R&D, REC.

Source Documentation

- The investigator/clinical research nurses will maintain electronic clinical case notes on the hospital's secure electronic medical record system. This will include all demographic and clinical information. A copy of the patient information and consent form will also be uploaded electronically in the patient's case notes (see above section on consent). All information will be traceable to and consistent with the participant's hospital electronic case notes.

Errors and Corrections

- Any change or correction will be dated, initialled, and explained (if necessary) and will not obscure the original entry (i.e. an audit trail will be maintained).

Storage of Documents

- Electronically uploaded forms and electronic clinical case notes will be stored securely on the hospital's password locked electronic medical records.

Retention of Documents

- All study specific documentation will be stored for 12 months after the last patient has completed their last visit.

Monitoring and Audit

- Upon request of the monitor, auditor, Sponsor, R&D, REC, MHRA or other regulatory authority, the Investigator will make available for direct access all requested study-related records.
- The project data will monitored by an appointed member of the R&D department at the Royal Papworth Hospital NHS Foundation Trust.

Section 7. Adverse and Serious Adverse Events

The definition of an adverse event is: 'Any untoward medical occurrence in a patient which does not necessarily have a causal relationship with this treatment'. This includes 'any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study drug'. This may include, for example, a cold or an accident.

The definition of a serious adverse event is one that fulfils at least one of the following criteria:

- Is fatal- results in death
- Is life threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity

OR

- Is a congenital anomaly/birth defect

The definition of a suspected unexpected serious adverse reaction (SUSAR) is a serious adverse event that is thought to be possibly or definitely related to the study drug.

Recording and Reporting

- Studies have shown HFCWO to be safe. There are however risks involved with HFCWO and FEV_1 including haemoptysis, rib fractures, tenderness, bronchospasm, breathlessness and fainting. These occur rarely and supervision and guidance throughout testing procedures will also minimise the chance of risks occurring. There is equal chance of these risks occurring during patient's normal medical care and airway clearance treatments.
- Additional ionising radiation exposure via 3 low dose HRCT's over the 28-day period will occur. The estimated radiation dose per scan is 3.6mSv. The total research protocol dose is therefore 11mSv, which is equivalent to that received, on average in the UK, from natural sources of background radiation in approximately 5 years. For adults in the general population, this dose is estimated to correspond to a cancer risk of around 1 in 2,500. This can be compared with the natural lifetime risk of cancer in the UK of about 1 in 2 and it should be noted that the latency period for radiation induced cancer is about 5 years for leukaemia and decades for solid tumours.
- All research staff in contact with participants will be responsible for noting adverse events that are reported by the patient and making them known to the Principal Investigator. All AE's will be documented in the participant's electronic clinical case notes, as per usual standard of care.
- At each visit or study assessment, adverse events that have occurred since the previous visit will be elicited from the patient. The event will be detailed in the participant's electronic clinical case notes, as source document verification, including the start date (if known) and end date.
- The action taken regarding the study procedure will be documented.
- Any treatment/medication given for the event, including the dates the treatment/medication was commenced and the date it was stopped/changed, if applicable, will be documented.
- Documenting of adverse events will be the responsibility of the Principle Investigator, Co-Investigator and Clinical Research Nurse/Assistant
- Events, which are ongoing at the final study visit, will be followed up as clinically indicated.
- All serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARS) will be documented as above.
- SUSARS will be reported to the Sponsor within 48 hours of the Chief / Principle Investigator/Clinical Research Nurse being aware.
- All Unexpected SAEs and SUSARs will be reported to the hospital R&D department and may be require analysis through the hospital incident reporting system.
- Expected SAEs will be reported to the Main REC in the annual REC report; the REC who performed the locality assessment does not need to be informed.
- All completed SAE forms will be uploaded to the participant's electronic medical record.

8. Amendments

Substantial amendments will be submitted to the Health Research Authority and Research Ethics Committee for review and approval.

9. References

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