COMPIN

Cognitive Muscular Therapy versus Psychologically Informed Physiotherapy in non-specific chronic Neck pain: a feasibility study

STATISTICAL AND HEALTH ECONOMIC ANALYSIS PLAN

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Version date:

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Version no. 3.0

Contents

1. Document scope and relevant SOPs and guidance documents

This analysis plan deals with the statistical analysis of effectiveness and cost-effectiveness. The statistical analysis of the clinical data will be conducted by Stephen Preece (University of Salford), and the health economic analysis will be conducted by Joshua Pink (University of Salford)

This analysis plan was written prior to the completion of recruitment and was prepared according to UoS SOPs and guidance documents.

2. Definition of terms/acronyms

AE	*Adverse event*
CONSORT	*Consolidated standards of reporting trials*
CMT	*Cognitive muscular therapy*
NIHR	*National Institute of Health Research*
CTIMP	*Clinical trial of Investigational Medicinal Product*
RCT	*Randomised controlled trial.*
SAE	*Serious adverse event*
SAP	*Statistical analysis plan*

3. Design

This study is an open, multi-centred, two-armed feasibility, randomised trial with allocation at the patient level, with embedded health economic and qualitative evaluations (not detailed further in this SAP). The two arms are: cognitive muscular therapy (CMT) and psychologically informed physiotherapy

Full details of the background and design of the trial are presented in the protocol (Protocol-(COMPIN)- v5 (17-04-24).docx)

4. Trial objectives

This trial aims to deliver key parameters that are required to run a future, pragmatic, two-arm RCT.

4.1 Primary objective

This trial aims to gain insight into whether CMT is more effective than PiP for patients with chronic non-specific neck pain.

4.2 Secondary objectives

This trial will examine, and aims to gain insight into, the following secondary objectives:

- Can sufficient numbers of study participants be recruited and retained to enable an RCT? (feasibility trial)
- What is the physiotherapist acceptability of the intervention? (qualitative evaluation)
- What is the patient acceptability of the intervention? (feasibility trial via adherence, and qualitative evaluation)
- What is the suitability of various outcome measures for use in an RCT? (feasibility trial)

The following stop-go criteria will be monitored to indicate overall trial feasibility.

1 Recruitment: Average participants recruited per month: red: <4 per month; amber: 4-6 per month; green> 6 per month.

2: Adherence/retention: Participants attending >5 (of 7) clinical sessions: <60%; amber=60-79%; green≥80%.

3: Outcomes: Participants providing 14-week and 6 month data: red<60%; amber=60-79%; green≥80%. Appropriateness of outcomes determine via qualitative evaluation.

4 Acceptability to patients. Determined via the qualitative evaluation.

5. Outcomes

5.1 Primary outcome(s)

This research is a feasibility trial and therefore does not have a primary clinical outcome measure. The primary outcomes will therefore relate to the feasibility of conducting a future, fully powered RCT (recruitment, retention, and intervention adherence rates) and obtaining parameters required to inform its design and conduct, such as the standard deviation of outcome measures that may feed into the sample size calculation.

5.2 Secondary outcomes

Clinical data will be collected using the following questionnaires:

1. Neck Disability Index (NDI)

2. Numerical rating scale of pain scale (0-10)
3. 13-item Tampa Scale of Kinesiophobia (TSK- 13)
4. Pain Catastrophising Scale (PCS)
5. EQ-5D-5L (EuroQol)
6. STarT MSK Screening Tool

5.2.1 Pain and function

The Neck Disability Index (NDI) is a self-report questionnaire used to determine how neck pain affects a patient's daily life and to assess the self-rated disability of patients with neck pain. The NDI consists of ten questions in the following domains: Pain Intensity, Personal Care, Lifting, Reading, Headaches, Concentration, Work, Driving, Sleeping, and Recreation.

Scoring: Each question contains six answer choices, scored from 0 (no disability) to 5 (complete disability). All section scores are then totaled. Scoring is reported on a 0-50 scale, 0 being the best possible score and 50 being the worst. Alternately, the score can be reported from 0-100. The score is often reported as a percentage (0-100%).

