Collaborative case management to aid return to work after long-term sickness absence (CAMEOS)

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List of Abbreviations

AE  Adverse Event
AR  Adverse Reaction
CA  Competent Authority
CI  Chief Investigator
CRF  Case Report Form
CCM  Collaborative Case Management
CTA  Clinical Trial Authorisation
CTPM  Clinical Trial Project Manager
DMC  Data Monitoring Committee
EC  European Commission
EU  European Union
FFWS  Fitness for Work Services
GCP-ICH  the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95)
ICF  Informed Consent Form
IDMC  Independent Data Monitoring Committee
ISF  Investigator Site File
ISRCTN  International Standard Randomised Controlled Trial Number
LFFW  Leicestershire Fit For Work
MAHSC-CTU  Manchester Academic Health Science Centre- Trials Coordination Unit
MURT  Manchester University Research Team
NIHR-PHR  National Institute for Health Research – Public Health Research
NHS R&D  National Health Service Research & Development
OH Assist  OH Assist
PHQ  Patient Health Questionnaire
PI  Principal Investigator
PIS  Participant Information Sheet
OM  Outcome measure
QA  Quality Assurance
QC  Quality Control
RCT  Randomised Control Trial
REC  Research Ethics Committee
SAR  Serious Adverse Reaction
SAE  Serious Adverse Event
SFHS  Short Form Health Survey
SDV  Source Document Verification
SOP  Standard Operating Procedure
TM  Trial Manager
TMG  Trial Management Group
TSC  Trial Steering Committee
USAR  Unexpected Serious Adverse Reaction
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Lay Summary

Common health disorders such as back pain, heart problems and depression cause hardship to people and to their families. Such disorders are also a frequent cause of sickness absence (time away from work off sick), which may result in financial hardship, and significant periods of sickness absence can lead to long term impacts on employment, health and quality of life. Although there is a variety of support for workers on long term sickness absence in many organisations through occupational health and employee assistance programmes, many of the interventions provided have limited evidence that they work.

This research seeks to develop a simple, low cost intervention which has the potential to be an effective and cost effective intervention among employees on long term sick absence, improving their well-being and encouraging return to work. Collaborative case management draws on current best practice in the management of a range of long-term conditions (such as depression and back pain) and has been proven effective in a number of randomised trials in a range of contexts and patient populations.

As collaborative case management in an occupational health context is a new and developing approach, we propose an initial 2 phase study:

In Phase 1 (development) we will work with stakeholders representing employees and employers to adapt the intervention to the UK context and to maximise acceptability and effectiveness.

In Phase 2 (internal pilot), we will assess intervention delivery and trial recruitment within an internal pilot randomized controlled trial. The collaborative case management intervention will be delivered in occupational health settings in a range of organisations. The intervention will be delivered by staff in existing employee assistance programs, who will be retrained to deliver the protocol with appropriate support and supervision.

As well as feasibility and acceptability outcomes, baseline and follow-up data will be collected through self-report questionnaires. The primary outcomes will be wellbeing and return to work.
**Background**

**Existing Research**

Despite relatively high levels of employment among working age adults in the UK, there are still a significant minority who are off work with ill health at any one time (so called ‘sickness absence’). Before the turn of the century, employees were taking an average of 7-8 days off in sickness absence,\(^1\),\(^2\) representing 175 million working days, although there is evidence that this is falling over time. The Confederation of British Industry suggests that although longer absences of greater than 4 weeks affect around 1% of employees and comprise only 6% of total absences, they contribute to nearly half the total days lost.

Common mental health problems (such as depression and anxiety) and musculoskeletal problems (such as back and joint pain) account for the bulk of sickness absence. Employees who suffer significant periods of sickness absence are at increased risk of longer-term problems, with profound implications for their long-term health, wealth and social inclusion.

