Study Title: Maintaining Musculoskeletal Health (MAMMOTH) Study

STATISTICAL ANALYSIS PLAN

Document History

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	Signature	Date
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1. INTRODUCTION

1.1. BACKGROUND

Chronic widespread pain (CWP), the characteristic feature of fibromyalgia, is associated with reduced productivity at work, mental ill health, and poor quality of life. Current guidelines recommend drug therapy, physical and psychological therapies, although different guidelines put different emphasis on how important each type of therapy is. There is good evidence that the longer a patient experiences an episode of pain, the less likely that symptoms are to improve. This is particularly true for CWP – so it is important to manage symptoms early or, better, to try to prevent onset. An Arthritis Research UK report on fibromyalgia/CWP, based on a think-tank held in July 2012 with patient input, identified prevention as a research priority. We have previously shown short and long-term effectiveness of CBT delivered by telephone (tCBT) for CWP in an Arthritis Research UK funded study and we have now developed effective ways to predict who is at high risk of developing CWP.

People who consult their general practitioner with musculoskeletal pain and who also have, in addition, at least two of the following characteristics are at high risk of developing chronic widespread pain (CWP), the main feature of fibromyalgia:

- disturbed sleep,
- several other bodily symptoms (apart from pain),
- specific beliefs about their symptoms (e.g. have strong worries or perceptions that their symptoms indicate a serious illness, even though this is not supported by clinical assessment)

1.2. STUDY OBJECTIVES

The primary objectives are:

We will test the hypothesis that among patients who report regional pain for which they have already sought a consultation in primary care, and who are identified as high risk of developing chronic widespread pain, a short course of telephone-delivered Cognitive Behaviour Therapy (tCBT) reduces the onset of CWP.

We will further determine the cost-effectiveness of such a preventative intervention.

We wish to find out whether, among patients identified as being at high risk of developing CWP, a short course of tCBT reduces the risk of CWP onset. We will determine during therapy/usual care (3 months after treatment/dummy treatment start date), after therapy has finished (12 months), and in the long-term (24 months) how many persons have developed CWP and whether this is different between the two treatment groups. The primary outcome is the between arm difference in the proportions of people developing CWP from baseline to 12 months. Appropriate adjustment will be made for the stratification factor used in the randomisation (the number of non-pain “high-risk” factors that a participant reports at baseline).

Secondary objectives:
We will also measure patients' overall perceptions of their condition, their quality of life, fatigue and psychological ill health, in order to get a full picture of the effects of the tCBT. Secondary outcomes will be described at the three follow-up times: 3, 12 and 24 months, using appropriate summary statistics.

Comparisons with appropriate hypothesis tests will be used for the secondary outcomes, pain,

illness behaviour, somatic symptom reporting, sleep problems, quality of life and wellbeing, psychological distress, patient global impression of change measure and fatigue. Appropriate adjustment will be made for the stratification factor. The baseline value of the relevant outcome variable will also be included as a covariate.

1.3. STUDY DESIGN

This study is a two-arm randomised controlled trial testing a short course of tCBT against usual care. Subjects will be eligible if they are evaluated as “at high risk” of developing CWP, namely have had a primary care consultation with regional pain and at least two of: a maladaptive behavioural response to illness, a high number of somatic symptoms and/or sleep disturbance. If successful this study would provide general practitioners with an intervention option to reduce the risk of CWP development.

1.4. SAMPLE SIZE CALCULATIONS

Our previous longitudinal study of onset of CWP (and subsequent replication) has suggested that 21% of "high risk" persons identified will develop CWP over the course of the next twelve months. Our previous data is based on persons with pain and at least 2 out of 3 other "risk factors". There are no published studies of prevention of CWP on which to base our measure of effect. However in the MUSICIAN study some subjects, although reporting CWP at the screening survey, no longer had CWP at the enrolment interview. They were however still eligible to take part, provided they had regional pain. Therefore those subjects with regional pain provide a sub-population on which to base the likely effects of the tCBT. Amongst such subjects, those who received tCBT had a reduced odds of having CWP at the end of the study OR 0.5 95% CI (0.2-1.4) compared to those in usual care.

