TACT Trial

Statistical Analysis Plan

4.0 (Final Version)

Started: 29th January 2021
Finalised: 22nd April 2021

Title	Treating Auditory impairment and CogniTion: a randomised, parallel, pilot trial in older adults with mild cognitive impairment and hearing loss of an intervention to provide and support hearing aid use vs a health education intervention for dementia risk (TACT)
Short title	TACT Trial
Chief Investigator	Dr Sergi Costafreda Gonzalez
Statisticians	Prof Rumana Omar and Dr Menelaos Pavlou

Study Summary

To establish the feasibility of a future fully powered trial of early hearing aid provision in people with Mild Cognitive Impairment (MCI) and hearing loss in terms of delaying the onset of dementia. The pilot trial will test recruitment, attrition, and acceptability of two interventions: the hearing and healthy ageing interventions. During the COVID-19 pandemic, the trial will instead pilot a remotely delivered version of the active intervention of early hearing aid provision and support to test recruitment, feasibility, and acceptability (the Remote Hearing Intervention or RHI sub-study).

Signatures

Chief Investigator

Dr Sergi Costafreda Gonzalez

[redacted] 22/04/2021

Signature Date

Trial Steering Committee (TSC) Chair

Prof Finbarr Martin

Finbarr Martin [redacted] 06/05/2021

Signature Date

1 Introduction

1.1 Purpose and scope of the statistical analysis plan

This document describes the main statistical analyses to be applied to the data from the TACT Trial.

1.2 Authors of the Statistical analysis plan

This Statistical Analysis Plan was written by Rumana Omar and Menelaos Pavlou.

1.3 Analysis organisation

Unmasking of the data and the final analysis will be performed after the last patient has completed follow-up, all relevant data have been entered, checked, and locked, the analysis plan has been finalised and approved.

1.4 Data checking

Before analysis, basic checks will be performed to check the quality of the data. Incomplete or inconsistent data include:

- Missing data
- Data outside expected range
- Other inconsistencies between variables e.g. in the dates the questionnaires were completed

If any inconsistencies are found, the corresponding values will be double checked with the researchers and corrected if necessary. All changes will be documented by the trial statistician.

2 Description of the trial

TACT is a pilot randomised, parallel group trial in participants with MCI and hearing loss. Participants with hearing loss and MCI will be randomised to a hearing intervention (home-based provision of hearing aids, and adherence support) or a healthy ageing intervention (home-based educational intervention, to match intensity of social contact). Participants will be assessed on their hearing, cognition, quality of life, physical activity, mood, social interactions, and daily function at baseline and 6 months. During the COVID-19 pandemic the RHI sub study is conducted to pilot a remotely delivered version of the active intervention of early hearing aid provision and support and to test recruitment, feasibility, and acceptability. This single arm non-randomised sub-study will have a 4-week follow-up.

Main inclusion/exclusion criteria

Participants will be 55 years of age or older, with a diagnosis of MCI, and with mild to moderate adult-onset hearing loss, community-dwelling, without any self-reported hearing aid use in the past month.

For the single-arm RHI sub-study participants who had consented for the randomised trial prior to the onset of COVID-19 will be invited to participate.

Sample size

With 76 randomised participants, we will achieve the following 95% confidence intervals (CI) for our expected estimates of dropout, acceptability of the intervention, and difference in hearing aid adherence between the Hearing Intervention and Healthy Ageing Intervention at the end of trial :

1. Estimate attrition rate of 20% randomised participants with complete follow-up at 6 months, 95%CI [10% to 30%].
2. Acceptability of the Hearing Intervention: proportion of participants allocated to the Hearing Intervention completing ≥2 intervention sessions – expected value ≥80% of intervention group, 95% CI with n=76 would be [70% to 90%].
3. Difference in daily hearing aid adherence between arms: target of 50% difference between the Hearing Intervention and Healthy Ageing Intervention arms in the proportions of participants maintaining hearing aid use at 6 months (end of follow-up), 95% CI with n=76 would be [31% to 69%] with 20% attrition it would be [29.5% to 71%].