It is estimated that the total costs of such absence to the taxpayer (including NHS costs, benefits and lost revenue) are at least £60 billion per annum.\(^2\) The recent report on ‘Working for a healthier tomorrow’ outlined the changes in attitudes to work and health that are required to manage these problems more effectively, and the organizational and service delivery challenges that such changes are likely to introduce.\(^2\) However, developments in this area are also hampered by the lack of a strong evidence base to inform policy and practice. Despite the clear case for robust intervention, evidence is lacking in this area, with a preponderance of less rigorous designs, and the use of interventions with a very broad focus (such as employee assistance programmes or counselling) with limited theoretical or evidential support.

**Current evidence on return to work interventions**

Work on the evidence for the effectiveness and cost-effectiveness of Employee Assistance Programmes (EAPs) commissioned by the British Occupational Health Research Foundation\(^3\) concluded that there is a lack of evidence about the effectiveness of EAPs. Despite the prevalence of EAPs, no studies were found that could demonstrate EAPs are more effective than no intervention on a range of outcomes including sickness absence.

A review of long-term sickness absence interventions conducted for NICE\(^4\) to support public health guidance in this area identified 45 effectiveness evaluations of interventions mainly targeting musculoskeletal interventions. The evidence base was heterogeneous and limited but identified three intervention strategies that...
merited further investigation: early intervention, multi-faceted approaches and interventions with a workplace component. Economic modelling based on this review found that any intervention which returns at least an additional 3% of employees to work and costs less than an additional £3000 per 2 employee, is likely to be considered economically attractive compared with usual care, relative to other interventions routinely funded by the NHS.  

A further review of the evidence for workplace involvement on return to work rates following long term sickness absence found that only a particular type of workplace involvement intervention was consistent in achieving positive return to work results. The evidence was limited to employees with back pain and found that active, structured consultation among employee, employer and occupational health practitioners, and agreements regarding subsequent, appropriate work modifications, appear to be more effective at helping employees on long-term sick leave to return to work than those interventions which lack such components. This type of intervention was also more cost effective than other workplace-linked interventions, including exercise. These findings are further confirmed in other reviews focusing on the characteristics of successful return to work interventions which highlight the importance of early intervention (i.e. in the first six weeks of absence) and the use of multi-faceted interventions (particularly those including a workplace consultation component).

A recent report on vocational rehabilitation suggested that a variety of responses were required to better manage different patterns of workplace absence and the needs of different groups. Simple, low cost workplace interventions might be sufficient for those with short term absence, with effective vocational rehabilitation programmes combining health and occupational assistance for those with longer-term absences. The delivery of a range of interventions of different intensity according to need echoes the adoption of ‘stepped care’ services in the NHS to manage some long-term conditions, including depression. The report also highlighted the need for systematic adoption of ‘basic principles’ related to the management of these problems, irrespective of whether they were work related or comparable health conditions. However, the significant challenges associated with effective implementation of such principles in routine practice were also highlighted.

**Current approaches to the management of long-term conditions**

The call for adoption of core ‘basic principles’ is in line with current thinking in chronic disease (or ‘long term condition’) management in healthcare. There has been significant development in our understanding of the nature of long-term conditions, and it is widely acknowledged that many long-term conditions raise common challenges for patients, and that the organisational and therapeutic interventions required involve common elements:
(a) individualised assessment of behaviour
(b) collaborative goal setting
(c) skills enhancement
(d) proactive follow up
(e) self-management support for healthy behaviour change
(f) access to resources

As noted previously, the bulk of long-term sickness absence relates to musculoskeletal problems and mental health, and both of these problems have proven themselves amenable to adoption of these ‘basic principles’. Depression and distress are a common feature of long term sickness absence. The application of the principles of chronic disease management in depression has been demonstrated through the literature on so called ‘collaborative care’ models.

