**Managing Agitation and Raising QUality of LifE in dementia (MARQUE)**

Cluster RCT to improve agitation for people with dementia in care homes (workstream 3)

**Statistical and Health Economic analysis plan**

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**Introduction**

This analysis plan sets out the methods of analysing the predetermined primary, secondary and health economic outcomes of the MARQUE cluster randomised trial (work stream 3), which will be reported in peer review papers) at the end of the trial

The analysis of this cluster randomised trial will comply with the CONSORT statement guidelines and the associated extension for cluster randomised trials1, 2 and ICH E93. It will also follow the appropriate Priment Clinical Trials Unit standard operating procedures. This analysis plan covers the statistical analysis of the clinical outcomes as well as the health economics analysis.

Further information on this trial can be found in the protocol version 2.0 (15/02/2016). The protocol is stored on: S:\Pop\_Health\PCPH\_Priment\Projects\Current\Non CTIMPS\MARQUE\Protocol\15.02.2016\_Protocol stream 3\_v3.pdf and registered on ISCTRN.

**Trial summary**

**Aims**

To improve agitation levels (and to prevent emergent and manage existing agitation) and quality of life for people with dementia in care homes by changing care home culture. Primary outcome mean agitation and secondary clinically significant agitation.

**Objectives**

To discover whether the MARQUE intervention for changing care home culture delivered to staff changes the mean level of agitation (Cohen-Mansfield Agitation Inventory (CMAI)) in residents with dementia at 8 month follow up compared with usual care.

To determine whether the intervention changes quality of life for people with dementia as measured by the DEMQOL-proxy rated by paid carers who know the resident well eg key worker

To examine whether DEMQOL-proxy ratings recorded by family carers for people with dementia suggest the intervention changes quality of life

To determine whether the intervention reduces overall neuropsychiatric symptoms

To investigate whether there is a difference in staff competence between those randomised to the intervention and those that are not.

To discover whether there is a difference in staff burnout between those in the intervention and those not.

To determine whether there are differences between potentially abusive behaviours and positive behaviours between randomised groups.

To evaluate the cost-effectiveness of the MARQUE intervention using as measure for outcome the quality adjusted life year (QALY; EQ-5D-5L and DEMQOL proxy and the clinical outcome (CMAI)).

**Study population**

*Inclusion criteria*

Care homes

* The minimum number of care home residents with dementia is 17
* Care home is willing to be randomised
* Will commit to allow mandatory training sessions, training staff champions to continue implementation (two per home to take account of possible staff turnover) and changing management procedures, to integrate the new techniques into care
* Will commit to approaching residents and relatives
* No plans to close over the following year

Paid carers

* Provides face to face care for residents at least some of whom have dementia
* Willing to complete the questionnaires about residents with dementia whom they know well
* Willing to answer questions about their own coping
* Carer able to attend training sessions during day shifts
* Carer is expected to be working in the care home for at least the next 3 months (as far as is known) after baseline assessments

Residents with dementia

* Dementia diagnosis according to Noticeable Problems Checklist or known dementia diagnosis
* Can give informed consent themselves or their consultee agrees. Residents will be included in the study if they or their consultee consents to data being collected about them, regardless of whether they have a family carer who consents for their own (carer) participation
* Residents will not be required to be agitated to be included as this trial aims to reduce new agitation symptoms as well as treat agitation

Family carer

* Primary family carer for a resident in the study
* Sees their relative with dementia at least monthly

*Exclusion criteria*

Care homes

* <60% of the staff consent to the study after the care home manager has agreed to the study but before randomisation.

**Trial design**

This is a cluster randomised trial, where the care home is the unit of randomisation, and the intervention is aimed at the care home staff to enable ways of reducing agitation in the residents.

**Randomised treatments**

*Intervention*

The intervention will be a manualised method to enable care home workers to reduce agitation in those residents with dementia. It will be delivered to groups of paid carers by two trained psychology graduate research assistants per group. The paid carers each have a manual. The intervention is designed to be delivered in six sessions over 8-14 weeks at the care home, followed by fortnightly supervision by a clinical psychologist and the psychology graduate research assistants over the three months after the training has been delivered.

*Treatment as usual*

This is the care that would normally be received whilst in the care home. There will be no restrictions on treatment options for carers as this would be unethical, and we are proposing a pragmatic trial to assess the benefits of this treatment package in addition to usual care.