Thus the study is powered on the ability of the current study to reduce the onset of CWP from 21% to 12%, with 90% power and a 5% significance level. We further assume, based on prior data, that 75% of persons allocated to the tCBT arm will be adherent to the intervention, and that 80% of all subjects will return the follow-up questionnaires to assess outcome.

Final Sample Size

Accordingly we require 473 subjects per arm that is a total of 946 subjects recruited. In MUSICIAN exactly 50% of those found eligible and willing to consider taking part ultimately were randomised. A previous trial of a cognitive-behavioural intervention to prevent chronic pain found that 36% of patients identified as eligible ended up being recruited to the study. If 80% of eligible patients agreed to be contacted about taking part, this equates to 45% of those eligible and willing to consider taking part being randomised - higher numbers for a clinical trial of CWP reflect the fact that this is a prevention trial rather than a treatment trial and may be less attractive to potential participants. Thus we aim to find a total of 2102 subjects who are eligible and willing to consider taking part. Assuming a participation rate to the survey of 30%, that 1 in 4 people will be "at risk", and (using data from MUSICIAN) that 80% of people who return a questionnaire agree to consider taking part, we require to survey 35,037 persons.

1.5. STUDY POPULATION

Three health boards in Scotland will be research sites for the study. The three health boards are NHS Grampian, NHS Highland, and NHS Greater Glasgow and Clyde. We will require the involvement of 7 or 8 equivalent general practices. We will mail a randomly selected sample of adults aged 25 years and over registered with participating general practices in the study areas.

Searches are undertaken at each GP practice before the screening survey questionnaires are sent out by Health Informatics Centre Services in Dundee on behalf of the practice. Patients will return completed survey questionnaires to the research team at the University of Aberdeen where they will be assessed by the research team for eligibility and sent invitation letters if eligible.

The "screening questionnaire" will determine whether a) they meet the study eligibility criteria and b) they would be willing to be contacted again regarding a treatment trial for "musculoskeletal health". Specific criteria for inclusion and exclusion of participants can be found in the protocol (version 4.0 26/02/2016).

A list of eligible patients will be provided to the general practitioner in advance, with the option of indicating any as unsuitable for the study. Patients would then be sent information about the study and subsequently contacted by a member of the research team by telephone and, if appropriate, consented and recruited into the trial.

1.6. STATISTICAL ANALYSIS PLAN (SAP)

1.6.1.SAP OBJECTIVE

The objective of this SAP is to describe the quantitative statistical analyses to be carried out for MAMMOTH. This SAP is based on protocol version 4 (26/02/2016). Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary and any changes to the SAP will be documented under version control.

1.6.2.GENERAL PRINCIPLES

Categorical variables will be described with number and % in each category. Continuous variables will be described with mean and standard deviation (SD) or median and inter-quartile range (IQR) depending on their distribution. The amount of missing data will be provided for each variable.

ABBREVIATIONS

CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CTA	Clinical Trial Authorisation
EQ-5D	European Quality of Life Questionnaire
ITT	Intention To Treat
PP	Per Protocol
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SD	Standard Deviation
TSC	Trial Steering Committee

1.6.3.SOFTWARE

All analyses will be carried out using STATA version 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Data will be stored on a secure drive, with limited access to those who need it.

2. ANALYSIS

2.1. STUDY POPULATIONS

Comparison between arms will be on an intention-to-treat basis (main analysis) with a per protocol sensitivity analysis.
Intention to treat (ITT) population