A minimum of 10 and up to 12 participants will be recruited to the RHI sub-study.

3 Data collection

3.1 Primary outcome measures

This pilot trial aims at establishing the feasibility of a full-size trial of the hearing aid intervention versus healthy ageing intervention in people with MCI. This future trial will be a scaled-up version of the present pilot, modified with any lessons learnt in the current trial. The pilot's primary objective is therefore to establish feasibility of recruitment, randomisation, retention, and the acceptability of the trial interventions as follows:

- Recruitment: Proportion of eligible participants who are randomised into the trial.
- Attrition: proportion of participants who are lost to follow-up at 6 months of trial duration, and endpoint measures are not obtained.
- Acceptability of the Hearing Intervention: proportion of participants allocated to the Hearing Intervention completing >2 intervention sessions.

3.2 Secondary outcome measures

- Cognition (ACE), Trail Making Test (TMT), Delayed Word Recall Test (DWRT)
- Quality of Life (SF36,EQ-5D)
- Functioning (IADL Lawton-Brody Instrumental Activities of Daily Living), Social activities (SF-DEM), Loneliness (UCLA)
- Frailty (grip strength)
- Physical activity (accelerometer)
- Mood (GDS)
- Self-reported hearing (HHIE-S)
- Hearing aid usage: measured in hours per day by self-report. For some intervention arm participants logged data on hearing aid usage are also available.

In addition to continuous measures of hearing aid use, a binary measure of adequate hearing

aid use will be defined as a minimum of 4 hours a day on average since last trial assessment (when at home and in usual health) as defined at 6 months (end of trial), based on the hearing aid with the highest average use (as each participant has two hearing aids). Other data on adherence to the use of hearing aids will also be recorded, including the number of hearing aids lost by participants in the intervention arm.

Assessing diagnostic accuracy of hearing screening tools:

Single question, Shoebox, HearCheck, HHIE-S will be compared to the gold standard - Audiologist-delivered PTA (best ear average of the 4 PTA frequency values from 500 Hz to 4000Hz) to assess their accuracy in diagnosing hearing problems. In addition, agreement between Shoebox and audiologist delivered PTA will be assessed for the following: auditory thresholds at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and average of the 4 frequencies.

Outcome assessment for the RHI sub-study

At the end of the RHI there will be an outcome collection contact (contact 5). Outcome collection will be done at 4 weeks (+/2 weeks) after receiving the hearing aids (expected duration 45-60 minutes total). These will include the same assessment tools administered at the RHI sub-study baseline assessment (a simplified version of the TACT assessment battery), namely:

- Mood: Geriatric depression scale (GDS) [28]
- Cognition: Addenbrooke Cognitive Examination (ACE-III) ; these will include only those items that can be obtained by remote assessment

4 Baseline characteristics of participants

List of variables to be used to assess baseline comparability of the randomised groups:

- Age
- Sex
- Cognition scale: Addenbrooke Cognitive Examination (ACE-III) score, Trail Making Test (TMT) (Parts A & B), Delayed Word Recall Test (DWRT)
- Quality of life: SF36, EQ-5D
- Function: 4-item Lawton-Brody IADL
- Social activities: SF-DEM
- Loneliness: UCLA loneliness
- Frailty: grip strength
- Physical activity: as measured by accelerometery at baseline
- Geriatric Depression Score
- Self-reported hearing disability - Hearing Handicap Inventory for the Elderly – Screening version (HHIE-S)
- Hearing Threshold PTA average (best ear average of the 4 PTA frequency values from 500 Hz to 4000Hz)
- Quicksin: units in dB SNR loss (List 1 SNR Loss and List 2 SNR loss, to take as an overall average SNR loss per participant)
- Ethnicity
- Cardio-vascular history as assessed by:
    - Diabetes
    - High Blood Pressure
    - Ischaemic Heart Disease
    - Stroke
    - Smoking history