**Sample size (from protocol)**

Our systematic review found a standardised intervention effect size of 0.5 in care home participants for reducing emergent or symptomatic agitation, ie preventing many participants from becoming agitated. To detect this clinically significant change4 with 90% power and 5% significance requires 54 residents per group for an individually randomised design based on analysis of covariance (correlation=0.6)5. We aim to recruit 20 care homes to the trial (10 per randomised group) and must account for the clustering effect of team in our sample size calculation. To maintain 90% power to detect a clinically significant change in the primary outcome, each team must recruit a minimum of 15 residents (assuming an ICC of 0.0876 and 30% loss to follow-up (often because of death)) and to account for the possibility that two homes may drop out each cluster should consist of 17-18 participants.

**Randomisation**

Recruitment and consent of a given care home and its residents with dementia will take place prior to randomisation. Randomisation will be carried out using SAS. Further details on this can be found in the randomisation protocol. There will be stratification by type of home (residential or nursing). Blocks will be of size 2.

**Blinding**

Paid carers will not be blinded to the intervention but residents with dementia, family carers and research assistants who collect data will be blind to allocation. The statisticians and health economists will also be blinded to allocation until the results have been agreed.

**Outcomes**

*Primary outcome*

The Cohen-Mansfield Agitation Inventory (CMAI)7 assesses the frequency of 29 agitated behaviours on a seven point Likert scale; 1=never and 7=several times an hour. The item scores are added to give a total agitation severity score, with a possible range between 29 and 203.

*Secondary outcomes*

Clinically significant agitation This will dichotomise the CMAI to >45 versus those that score <468-10.

The Neuropsychiatric Inventory (NPI)11 assesses the participants’ behavioural disturbances via the carer. It assesses 12 domains. Each domain has an entry present/ absent question, and then there are additional questions within each domain. There is also a frequency (4 ratings, occasionally – very frequently), severity (3 ratings, mild – marked), caregiver distress score (6 ratings – not at all – very/extremely), and carer self-efficacy score (4 ratings, not at all confident – very confident).

Thus, for each behavioural domain there are four scores: frequency, severity, total (frequency x severity), and caregiver distress. This study will use the total score. A total NPI frequency x severity score gives a score from 0 to 144 over all 12 domains (0 if there are no behavioural disturbances).

The DEMQOL – proxy12 is a quality of life measure for people with dementia. This proxy version is filled in by people who know the person with dementia well (in MARQUE this will be their main carer in the care home and their main family carer). Items are scored 1=a lot and 4=not at all, with several items being reverse scored (1, 4, 6, 8, 11, 32), so that a higher score equals a better quality of life. If there is less than 50% missing data, the within participant mean is used for each missing item score. The total score is derived by summing the scores of the first 31 items (not item 32), giving a total score ranging from 31 to 124.

*Other outcomes*

The Sense of Competence in Dementia Care Staff (SCIDS) scale13 is a 17 item scale. Items are scored 1=not at all and 4=very much. Scores are added to give an overall score ranging from 17 to 68 with higher scores indicating higher levels of confidence. There are also subscales: Professionalism 7, 8, 9, 10, 12 (scores ranging from 5 to 20); Building Relationships 1, 2, 3, 4 (scores ranging from 4 to 12); Care Challenges 13, 14, 15, 17 (scores ranging from 4 to 12); and Sustaining Personhood 5, 6, 11, 16 (scores ranging from 4 to 12). The overall score will be used, and the subscales explored.

Maslach Burnout Inventory (MBI)14 consists of 22 items, which comprise three subscales; emotional exhaustion (items 1, 2, 3, 6, 8, 13, 14, 16, 20), depersonalisation (5, 10, 11, 15, 22) and personal accomplishment (4, 7, 9, 12, 17, 18, 19, 21). All items are scored 0=never to 6=every day with scores summed within each subscale. All subscales will be used.

The Modified Conflict Tactics Scale for professional carers15 comprises 10 potentially abusive items and six positive care items. Staff are asked whether they have seen or carried out any of these behaviours in the previous three months. Responses are given in categories: never, almost never, sometimes, most of the time or all of the time. The outcomes will be any abuse at least sometimes and any positive behaviour almost never or never (if numbers reporting this behaviour are not prohibitively small). This measure is completed anonymously however the care home the member of staff works in will be known and an unique code comprised of letters and numbers from personal information is being used to potentially enable data collected at baseline to be linked to data collected at eight months follow up.