Historically, conventional approaches to depression were oriented to the management of depression as an acute problem, where patients seek help when they deem it necessary, and professionals respond to those patients seeking help. However, depression is a disorder where motivation to seek and adhere to care is low, and services that only respond to patient presentations are unlikely to be optimal for managing depression in the community. The full range of interventions employed in collaborative care models varies, but generally includes education of primary care professionals (through short courses and provision of clinical guidelines), systematic screening to identify depression in the wider population, enhanced patient education and self-management support, and consultation between specialist and primary care provider. However, a critical component is case management. Case management involves specific professionals taking responsibility for the assessment, support and follow up of individual patients in a proactive fashion.

Collaborative care for depression has been the participant of a large number of randomised controlled trials, systematic reviews and meta-analyses. Most reviews agree that the model has shown robust evidence of improvements to patient outcomes. In a recent comprehensive Cochrane review of 79 randomised controlled trials (including over 24,000 patients), collaborative care showed improved outcomes in the short to medium term and some evidence of longer-term benefit. These benefits seem to be achieved in a variety of settings, but what is of equal importance is that the general collaborative care approach appears to be relevant for depression and patients with combinations of depression and other long-term conditions. Given that the problems faced by employees on long-term sickness absence are likely to involve a complex mix of physical and psychological symptoms, it suggests that the broad ‘collaborative care’ model could be highly relevant to this population.
Collaborative care in occupational health

Although chronic disease management models and collaborative care for depression developed in health settings, there is evidence of the relevance of these models in an occupational health context. Vlasveld and colleagues developed a version of collaborative care, including many of the conventional elements described above (6–12 sessions of problem-solving treatment, manual-guided self-help, and antidepressant management monitored by an occupational case manager and supported by a mental health specialist). The programme also included elements specific to the occupational health context, including workplace assessments and adjustments, with the case manager mediating between employee and employer. The study randomised 126 patients with depression between the collaborative care intervention and usual care, and reported a significant difference between 4 groups in the proportion of clients achieving 50% reduction in depression symptoms (50% in collaborative care and 28% in usual care group, odds ratio 2.5, 95% CI 1.04 to 6.1). However, there was less evidence of benefit in measures of return to work.

A second trial recruited 604 workers from diverse sectors of the US economy, and randomised them to a telephone led case management programme or usual care (which included encouragement to enter existing treatment programmes). Case management included brief interventions direct from the case manager for patients who refused to seek help elsewhere, including 8 sessions of CBT for those with persistent symptoms. The results showed improvements in depression associated with case management similar in magnitude to existing evidence on collaborative care (approximately one third of a standard deviation), and better rates of recovery (31% versus 21%) at 12 months. Patients in case management also reported 2 additional hours work per week (approximately 2 weeks of additional work over a 12 month period). The potential of collaborative care models in occupational health has been demonstrated, but the case is far from proven, and it is unclear whether these models will generalize to a UK occupational health context, or whether the benefits found in patients with diagnosed depression will generalize to a broader mix of problems reported by employees currently on long-term sickness absence. A definitive trial of the potential of these models in the setting of occupational health in the United Kingdom is thus indicated.

Research objectives

The trial consists of two phases:
1. **Phase 1 (Development Phase):** we adapt a collaborative case management intervention to the needs of UK employees in a range of occupations and organisations who are entering or experiencing long-term sick absence.

2. **Phase 2 (Internal Pilot Phase):** as well as feasibility and acceptability outcomes, baseline and follow-up data will be collected through self-report questionnaires. The primary outcomes will be wellbeing and return to work. During this phase we test the following:

   2.1. recruitment of employees on long-term sickness absence to a trial
   2.2. delivery of the intervention in an occupational health setting
   2.3. engagement and acceptability among employees on long-term sickness absence
   2.4. appropriateness of inclusion criteria and outcome measures
   2.5. evaluation of the rate of return to work in those receiving Collaborative Case Management intervention compared to those receiving Care as Usual.

**Methods**

**Design**

The proposed study is a two arm randomised controlled trial evaluating the feasibility and acceptability of a collaborative case management intervention for employees who have been on long-term sickness absence. The collaborative care intervention will be delivered by existing occupational health staff who provide services to the participating companies.