    - Alcohol consumption/week
- History of falls
- Presence of Communication partner

5 Pre-intervention procedures for RHI sub-study (during COVID-19)

After consent, participants' baseline outcome measures will be obtained through remote interview. These will include

- Mood: Geriatric depression scale (GDS)
- Cognition: Addenbrooke Cognitive Examination (ACE-III) ; these will include only those items that can be obtained by remote assessment

6 Data analysis

6.1 Recruitment and representativeness of recruited patients

A CONSORT flow chart will be constructed. This will include the number of patients approached and assessed for eligibility, number of patients agreeing to enter the trial, then by treatment arm: the number continuing through the trial, the number withdrawing at each time point, the number lost to follow-up at each time-point and the numbers excluded/analysed.

6.2 Statistical Analysis

Summary measures for the baseline characteristics of the intervention and control groups will be presented as means and standard deviations or medians and inter-quartile ranges for continuous variables as appropriate, and frequencies and percentages for categorical variables. The number of missing observations will be reported.

Given this is a feasibility study, our main outcomes of interest are rate of recruitment, acceptability of randomisation, level of attrition and these data analyses will be descriptive using counts and proportions. The proportion adhering to the use of hearing aids, based on a predefined threshold of usage defined above, will be calculated for each trial arm and the difference in the proportions with 95% confidence intervals will be estimated. A logistic regression model will also be used to estimate the odds of adherence in the intervention group compared to the control group with 95% confidence intervals.

As part of the secondary analyses, linear regression will be used to estimate the intervention effect on hearing aid usage measured in hours. Additionally, we will investigate the relationship between the following individual-level potential predictors of adherence to hearing aids:

- Higher objective HL (average PTA at baseline)
- More awareness of HL issues (higher HHIE-S score at baseline)
- More cognitive impairment (lower total ACE-III score at baseline)
- More depressed (higher GDS score at baseline)

We shall perform descriptive analyses of adherence using hearing aid usage measured as both continuous and binary variables, as per categories below:

- Mild vs Moderate-Severe : mild defined as PTA average in better ear < 35dB

- HHIE-S: no handicap (defined as HHIE-S at baseline <9) vs handicap

- More cognitive impairment (defined as ACE-III total <83%)
- Above cut-off for depressed (GDS at baseline >=5) vs not depressed.

If appropriate (depending on sample size) we will also perform linear and logistic regression analyses to investigate association between these factors and hearing aid usage and present estimates of association with 95% confidence intervals.

Appropriate regression models adjusted for baseline values of the outcome will be used to estimate the intervention effect for some of the clinical and quality of life outcomes listed in section 3.2. Mixed effects models will be used to estimate the intervention effects for repeated measures outcomes adjusted for time and baseline values of the outcomes. The results from all regression analyses will be reported as estimates with 95% confidence intervals. Since this is a feasibility trial with no sample size calculation performed based on statistical significance tests, P-values will not be reported. Audiological measurements will be summarised descriptively. The agreement between self-reported hearing usage data and logged hearing data for the intervention arm will be compared using plots. The means for the self-reported and the logged hearing usage data will be calculated and compared descriptively. Diagnostic accuracy of hearing screening tools in comparison to the gold standard will be assessed by calculating sensitivity and specificity with corresponding 95% confidence intervals, as part of an exploratory analyses. Agreement between raters measuring hearing loss will be assessed using Kappa or spearman rank correlation as appropriate.

The quantitative data from the single arm RHI sub-study will be analysed using means/SD or medians/IQ range and counts/percentages as appropriate.

6.3 Adherence to allocated treatment and attrition

The proportion of participants missing each outcome will be summarised in each arm. Characteristics of patients with missing outcome data will be reported. Reasons for withdrawal from the trial will be summarised where available. Data assessing delivery of intervention according to the protocol will be summarised descriptively.

7 Software

All the statistical analysis will be performed using Stata version 16.