Use of psychotropic medication at follow up will be operationalise as any psychotropic drug (antidepressant, antipsychotic, anxiolytic or hypnotic) and also these drug groups separately.

*Health economic outcomes*

EQ-5D-5L – proxy16 is a descriptive system that comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The proxy version is for use when patients are mentally or physically incapable of reporting on their health-related quality of life, for instance because of severe intellectual disability or mental health problems. The caregiver (the proxy) is asked to rate the patient’s health-related quality of life in their (the proxy’s) opinion. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient’s health state.

Client Service Receipt Inventory (CSRI)17 is a tool used to collect information on income, accommodation and a record of services that may be used grouped into subsections such as hospital care, primary care, community-based specialist or generic health care, social care, etc. Its primary purpose is to allow resource use patterns to be described and support costs to be estimated using an appropriate unit cost. We will use a modified version for care homes.

DEMQOL – proxy – as above

**Data collection**

*Baseline*

Care home

Number of residents (in total and with dementia)

Staffing levels

Details of regular home activities

Care Quality Commission (CQC) ratings

Whether public sector, charity or private

CQC classification (nursing, Care home without nursing, dementia registered, for dementia only, for physical illness, mental health registered or any other, resident age specifications (age >65 years only or not))

Location

Whether staff caring for residents with dementia have a specific team

Whether people are moved as they become more ill, if so, the criteria

Dementia specific training

Therapeutic Environment Screening Survey for Nursing Homes and Residential Care (TESS-NH/RC)

Paid carers (carer proxy)

Socio-demographic details for the included participants with dementia: age, sex, ethnicity, marital status level of education

Cohen-Mansfield agitation inventory

Neuropsychiatric inventory

Clinical Dementia Rating (CDR)

EQ-5D-5L

Client Service Receipt Inventory (CSRI) modified for care homes

Medication use

Greening dementia

Paid carers (about themselves)

Demographics (age, sex, ethnicity, level of education)

Short COPE

Maslach Burnout Inventory (MBI)

Sense of Competence in Dementia Care Staff (SCIDS) scale

Staff tactics scale

Resident with dementia

DEMQOL

Family carer

Demographics (age, sex, relationship to the resident)

How often they visit the person with dementia

DEMQOL-proxy

Non-participating, eligible residents

Age

Sex

*8 months*

Care homes

Staffing levels

Staff turnover

Details of regular home activities

Therapeutic Environment Screening Survey for Nursing Homes and Residential Care (TESS-NH/RC)

Paid carers (carer proxy)

Cohen-Mansfield Agitation Inventory (CMAI)

DEMQOL - proxy

EQ-5D-5L-proxy

Neuropsychiatric Inventory (NPI)

Clinical Dementia Rating (CDR)

Greening dementia

Client Service Receipt Inventory (CSRI) modified for care homes

Psychotropic medication (antipsychotics, antidepressants and mood stabilisers)

Withdrawal

Paid carers (about themselves)

Short COPE

Maslach Burnout Inventory (MBI)

Sense of Competence in Dementia Care Staff (SCIDS) scale

Staff tactics scale

Withdrawal

Adherence to the intervention

Resident with dementia

DEMQOL

Family carer

How often they visit the person with dementia

DEMQOL-proxy

*At any time*

Care home

Serious adverse events

**Data entry and checking**

Data will be entered using a web based system set up by Sealed Envelope18 by research assistants. This has been set up so that it mirrors the data collection sheets in order. It also has range checks, consistency checks and for closed questions gives a number of options plus “other” where appropriate. Data will be cleaned by a statistician and health economist (all CSRI data, EQ-5D-5L). If there are any values that are inconsistent and/ or out of range, these will be sent to the Study Manager/ Research Assistants for checking and changing as necessary.

**Statistical analyses**

Analyses will be carried out when data are finalised and cleaned. The statisticians and health economists will remain blinded until all analyses have been completed.

Analyses will be conducted using Stata version 1419

*Summary of recruitment and follow-up*

A CONSORT flow diagram will be constructed by/ in collaboration with the Study Manager/ Research Assistants/ Study Administrator who will have logs of care homes, paid carers, residents with dementia and family carers who do and do not agree to take part in the study. Content of the flow diagram will follow CONSORT guidelines, including number of care homes eligible and randomised to each arm of the trial and number of residents with dementia at baseline and follow up and those with data for the primary analysis.