The numerical rating scale is a scale designed to help assess the extent of an individual's pain. The NRS consists of a numeric version of the visual analog scale. The most common form of the NRS is a horizontal line with an eleven point numeric range. It is labeled from zero to ten, with zero being an example of someone with no pain and ten being the worst pain possible. This type of scale can be administered verbally. It can also be administered via paper to be completed physically.

5.2.2 Catastrophising

The Pain Catastrophising Scale has 13 items rated on the Likert scale of 0='Not at all', 1='To a slight degree', 2='To a moderate degree', 3='To a great degree', and 4='All the time', such that a higher score indicates a higher level of catastrophizing. Items can be summed to produce three subscales (Helplessness [PCS-H] items 1, 2, 3, 4, 5 and 12; Magnification [PCS-M] items 6, 7 and 13; and Rumination [PCS-R] items 8, 9, 10 and 11) and a total score (sum of three subscales, range 0-52). If there are up to two missing items across the whole scale, these can be replaced by the mean of the completed items, and then the subscale and total scores calculated (3) Otherwise, scores can only be completed where there are no missing items within a subscale. A total score of 30 indicates a clinically relevant level of catastrophizing.

5.2.3 Kinesiophobia

The Tampa Scale of Kinesiophobia is a 13-item questionnaire evaluating fear of movement, fear of physical activity, and fear avoidance. Items are scored 'strongly agree', 'disagree', 'agree' and 'strongly agree'. For questions 1, 2, 3, 5, 6, 7, 9, 10, 11, 13 the responses range from 1-4 respectively.

The total score of the scale ranges from 17-52 and the score is calculated by adding up the responses to all items (up to two missing items can be replaced by the mean of the other completed items, otherwise the instrument is invalid). A total score of more than 37 indicates presence of kinesiophobia.

5.2.4 Risk of chronicity

The STarT MSK tool aims to ensure that patients with common musculoskeletal conditions receive the right treatments at the earliest opportunity. The tool contains 10 items that once scored can place patients into three categories based on their risk of a poor outcome (low, medium, and high). The Keele STarT MSK Tool has 10 items that ask about predictors of poor outcomes for a range of conditions. The items ask about the function and disability, pain and coping, comorbidity and the impact of pain. There is a visual analogue scale (VAS), which records participants' overall evaluation of their pain from 0 'no pain' to 10 'pain as bad is it could be'. This followed by 9 questions with 'yes' or 'no' responses. A total maximum score is 12.0-4 represents low risk, 5-8 medium risk and 9-12 high risk of chronicity.

5.2.5 Health-related quality of life

The EQ-5D™ (4) is a widely used self-reported generic measure of HRQoL which comprises two parts: the classification of 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analogue scale (VAS), which records participants' overall evaluation of their health on a scale from 0 (worst imaginable health) to 100 (best imaginable health). The EQ-5D has been validated in many different patient populations including diabetes, cardiovascular problems, chronic obstructive pulmonary disease, cancer, chronic pain, and rheumatoid arthritis.

The EQ-5D-5L has five levels of responses for each domain (1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = unable to do/extreme problems), which lead to 3125 unique combinations of health states where each health state is mapped to a utility index score (the utility values are on a scale where negative values correspond to a state worse than death, 0 corresponds to a health state equivalent to being dead

and 1 corresponds to perfect health) by making use of a valuation set. Participants who die can be given a score of 0 for any assessment time point following their date of death. There is a valuation set for the EQ-5D-5L available for England (5); however, this is currently under revision. Meanwhile, the UK's National Institute for Health and Care Excellence (NICE) recommends that utility values should be calculated using the crosswalk developed by van Hout et al (6). Utility scores will be calculated following the NICE guidance at the time of the analysis and detailed in the final report.

5.3 Other collected variables

5.3.1 Baseline demographics

Age, gender, height and weight (which will be used to calculate BMI) will be recorded at baseline.

5.3.2 Trial retention

The proportion of withdrawals and the proportion of completed 6-month questionnaires will be used to determine trial retention. Withdrawals and losses to follow up will be classified as:

- Participant withdrawn from follow-up only
- Participant withdrawn from the intervention but agrees to further follow-up
- Participants fully withdrawn from the intervention and follow up
- Participants lost to follow-up
- Participant has died

5.3.3 Intervention adherence

The number of participants attending clinical sessions will be monitored at each site throughout the trial. The intervention consists of up to 7 sessions.