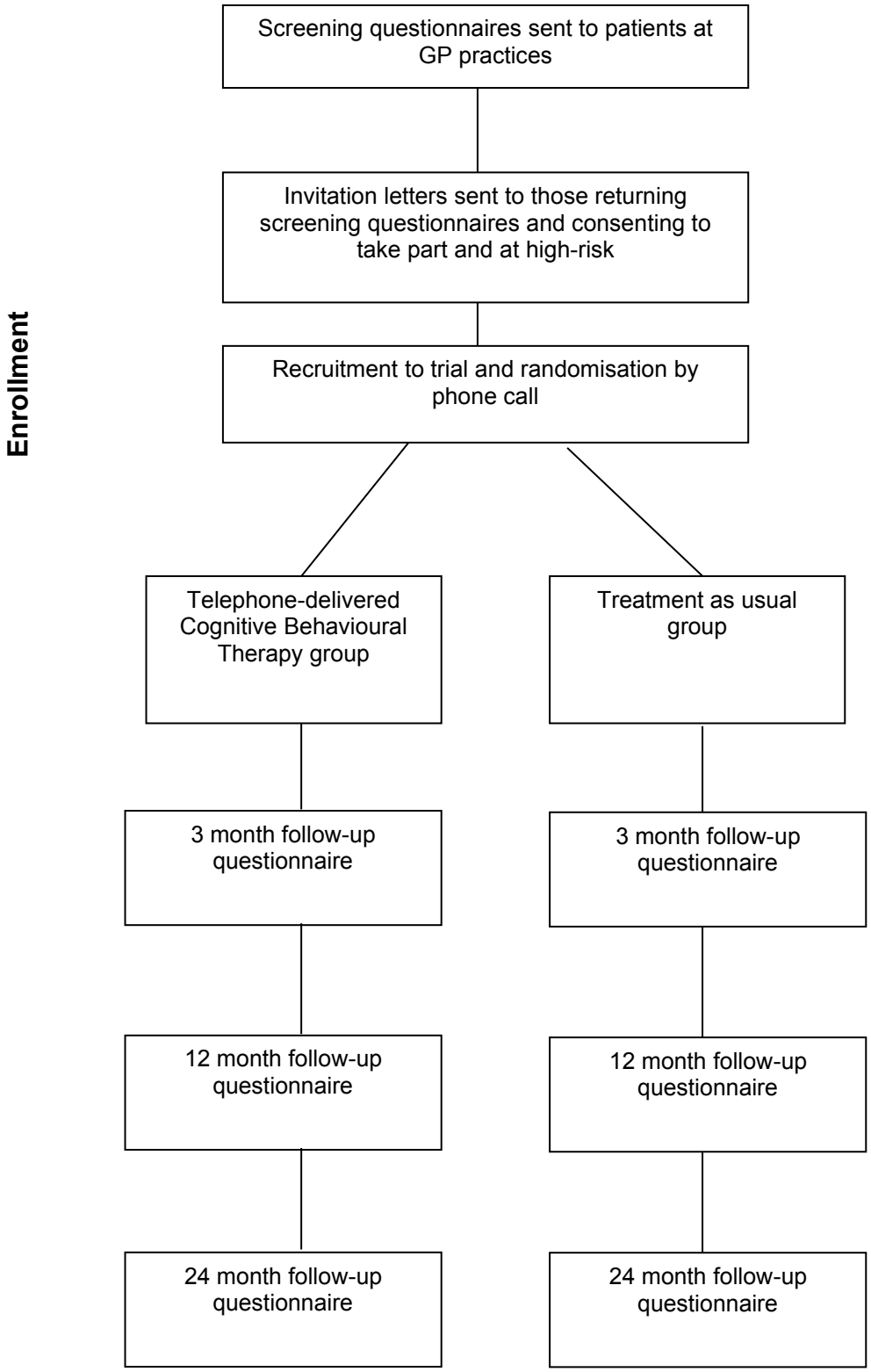
Intention to treat analysis will be of all participants who were randomised and for whom at least one follow-up observation of the primary outcome is available. Participants will be analysed in the group to which they were randomised.
Per protocol (PP) population

Pre protocol analysis will be of all participants of the ITT population excluding participants who were not compliant with their randomised study arm. Non-compliance is defined as those not having any primary outcome data and/or those not completing treatment as in the definition below.

Full intervention will consist of an initial assessment (45-60 minutes), 6 weekly sessions (each 30-45 minutes) over six weeks, and then booster sessions at 3 and 6 months. The per protocol analysis will be those receiving the completed treatment (defined below) vs. all others.

A participant in the CBT group has completed treatment if: there is mutual agreement between therapist and participant to stop treatment AND at least one session (the initial assessment) has been attended; OR, participant has at least 3 sessions of CBT (including the initial assessment)

2.2. FLOW DIAGRAM



2.3. EFFECTIVENESS OUTCOMES

2.3.1.PRIMARY OUTCOMES

The primary outcome measure is the proportion developing CWP at 12 months post intervention. The primary treatment comparison is the between arm difference in the proportions of people developing CWP from baseline to 12 months.