*Comparison of characteristics between those consenting and not consenting*

We will summarise and compare age (mean (SD)) and sex (frequency (%)) for those residents who took part in the trial and those who were eligible but chose not to take part. Comparison will be based on appropriate two sample methods.

*Summary of baseline data*

*Individual level data (paid carers, residents with dementia and family carers)*

For those who participated in the trial, the distribution of continuous variables will be explored, both overall and by randomised group, with appropriate measures of central tendency, and variability. For categorical variables frequencies and percentages with given characteristics will be summarised both overall and by randomised group.

*Care home level data:*

Care home characteristics will be summarised by randomised group in a similar way as described for the individual level data.

Any notable differences between randomised groups will be identified.

*Analysis of the primary outcome*

CMAI score at 8 months will be summarised by randomised group using means and standard deviations. Average score will be compared between groups using a two level random effects linear regression model adjusting for baseline CMAI score, type of care home (residential versus nursing as used for stratified randomisation) and baseline severity of cognition (measured using the CDR),allowing for care home clustering. Treatment effect estimates will be reported with 95% confidence intervals, P-values and estimates of the intra cluster correlation coefficient (ICC).

If assumptions of the planned primary model are violated, we will analyse the data using a transformation of the outcome or using a valid alternative approach with good justification.

*Analysis of the secondary outcomes*

Similar analyses will be carried out for the secondary outcomes using appropriate summary statistics and regression models; NPI and DEMQOL will utilise means (SD) and random effects linear models and for the binary agitation outcome (Clinically significant agitation or not) we will report frequency (%) by group and use random effects logistic regression to estimate the effects of the intervention. All models will be adjusted for baseline score and type of care home (residential versus nursing) and baseline CDR. Assumptions of methods will be checked and alternative approaches taken if necessary.

Results from all secondary outcome analyses will be presented as estimates of the treatment effect with 95% confidence intervals and ICCs.

*Analysis of other trial outcomes - SCIDS, MBI, Modified conflict tactics scale, use of psychotropic drugs.*

SCIDS and MBI scores for all subscales will be summarised by randomised group using mean (SD) or median (IQR) as appropriate. Estimates of treatment effects will be obtained using random effects linear models adjusting for baseline score and type of care home. Appropriate alternative models will be used if model assumptions are not met.

Use of psychotropic drugs will be analysed using mixed effects logistic regression, controlling for the same psychotropic drug use at baseline.

Prior to the analysis of the Modified Conflict Tactics Scale for professional carers we will attempt to match data from the staff tactics scale from baseline and 8 months to individuals using Merge Toolbox (MTB)20-22. Initially we will analyse the 8 month data without consideration of baseline but with adjustment for type of care home. A subsequent analysis will include adjustment for baseline using successfully matched data. Random effects logistic regression models will be used. Since MCTS data are not identified by paid carer ID, other factors included in the models (in supportive analyses below) will be aggregated at the care home level because we will not know which member of staff filled in the modified conflict tactics scale, but will know which care home they work at.

*Missing data*

Reasons for missing outcome data will be described and frequency (%) of subjects with missing data, by reason will be calculated for each randomised group (and for each outcome).

Characteristics of residents with and without missing outcome data will be compared using random effects logistic regression models (with missing yes/no as the outcome) and characteristics that predict missingness identified.

*Supportive analyses for primary and secondary outcomes*

The following supportive analyses will be carried out for the primary and secondary outcomes using the same modelling approaches as described previously:

* Estimation of an unadjusted treatment effect estimate from random effects models allowing for clustering.
* Estimation of the treatment effect with additional adjustment for baseline predictors of missingness.
* Estimation of the treatment effect based on multiply imputed data (if imputation is considered appropriate). Multiple imputation models will account for the clustered nature of the data and include all outcomes, predictors of missingness and all variables that are adjusted for in any of the supportive analyses. Other variables may be included after clinical input.
* Estimation of the treatment effect adjusting for any concerning imbalances in baseline characteristics.
* Estimation of the treatment effect accounting for therapist clustering (if this is possible).

*Process outcomes*

Adherence to the intervention in terms of number of sessions delivered in each home, number of staff attending, number of sessions each member of staff attended and fidelity scores will be reported descriptively using median (IQR) or frequencies (%) as appropriate. We will also describe the proportion of care homes where more than 80% of staff attended all six sessions (either in group or catch up).