5.3.4 Intervention fidelity

The PiP arm will be monitored for fidelity through the review of clinical notes.

Step 2- Consistency of fidelity check between two raters

- Same set of five notes will be analysed by both raters.
- Following this, the scoring will be compared for consistency, aiming for a cohens kappa score of 0.7 . If above 0.7, ok to continue to step 3. If below 0.7, discussion to clarify areas of inconsistency.
- Following this, an additional set of five notes checked. Consistency scored with cohens kappa. If continues below 0.7, consider change of methods, fidelity assessment structure or processes. Repeat stage 1 and 2. If above 0.7, continue to step 3

Step 3- intra tester reliability

- Same set of five notes analysed again 2 weeks later.

- Intraclass Correlation Coefficient (ICC) calculated. If above 0.75, ok to continue to step 4. If below 0.75. Repeated 1 week later.
- If repeated test below 0.75, review understanding of checklist and processes.
- Repeat 1 week later, if below 0.75, repeat step 1.

Step 4- stratified sampling of participants into red (2 sets) /amber (3 sets) /green participants (4 or 5 sets)

- Participants stratified into red/ amber/ green.
- Once stratified, participants randomly sampled for fidelity assessment using Microsoft excel. Aiming for 4 green= 16-20 notes, 4 amber= 12 notes and 4 red participants= 8 notes. Maximum sets of notes = 40 notes + 10 pilot notes= 50 sets of notes.
- Participants then randomly allocated to rater 1 and rater 2 aiming for even distribution of red/amber/green participants.

Step 5- Assessments analysed

- Descriptive analysis of scores broken down into tester and red/amber/green categories. Mean (SD) scores presented.
- Kappa score for inter tester
- ICC for intra tester

5.3.5 Adverse events

Adverse events will be reported throughout the 6 month follow up period. The trial physiotherapists and participants are responsible for notifying the research team about adverse events. Adverse events related to CMT will be assessed for seriousness, expectedness and relatedness by the chief investigator and principal investigator. The 'NIHR- Decision Tree for Adverse Event Reporting- NON CTIMPS' will be used to guide this assessment. All adverse events will be recorded by the research trial coordinator. Any related or serious adverse events will be reported to the Research Ethics Committee by the chief investigator. Adverse events will be included in regular progress reports to the steering group committee.

5.3.6 Diversity and inclusion questionnaire

A diversity and inclusion questionnaire will be completed at baseline. This self- administered questionnaire asks about age, disability, ethnic background, gender, religion and socioeconomic background. The results will be summarised descriptively and the diversity and inclusion of the study will be reported for each category and group (CMT/ PiP).

5.3.7 Musculoskeletal Patient Reported Experience Measure

A patient reported experience measure will be completed at 14 weeks. This self- administered questionnaire asks about patient's experiences of undergoing an intervention for their condition. Questions 1-12 focus on satisfaction, being involved in decisions, feeling listened

to, explanations, time, care, confidence, review opportunities, information, care coordination, needs, guidance. Questions 1-12 have 3 levels of responses for each domain (3= yes, definitely, 2= yes to some extent, 1= no not at all. Question 13 has five levels of responses for each domain (5= extremely, 4= very, 3= moderately, 2= slightly, 1= not at all. Question 14 has five levels of responses (5= very good, 4= good, 3= neither good nor poor, 2= very poor, 1= don't know.

Follow-up

Participants in both arms will complete all secondary outcomes at baseline, 14 weeks and 6 months post-randomisation.

6. Data

7.1 Electronic/non-paper data

The secondary outcome measures described in section 5.2 have been set up on JISC (web-based digital resource for online surveys. Participants are sent an email from JISC which includes links to each of the outcomes. The participants will complete the outcome measure questionnaires online at baseline, 14 weeks and 6 months post-randomisation. The results are stored on JISC until analysis.

7.2 External datasets

1. Recruitment data will be stored in a recruitment screening log and spreadsheet by the trial research coordinator.
2. Consent data will be stored in a consent log and spreadsheet managed by the trial research coordinator.