2.3.2.SECONDARY OUTCOMES

Comparisons with appropriate hypothesis tests will be used for the secondary outcomes, pain, illness behaviour, somatic symptom reporting, sleep problems, quality of life and wellbeing, psychological distress, patient global impression of change measure and fatigue.

2.3.3.CLINICAL & SELF REPORTED ENGAGEMENT

Counts of the sessions that were completed by the participant
Completion of treatment (by mutual agreement with therapist AND at least one session (the initial assessment) has been attended; OR, participant has at least 3 sessions of CBT (including the initial assessment))

2.4. ANALYSIS

2.4.1.GENERAL PRINCIPLES

For the equivalence study, the adjusted mixed model ITT analysis will be deemed the primary analysis with an adjusted mixed model per protocol analysis as a sensitivity analysis. For the superiority study, in accordance with CONSORT guidelines, all comparative analysis will be conducted on an ITT mixed model basis with a per protocol mixed model analysis performed as a sensitivity analysis. All analyses will be governed by this comprehensive SAP which will be agreed by the Trial Steering Committee (TSC) prior to any analyses being undertaken. There will be no formal interim analyses undertaken. Unless otherwise specified, a 5% two-sided significance level will be used to denote statistical significance. Adjustments will be made for multiple testing of secondary outcomes as discussed below.

2.4.2.DATA DESCRIPTION

Characteristics of the study participants in the two treatment arms will be described using simple summary statistics for each treatment group separately and for all participants together. Descriptive statistics will include mean and standard deviation for normally distributed continuous data, median and inter-quartile range for skewed continuous data and count and percentage for categorical data. No formal statistical comparisons will be made between baseline characteristics. Outcomes will be described at the three follow-up times: 3, 12 and 24 months, using appropriate summary statistics.

2.4.3.FLOW DIAGRAM

A CONSORT flow diagram will provide the detail of the flow of trial participants, withdrawals and post-randomisation exclusions.

2.4.4. ANALYSIS OF PRIMARY OUTCOME

Primary outcome study

The primary outcome is the between arm difference in the proportions of participants developing CWP from baseline to 12 months. This comparison will be made using simple chi-squared tests at each follow-up time. Appropriate adjustment will be made for the stratification factor used in the randomisation (the number of non-pain "high-risk" factors that a participant reports at baseline) using multiple logistic regression.

The model for outcome CWP (yes or no at 12 months) will be a multiple logistic regression. The key adjustments will be for the blocking factors, the number of high-risk factors present (2 or 3 of illness behaviour score>4, somatic symptom score>2 and sleep problem score>4) and GP practice.

Logit(p(CWP)) = constant + treatment effect + blocking effect + other covariate effects + random error.

The treatment effect will be a fixed effect. The blocking effect will comprise the number of high-risk factors present (fixed effect) and GP practice (random effect, n=16 practices).

The other covariates that will be considered in the model are: age and sex. The expectation is that these covariates will be balanced through randomisation, but they are both known to be related to the likelihood of the development of CWP. Multiple imputation (MI) analysis will be used to examine sensitivity to missing data.

After discussion at the TSC it was decided that it will not be possible to consider the therapist effect in a formal way between the two arms. Only one arm will be exposed to the therapists and even descriptive approach was disregarded as the number of participants was expected to vary widely between different therapists.

2.4.5. ANALYSIS OF SECONDARY OUTCOMES

Secondary outcomes

Comparisons with appropriate hypothesis tests will be used for the secondary outcomes, pain, illness behaviour, somatic symptom reporting, sleep problems, quality of life and wellbeing, psychological distress, patient global impression of change measure and fatigue. Appropriate adjustment will be made for the stratification factor. The baseline value of the relevant outcome variable will also be included as a covariate. Given the multiple secondary outcomes, the p-value used to denote statistical significance will reflect the multiple comparisons.

An appropriate adjustment will be made for the stratification factor as described above, the blocking effect will be addressed through including the number of high-risk factors present (fixed effect) and GP practice (random effect).

There are 8 secondary outcomes. The most conservative approach would be to use Bonferroni p=0.05/8=0.00625 or a family-wise error rate of alpha=0.0065 (so 1-(1-alpha) ^{8} = 0.05). A less conservative approach would be to take p=0.01 for significance of the secondary outcomes and this was agreed as appropriate at the TSC meeting of 9 September 2016.