We will calculate the correlations between the staff proxy, family proxy and resident DEMQOL.

*Analysis of the interrater reliability data*

A research assistant and another team member not delivering the intervention will score adherence to the manual text and leader instructions for each of the subsections of the session recorded. The interrater reliability will be described and examined using the kappa statistic.

**Health economic analyses**

**Aim**

The aim of the economic evaluation is to determine if the MARQUE intervention is cost-effective compared with treatment as usual (TAU) for a range of values of willingness-to-pay for a quality adjusted life year (QALY) gained. Health service costs and QALYs will be calculated for the within-trial period (8 months). Study perspectives will be (1) health and social care system; (2) societal.

**Outputs**

* Mean cost per resident of MARQUE intervention in the intervention arm
* Mean cost of TAU for each trial arm
* Mean total health care costs per resident over 8 months for each trial arm
* Descriptive statistics of EQ-5D-5L and associated algorithms to calculate utility scores
* Descriptive statistics of DEMQOL and associated algorithms to calculate utility scores
* Mean total resident QALY for each trial arm
* Mean incremental cost per QALY of MARQUE intervention compared with TAU and 95% confidence intervals
* Mean incremental cost per CMAI score of MARQUE intervention compared with TAU and 95% confidence intervals
* Cost-effectiveness plane
* Cost-effectiveness acceptability curve

**Analyses**

*QALYs*

We will calculate the mean resident-level QALYs for each trial arm over 8 months. QALYs will be calculated using EQ-5D-5L and the associated algorithms23, 24, mapping25 the 5L descriptive system data onto the 3L valuation set as recommended by NICE26. The mean area under the curve for each trial arm will be calculated using values from each follow-up point from baseline to 8 months, controlling for any baseline differences using regression analysis including covariates for type of care home (residential versus nursing as used for stratified randomisation) and allowing for care home clustering as a random effect.

Missing utility scores due to either missing items or missing questionnaires will be imputed using multiple imputation. Bootstrapping will be used to calculate 95% confidence intervals for each trial arm.

*Cost of intervention*

The cost of implementing the intervention manual, including staff training and supervision, capital costs and delivering the intervention will be calculated for each care home. Cost per resident will be calculated as the cost to the care home divided by the number of residents with dementia.

*Health service resource use*

Descriptive statistics will be reported for health care costs by trial arm over 8 months. Health care resource, collected from the modified CSRI, will include overnight inpatient stay, outpatient contacts, accident and emergency attendances, primary care, community health or emergency services, social care, community based services and professional visits, and prescribed medication. Resource use will be multiplied by unit costs obtained from the most recent versions of the PSSRU (2017)27 and NHS national schedule of reference costs (2015/16)28 and BNF to obtain the total cost per resident.

*Total costs*

The costs components included in the analysis will consist of the cost of the intervention, cost of health care resource use and cost of prescribed medication. The mean cost per resident will be reported in addition to adjusted cost, adjusting for baseline service use using regression analysis including covariates for type of care home (residential versus nursing as used for stratified randomisation) and allowing for care home clustering as a random effect. Missing health care resource use will be imputed using multiple imputation. Bootstrapping will be used to calculate 95% confidence intervals for each trial arm.

*Incremental cost-effectiveness ratio (ICER)*

The mean costs and QALYs calculated above will be used to calculate the mean incremental cost per QALY gained of MARQUE intervention compared with TAU.

The mean costs and CMAI scores calculated above will be used to calculate the mean incremental cost per changes in CMAI scores of MARQUE intervention compared with TAU.

*Cost-effectiveness plane (CEP) and cost -effectiveness acceptability curve (CEAC)*

The results of the non-parametric bootstrap will be presented on a CEP. A CEAC will also be constructed using the bootstrap data for a range of values of willingness-to-pay for a QALY gained. The probability that the MARQUE intervention is cost-effective compared with TAU at a willingness-to-pay for a QALY of £20,000 and £30,000 will be reported.

**Secondary analyses**

A secondary analysis will be conducted where QALYs will be calculated using utility scores generated from the DEMQOL outcome29 measure following the same methodology as above. The results will be combined with costs as above to report the mean incremental cost per QALY gained of MARQUE intervention compared with TAU.

**Sensitivity analyses**

If any key assumptions become apparent during the analysis, these will also be tested for as part of the sensitivity analyses.

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