7. Sample Size

We plan to recruit 48 participants to the study. Assuming a dropout of 20%, this should provide approximately 19 in each group for the final analysis. The primary objective of this study is to assess the feasibility, and inform planning, of a future large-scale clinical trial. Sample sizes of between 24 and 70 have been recommended for feasibility trials to provide a reliable estimate of parameters required to calculate the sample size for a main trial, e.g. standard deviation of continuous outcomes, recruitment, and attrition rates. Our sample of 48 is therefore in line with these recommendations.

8. Randomisation

Randomisation will be carried out via a web-based randomisation system (https://www.sealedenvelope.com/). The allocation sequence will be generated by the lead or co-investigator not otherwise involved in the recruitment/treatment of participants. Once group allocation has been confirmed the intervention coordinator (member of the research team) will liaise with participants over the phone to schedule the appointments.

10. Analysis

10.1 Analysis software

Analyses will be mainly conducted in SPSS Statistics 28, whereas health economic analysis will be conducted in Stata (version 15 or later; Stata Corp LLC; College Station, TX).

10.2 Baseline data

Baseline data (demographics and outcome measures collected post-randomisation) will be summarised descriptively by treatment and control group both as randomised, and for participants followed up at 6 months. Continuous variables will be summarised using mean and standard deviation (SD), and number and percentage for categorical. A template of the table used to present baseline characteristics can be viewed in Appendix A. No formal statistical comparisons will be undertaken on baseline data.

10.3 Screening, eligibility, recruitment and follow-up data

A CONSORT diagram will be produced to detail participant flow through the trial (Appendix B). A recruitment, screening and consent log will be kept detailing participation in the study. This data will be used to determine:

- Numbers screened and sent PIS by clinical research nurse per research site.
- Proportion of participants screened who contacted the research coordinator per site.
- Proportion of participants who were eligible per research site.
- Proportion of participants consented per research site.
- Proportion of participants withdrawn per research site.

Recruitment graphs presenting the overall recruitment per month and the actual vs target recruitment will be produced.

The type and timing of withdrawals will be presented overall and by randomised group, with reasons where available. Templates of the tables used to present recruitment and retention data can be viewed in Appendix (C).

A log detailing the proportion of collected and analysable outcome data per follow up timepoint will be kept. This log will include:

- Baseline data for each arm and all outcome measures.
- 14-week data for each arm and all outcome measures.
- 6-month data for each arm and all outcome measures.

10.4 Outcome data

Outcome data will be summarised descriptively by group (treatment vs control) and timepoint. We will plot line graphs to look at the trajectory of each outcome over time, looking at both individual participants and the mean values for each randomised group. As this is a feasibility study, no formal hypothesis testing will be undertaken to compare outcomes between the groups. Templates of the tables used to present outcome data can be viewed in Appendix (C). Potential clinical effectiveness will be considered by investigating the number of participants who experience a 30% improvement in pain/ function as measured by the Neck Disability Index at 6 months. We will also calculate the mean difference in the NDI score between the intervention and control groups, with a one-sided 80% and 90% confidence interval (CI) for this difference to see whether the interval includes the kind of difference that we would be looking for in the main trial. If, for instance, we saw a negative point estimate and our CI excluded say a 0.3 SD difference then this would be suggestive that it may not be worth moving forward to the main trial - at least with the intervention as tested in the feasibility study.

10.5 Primary analyses

The recruitment rate (defined as the number of recruited participants divided by the number of eligible participants), will be estimated along with a 95% CI. The number of participants recruited will be presented by site, as will the overall average number of participants recruited per site per month.

The trial retention will be measured at the end of the 8-month study follow-up. For each outcome, an estimate of the attrition rate (the number of forms not returned divided by the number of forms due) will be produced along with a 95% confidence interval. This will be done for the study overall and by group (treatment vs control).

Intervention adherence will be measured at the 14 week follow up. Adherence will be expressed as a percentage with a maximum of 100% attendance reflecting 7 out of 7 treatment sessions attended for CMT and 5/5 attended for PiP. The total number and percentage of participants attending >66% of CMT sessions and 100% of PiP F2F sessions.

These summaries will be used to assess success of the trial against the pre-specified progression criteria.

10.6 Intervention fidelity

Intervention fidelity scores will be summarised (Appendix D).