The models will be generalised linear models (GLM) of the appropriate family depending on the outcome variable. Most will be ordinal logistic regression or linear regression with adjustments generally as described for the primary outcome. Multiple imputation (MI) analysis will be used to examine sensitivity to missing data.

2.4.6.TIMES OF EVALUATION

Follow-up questionnaires will be mailed to participants at 3, 12 and 24 months after the treatment start date (for participants in the active treatment group) or dummy treatment start date (for those in usual care). Instruments included in the follow-up questionnaires will be the same as in the screening survey questionnaire. Additionally, follow-up questionnaires will include the Patient Global Impression of Change (7-item scale from “very much worse” to “very much better”), and questions on health care usage. Mixed models analyses with an appropriate error structure will take into account the repeated assessment of the outcome data for the same patient across the three follow-up times.

Cut off for timed responses: the cut-off for counting person as responding to a follow-up request will be 3 weeks after first trying a telephone reminder.

Mixed models analyses with an appropriate error structure will take into account the repeated assessment of the outcome data for the same patient across the three follow-up times. Alternatives include mixed models and generalised estimating equations. Mixed models should be more generalizable to incorporate the three follow-up times and the fixed and random effects required to adjust for standardisation. Multilevel mixed-effects GLMs (meglm) in Stata will provide great flexibility in the modelling. Although there are only three time points and unequal time gaps, an AR1 structure will be appropriate. Robust errors may need to be considered.

2.4.7. MULTIPLE IMPUTATION METHODS

As part of sensitivity analyses, multiple imputation methods will be used, where appropriate, to address issues of missing data. However, these methods will not be applied if the use of imputation is contrary to specified rules for the relevant validated measurement scale.

Imputations of 100 repeat samples from the dataset will be used if processing speed allows. If not then at least 10-20 repeat samples will be used. MI routines within Stata will be employed using the relevant outcome variable and all risk factors that are candidates for inclusion in the relevant regression model (bearing in mind the restriction above).

2.4.8. ENGAGEMENT

The proportion of participants in the tCBT treatment arm who attended the initial assessment, 0 to 6 weekly sessions, and the booster sessions at 3 and 6 months will be tabulated. The proportion of participants completing treatment (there is mutual agreement between therapist and participant to stop treatment AND at least one session (the initial assessment) has been attended; OR, participant has at least 3 sessions of CBT (including the initial assessment)) will also be tabulated.

2.4.9. RESPONDER ANALYSIS

Within the treatment group, those participants in the treatment group who do not have the outcome chronic widespread pain (CWP) at 12 months will be compared with those in the treatment group who do have (CWP) in terms of other variables. The other variables will be the three risk variables: symptoms, illness behaviour and sleep problems; and in addition: age; gender; health board; distress from General Health Questionnaire; fatigue; QoL from EQ5D; QoL from ICECAP; completion of treatment; and length of time between randomisation and treatment start.

Simple comparisons between those within the tCBT treatment arm with CWP and without CWP will be made at each of the three time points. Binary and nominal categorical variables will be compared with chi-squared tests. Continuous and discrete variables will be compared with independent t-tests or Mann-Whitney tests as appropriate.

2.5. WITHDRAWALS

Participants will have the option to withdraw from the treatment or the study at any time. Those withdrawing from the treatment will continue to be sent follow-up questionnaires unless they specifically request not to receive them. Failure of any participant to complete a follow-up questionnaire at any particular time-point will not be counted as a withdrawal unless the participant requests not to receive any further follow-ups.

The number of participants withdrawing from the trial will be recorded within each randomised group. Details of reasons for withdrawal will be provided with the CONSORT diagram.

2.6. DATA STORAGE

Confidentiality: All evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access.

Data Protection: All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

Study Record Retention: All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

End of Study: The end of study is defined as data collection at 2 years from the last participant's date of beginning treatment or dummy treatment start date.

3. DUMMY TABLES

A consort diagram for the trial will be produced.

The following dummy tables are examples of what the final tables are expected to look like, but the actual final format may change.