**Setting**

We will be working with two partner organisations. One of our partners (OH Assist) has links with several large commercial organisations with approximately 250,000 clients, and up to 2000 new referrals per month. To access SMEs (Small and Medium Enterprises- with 250 or less employees) our other partner organisation is Leicestershire Fit for Work. These partners can provide access to public and private sector employers.

An overview of the trial assessments and randomisation is shown in the following Table 1.0 and Flow Chart 1.0.
### Table 1.0: Schedule of Assessments

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<th>Procedures</th>
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**Randomisation**

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<td>X⁴</td>
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<td>T/F/work</td>
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<td>MURT</td>
<td>T/P</td>
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1. MURT: carried out by Manchester University Research Team.  2. MURT will randomise participants via MAHSC-CTU.  3. Exit interview is done on patients who withdrew from the study (n=6) and a subset of Case Managers.  4. Follow up interview done by Case Managers.  

Abbreviations: T = telephone  P = by post  F = face to face  LFFW = Leicestershire Fit For work
Flow Chart 1.0: Overview of the CAMEOS Trial

- **Patient Identification**
  - Patients identified by OH Assist, GP or Leicestershire Fit For Work organisations

- **Consent**
  - Verbal consent obtained by GP, OH Assist or Leicestershire Fit For Work (LFFW)
  - Information Pack + OM sent to Participants from GP, OH Assist and LFFW
  - Participant details sent to MURT and MURT contact participant to answer questions
  - Participant returns signed copy of the consent to MURT

- **Screening**
  - Signed consent form received by MURT
  - MURT screen participants and issue Screening ID
  - If eligible for the trial outcome measures are posted to the participant and further dates are arranged to conduct baseline assessment

- **Baseline Assessment**
  - MURT Research team conduct baseline Assessment during one 45 min session
  - Outcome measures 1-8 completed
  - Arrangements made for randomisation

- **Randomisation**
  - MURT contact MAHSC-CTU randomisation line
  - Trial ID and participant allocation to one of the Trial arms assigned by MAHSC-CTU
  - MURT send letters to inform participants about trial arm allocation
  - MURT notify OH Assist or LFFW about participant allocation to CCM.

- **Intervention**
  - OH Assist or LFFW deliver Intervention or Care as Usual
  - Care as Usual arm receives varied forms of care. Not monitored
  - Intervention arm receives one 60 minute participant centred assessment followed by 4-5 sessions (45 minutes) including one/two or combinations of all three forms of intervention: Sign Posting, Psychological intervention or Facilitation at Work

- **Follow up**
  - MURT contact Participants by phone at 12th week post intervention.
  - Interviews with Case Managers and a subsample of 20 Participants in the treatment arm (including up to 6 who were randomised but failed to engage with the intervention).

- **Data Analysis & End of Trial**
  - Qualitative Data analysis
  - Quantitative Data analysis
  - End of Trial Publication
Participants

Employees experiencing or entering long-term sick leave will be identified using routine recording systems in their employing organisations, or through referral to relevant employee assistance organisations (OH Assist/ Leicestershire Fit for Work). Long-term sickness absence is defined as those who have been off work for at least 4 weeks or who have been signed off for sick leave for at least 4 weeks and for up to 12 months.

We expect the study sample to contain employees with a range of patterns of sickness absence, and a complex mix of mental health and physical health problems, with high proportions suffering from symptoms of depression and anxiety, and musculoskeletal symptoms.

We will recruit those who report a minimum level of baseline distress, defined as a score of 11+ on the CORE-OM (measure of general health and well-being: Clinical Outcomes in Routine Evaluation Outcome Measure). We require a minimum level of distress on the CORE-OM to ensure that there is significant room for improvement in outcomes associated with collaborative case management intervention in the trial.

Inclusion Criteria

1. Adults aged 18-65 years
2. Adults who have been off work for at least 4 weeks or who have been signed off for sick leave for at least 4 weeks and for up to 12 months.
3. Minimum baseline distress level as determined by CORE-OM score of 11 or over.