10.7 Adverse events

Adverse events and serious adverse events will be presented by trial arm and site, itemised with descriptions (Appendix E).

10.8 Health Economics

We will be collecting patients' response to EQ-5D-5L instrument and patient-reported questionnaire on health resource utilisation at baseline, 14 weeks and 6 months as part of the health economic evaluation. All data will be summarised descriptively by group and follow-up time points.

The feasibility of undertaking an economic evaluation of the CMT intervention versus control group will be the primary objective of the health economic analysis. Of note, a full economic evaluation will not be conducted. Instead, an economic evaluation framework will be established to assess the feasibility of data collection methods being used in this study and help identify the appropriate instruments for the collection of relevant health economics data in order to inform full economic evaluation of the future pragmatic RCT.

The distribution of participants' response to the five dimensions of EQ-5D-5L instrument and utility will be tabulated at baseline, 14 weeks and 6 months. QALYs of each participant at each follow-up time points and total QALYs will be generated with the "area under curve" (trapezoidal) method by assuming linear interpolation between measurements over time. In accordance with NICE's position statement, patients' responses to the EQ-5D-5L questionnaire will be mapped to EQ-5D-3L to derive the health utility of patients at each follow-up time point.

An NHS and Personal Social Services (PSS) perspective will be adopted for the analysis of health care resource utilisations, which means all health care-related resources used by the

patients that are reimbursed by NHS will be considered. Health care utilisation data at each follow-up time point will be collected and presented for relevant resources used by patients in primary care, community (i.e. appointments with a GP, nurse, physiotherapist, occupational therapist, and other primary/community care healthcare professionals) and hospital setting (i.e. hospital outpatient attendances, accident and emergency admissions, day case attendances and inpatient admissions). Participants will be asked to record their resource use specifically in relation to neck pain and whether the appointment/contact was face-to-face or remote (phone/online). Mean resource use by cost category will be summarised, and completion rates will be presented. Considering that this is a feasibility trial and full economic evaluation was deemed unnecessary, unit costs for the healthcare resources will not be attached to the units of resource utilisations to derive the total costs.

Missing EQ-5D-5L and resource utilisation data will be inspected to understand the likely mechanism of missingness to help guide appropriate imputation methods to deal with the missing data.

As full economic evaluation is not necessary, the common issues around trial-based economic evaluation such as baseline imbalances, correlated costs and effects, and skewness of costs and effects will not be considered in our study. The sampling uncertainty will not be considered as well and as a result, non-parametric bootstrapping will also not be applied.

9. SAP amendment log

Amendment/addition to SAP and reason for change	**New version number, name and date**
Draft	V1.0
Draft	V2.0
Signed version	V3.0

10. Signatures of approval

Sign-off of the final approved version of the Statistical Analysis Plan by the principle investigator and trial statistician(s) (can also include Trial Manager/Co-ordinator)

Name	Trial Role	Signature	Date

11. References

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12. Appendices

Appendix A: Baseline table

Table 1. Baseline demographics and outcome measures of randomised participants, both as randomised and for those completing the 8-month timepoint assessments

Characteristics	**As randomised**			**Followed up at 6 months**		
	Intervention (n=x)	**Control (n=x)**	**Overall (n=)**	**Intervention (n=x)**	**Control (n=x)**	**Overall (n=)**
Age, years						
N, mean (SD)						
Gender, n (%)						
Male						
Female						
Trans						
BMI						
N, mean (SD)						
Outcome measures, N, mean (SD)						

Neck Disability Index						
NRS						
PCS-H subscale						
PCS-M subscale						
PCS-R subscale						
PCS total score						
Tampa scale						
START MSK						
EQ-5D-5L index value score						
EQ-5D-5L VAS						

Table 2. Diversity and inclusion demographics

Age	**Intervention (n=x)**	**Control (n=x)**	**Overall (n=x)**
Up to and including 24 years			
25-34 years			
35-44 years			
45-54 years			
55-64 years			
65- 74 years			
75+ years			
Prefer not to say			
Disability	**Intervention**	**Control**	**Overall**
Yes			
No			
Prefer not to say			
Yes – substantial barriers or limitations			
Yes – some/small barriers or limitations			
No			
Ethnicity	**Intervention**	**Control**	**Overall**
Bangladeshi			
Chinese			
Indian			
Pakistani			