Table 1: Number of patients in the Intention to treat (ITT) and per protocol (PP) populations, overall and by treatment group

Population	tCBT	Usual care	Overall
ITT	xx	xx	xx
PP	xx	xx	xx

Table 2: Number randomised by practice

Practice	Randomised
1	xx
2	xx
3	xx
…	…
14	xx
Total	xx

Table 3: Number of patients in the Intention to treat (ITT) population by study practice and treatment group

Practice	tCBT	Usual care	Overall
1	xx	xx	xx
2			
…	xx	xx	xx
14	xx	xx	xx
Total	xx	xx	xx

Table 4: Number of patients in the per protocol (PP) population by study practice and treatment group

Practice	tCBT	Usual care	Overall
1	xx	xx	xx
2			
…	xx	xx	xx
14	xx	xx	xx
Total	xx	xx	xx

Table 5: Measures of treatment engagement in the tCBT arm

	tCBT
Initial session n (%) No Yes Number of weekly sessions attended n (%) 0 1 2 3 4 5 6 Booster session at 3 months n (%) No Yes Booster session at 6 months n (%) No Yes	
Treatment completed n (%) No Yes	

Table 6: Baseline characteristics by treatment arm in the ITT population

	tCBT (n=)	Usual care (n=)	Overall (n=)
Gender n (%) Male Female Age (n) Mean (SD) Median (IQR) (min, max)	xx xx	xx xx	Xx xx
Pain self-report n (%)			
Illness behaviour Score > 4 n (%) Symptoms scale Score > 2 n (%) Sleep problems Score > 4 n (%)			
2 factors present n (%) 3 factors present n (%)			
GP practice n (%) Distress - General Health Questionnaire Median (IQR) QoL from EQ5D Median (IQR) QoL from ICECAP Median (IQR) Fatigue Median (IQR) Global impression of change measure Median (IQR)			

Table 7: Outcomes at the three time points 3 months, 12 months and 24 months by treatment arm in the ITT population

	tCBT (n=)	Usual care (n=)	Overall (n=)
CWP n (%)	xx	xx	xx
Presence of pain n (5)	xx	xx	xx
Illness behaviour Score Median (IQR)	xx	xx	xx
Somatic symptom reporting	xx	xx	xx
Sleep problems Score Median (IQR)	xx	xx	xx
Distress - General Health Questionnaire Median (IQR)	xx	xx	xx
QoL from EQ5D Median (IQR)	xx	xx	xx
QoL from ICECAP Median (IQR)	xx	xx	xx
Fatigue Median (IQR)	xx	xx	xx
Global impression of change measure Median (IQR)	xx	xx	xx

Note: Table repeated for outcomes at 12 months and 24 months by treatment arm

Table 8: Primary outcome 12 month unadjusted and adjusted analysis of presence of CWP in the tCBT and usual care arms on the ITT population

	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care						
Number of high-risk factors present: 3 vs 2						
Age						
Gender						
Random effect: GP practice						

Table 9: Primary outcome 12 month unadjusted and adjusted analysis of presence of CWP in the tCBT and usual care arms on the PP population (sensitivity analysis)

	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care						
Number of high-risk factors present: 3 vs 2						
Age						
Gender						
Random effect: GP practice						

Table 10: Primary outcome 12 month unadjusted and adjusted analysis of presence of CWP in the tCBT and usual care arms on the ITT population with multiple imputation (sensitivity analysis)

	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care						
Number of high-risk factors present: 3 vs 2						
Age						
Gender						
Random effect: GP practice						

Table 11: Primary outcome 3 and 24 month adjusted analysis of presence of CWP in the tCBT and usual care arms on the ITT population

	3 months			24 months		
	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care						
Number of high-risk factors present: 3 vs 2						
Age						
Gender						
Random effect: GP practice						

Table 12: Primary outcome 3 and 24 month adjusted analysis of presence of CWP in the tCBT and usual care arms on the PP population

	3 months			24 months		
	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care						
Number of high-risk factors present: 3 vs 2						
Age						
Gender						
Random effect: GP practice						

Note: This table will be repeated for 3 months and 24 months

Table 13: Secondary outcome adjusted analysis of presence of pain in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Note: As all patients have pain at baseline there is no adjustment for this as there is for other secondary outcomes

Table 14: Secondary outcome adjusted analysis of illness behaviour score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
Illness behaviour score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 15: Secondary outcome adjusted analysis of somatic symptom score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
Somatic symptom score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 16: Secondary outcome adjusted analysis of sleep problems score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
Sleep problems score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 17: Secondary outcome adjusted analysis of Distress - General Health Questionnaire score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
Distress - General Health Questionnaire score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 18: Secondary outcome adjusted analysis of QoL from EQ5D score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
QoL from EQ5D score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 19: Secondary outcome adjusted analysis of QoL from ICECAP score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
QoL from ICECAP score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 20: Secondary outcome adjusted analysis of Fatigue score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
Fatigue score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 21: Secondary outcome adjusted analysis of Global impression of change measure score in the tCBT and usual care arms on the ITT population

	3 Months			12 Months			24 Months		
	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care									
Global impression of change measure score at baseline									
Number of high-risk factors present: 3 vs 2									
Age									
Gender									
Random effect: GP practice									

Table 22: Primary outcome presence of CWP at 3, 12 and 24 months in multilevel model in the tCBT and usual care arms on the ITT population

	Multilevel at 3 time points		
	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care			
3 to 12 months			
12 to 24 months			
Number of high-risk factors present: 3 vs 2			
Age			
Gender			
Random effect: GP practice			

Table 23: Secondary outcome presence of pain at 3, 12 and 24 months in multilevel model in the tCBT and usual care arms on the ITT population

	Multilevel at 3 time points		
	Adjusted OR	95% CI	p-value
Treatment: tCBT vs Usual care			
3 to 12 months			
12 to 24 months			
Number of high-risk factors present: 3 vs 2			
Age			
Gender			
Random effect: GP practice			

Table 24: Secondary outcome illness behaviour score at 3, 12 and 24 months in multilevel model in the tCBT and usual care arms on the ITT population

	Multilevel at 3 time points		
	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care			
3 to 12 months			
12 to 24 months			
Illness behaviour score at baseline			
Number of high-risk factors present: 3 vs 2			
Age			
Gender			
Random effect: GP practice			

Table 25-Table 30 similar for somatic symptoms, sleep problems, distress - General Health Questionnaire score, QoL from EQ5D score, QoL from ICECAP score, fatigue

Table 31: Secondary outcome adjusted analysis of Global impression of change measure score at 3, 12 and 24 months in multilevel model in the tCBT and usual care arms on the ITT population

	Multilevel at 3 time points		
	Adjusted coefficient	95% CI	p-value
Treatment: tCBT vs Usual care			
3 to 12 months			
12 to 24 months			
Number of high-risk factors present: 3 vs 2			
Age			
Gender			
Random effect: GP practice			

Note: Global impression of change measure score may not need to be adjusted for baseline.

Table 32: Responder analysis (tCBT treatment group)

	CWP at 12 months (n=)	No CWP at 12 months (n=)	p-value
Presence of pain n (%) Illness behaviour Score Median (IQR) Somatic symptom reporting Sleep problems Score Median (IQR) Gender n (%) Male Female Age n Mean (SD) Median (IQR) Health board n (%) Distress - General Health Questionnaire Median (IQR) QoL from EQ5D Median (IQR) QoL from ICECAP Median (IQR) Fatigue Median (IQR) Global impression of change measure Median (IQR) Completion of treatment n (%) Length of time between randomisation and treatment start Median (IQR)			

Table 33: Patient withdrawals

Reasons for withdrawal	tCBT (n=)	Usual Care (n=)	Total (n=)
Number who withdrew from the study (%)			
Primary reason for withdrawal [1]			

[1] Denominator is the number of patients that withdrew from the study.

Table 34: Distribution of withdrawals by baseline characteristics

	Withdrawals (n=)	Non-withdrawals (n=)
Gender n (%) Male Female Age (n) Mean (SD) Median (IQR) (min, max)	xx xx	xx xx
Presence of pain n (%)		
Illness behaviour Score > 4 n (%) Symptoms scale Score > 2 n (%) Sleep problems Score > 4 n (%)		
2 factors present n (%) 3 factors present n (%)		
GP practice n (%) Distress - General Health Questionnaire Median (IQR) QoL from EQ5D Median (IQR) QoL from ICECAP Median (IQR) Fatigue Median (IQR) Global impression of change measure Median (IQR)		