Any other Asian background (please describe below)			
Black / African / Caribbean / Black British			
African			
Caribbean			
Any other Black / African / Caribbean background (please describe below)			
White			
English / Welsh / Scottish / Northern Irish / British			
Gypsy or Irish Traveller			
Irish			
Roma			
Any other white background (please describe below)			
Arab			
Hispanic			
Latina/Latino/Latinx			
Any other ethnic group			
Religion	**Intervention**	**Control**	**Overall**
No religion			
Bhuddist			
Christian			
Hindu			
Jewish			
Muslim			
Sikh			
Spiritual			
I have a religion or strongly held belief but prefer not to specify what this is			
Prefer not to say			
Any other religion or belief (please describe below)			
Socio-economic background	**Intervention**	**Control**	**Overall**
Modern professional & traditional professional occupations such as: teacher, nurse, physiotherapist, social worker, musician, police officer (sergeant or above), software designer, accountant, solicitor, medical practitioner, scientist, civil / mechanical engineer			
Senior, middle or junior managers or administrators such as: finance manager, chief executive, large business owner, office manager, retail manager, bank manager, restaurant manager, warehouse manager			

Clerical and intermediate occupations such as: secretary, personal assistant, call centre agent, clerical worker, nursery nurse			
Technical and craft occupations such as: motor mechanic, plumber, printer, electrician, gardener, train driver			
Routine, semi-routine manual and service occupations such as: postal worker, machine operative, security guard, caretaker, farm worker, catering assistant, sales assistant, HGV driver, cleaner, porter, packer, labourer, waiter/waitress, bar staff			
Long-term unemployed (claimed Jobseeker's Allowance or earlier unemployment benefit for more than a year)			
Small business owners who employed less than 25 people such as: corner shop owners, small plumbing companies, retail shop owner, single restaurant or cafe owner, taxi owner, garage owner			
Other (for example unemployed due to disability)			
Prefer not to say			

Table 3- Patient reported experience measure

Characteristics	**As randomised**			**Followed up at 6 months**		
	Intervention (n=x)	**Control (n=x)**	**Overall (n=)**	**Intervention (n=x)**	**Control (n=x)**	**Overall (n=)**
MSK PREM						

Appendix B: COMPIN CONSORT DIAGRAM

https://testlivesalfordac.sharepoint.com/sites/BEPKO298/Shared%20Documents/General/Trial%20-%20COMPIN/Ethics%20and%20recruitment/Recruitment%20and%20screening/COMPIN%20CONSORT%20diagram.docx

Appendix C: Recruitment and retention summary tables

Table 2: Recruitment log

Site	**Number Identified and sent PIS by CRN**	**Number contacted and screened** (95% CI)	**Number Consenting** (95% CI)	**Number Randomised** (95% CI)	**Number Withdrawn** (95% CI)
Total					

Table 3: Withdrawal's log

Site	**Participant ID**	**Reason for Withdrawal**

Table 4: Summary of outcomes by treatment group and time point

Continuous outcome measures, N, mean (SD)	**14 weeks**			**6 months**		
	Intervention (n=x)	**Control (n=x)**	**Overall (n=)**	**Intervention (n=x)**	**Control (n=x)**	**Overall (n=)**
WOMAC Pain subscale						
PCS-H subscale						

PCS-M subscale						
PCS-R subscale						
PCS total score						
Tampa scale						
EQ-5D-5L index value score						
EQ-5D-5L VAS						
Categorical outcome measures, n (%)						
PCS total score ≥30						
Tampa scale >37						
Severe (20-24)						

Appendix D: Notes audit log

Appendix E: Adverse events

ID	Description	Severity	Action taken	Outcome	Allocation

Adverse events	Intervention	Control	Total

	(N =)	**(N =)**	**(N =)**
Serious Adverse Events N (%)			
Relatedness			
Related			
Unrelated			
Expectedness			
Expected			
Unexpected			
Non-Serious Adverse Events N (%)			
Grading			
Mild			
Moderate			
Severe			
Relatedness			
Related			
Unrelated			
Expectedness			
Expected			
Unexpected			