Exclusion Criteria

Employees will be excluded if:

1. are currently attending formal psychotherapy either through NHS counselling services or private services
2. they require palliative care
3. are absent due to bereavement
4. they suffer from a severe and enduring mental disorder or if they are at risk of suicide and require immediate care from a crisis management team.
5. They are in advanced stage of pregnancy ( > 24 weeks pregnant)

Recruitment

Participant Information and Informed Consent

CAMEOS Protocol_v3
Date: 25 November 2014
We will obtain the participant’s consent to participate in the trial after a full explanation has been given of the intervention options, including the conventional and generally accepted methods of intervention for employees on long term sickness. We will give participants sufficient time after being given the trial Participant Information Sheet to consider and discuss with whoever they wish. Participants will be provided with a contact number of the research team at the University of Manchester should they wish to discuss any aspect of the trial. Following this, the research team will determine if the participant is fully informed of the trial in accordance with the RGFHS guidelines.

We will be working with two partner organisations: OH Assist and Leicestershire Fit For Work Service

**Participant identification**

**OH Assist:**

Initial identification of participants will be undertaken by occupational health and/or HR representatives working for OH Assist. Participants will be informed about the trial by post or telephone by their occupational health provider. If they are interested they will be asked for verbal consent for a member of the research team to contact them, with the view that this would be followed up by the written consent if they wish to take part. OHA would then send out an information pack (Participant Information Sheet, Consent to Contact form, Participant Consent form) and pass on the employees’ details to the research team who would answer any queries the person has and complete the screening and consent process.

**Fit For Work Service:**

Initial identification of participants will be undertaken by GPs in Leicester who have agreed to act as a recruitment site and who have worked with the FFWS in the past. The FFWS will contact GPs that they have worked with in the past or are currently working with, to tell them about the pilot study. If they agree to take part in recruiting patients, they will be asked to identify employees requiring sick notes and ask if they would be interested in information about the trial. If they assent they will be given an information pack containing: Recruitment Pack Cover, Participant Information Sheet, Consent to Contact Form and Participant Consent Form. The pack will also contain a cover sheet- which includes the Fit For Work Service contact details (as the local provider of the intervention and whom they may have had contact with in the past).
Participants from both centres will also be asked to indicate on the consent form if they would be willing to be considered to take part in an interview at the end of the study exploring their thoughts on, and experiences of, the intervention. If they are willing, they will be contacted closer to the time to check that they still would like to take part in an interview.

**Screening for eligibility**

Once employee details have been received by the MURT either by the return of the consent to contact form or by information passed on by the recruiting sites, with the employee’s verbal consent, they would then be contacted by a member of MURT. MURT will only receive details of potential participants if the participant consents to be contacted verbally first or the participant returns the consent to contact form by post.

If employees prefer to contact the FFWS directly they will be asked for verbal consent to pass their contact details to MURT. Information packs will be posted to the participant by FFWS for the patient to consider before making a decision. MURT would contact the potential participant and answer any queries the participant might have.

**Participant consent**

Once the employee details have been received and the trial Participant Consent Form has been signed by the participant and MURT, the screening process will commence and the participant will be assigned a unique identifier, non-repeatable (Screening Log ID). This screening ID consists of two letters identifying the centre (LFFW will use LF and OH Assist will use OH) followed by a three digit sequential number for example LF001. This ID will serve two purposes; first to prevent randomisation of participants without consent and second to track recruitment from each of the recruiting centres.

Actual and expected duration of long term sickness absence, the main reasons for the absence and the baseline distress level by completing the CORE-OM questionnaire will be recorded during the screening process.

If participant is eligible, has agreed to participate and meets the eligibility criteria they will be sent a copy of the signed consent form to keep and a copy will be kept in the Site file which is kept at Manchester University.

The right of the participant to refuse to participate in the trial without giving reasons will be respected. After the participant has entered the trial, in order to collect data necessary to inform our definitive trial, we will work closely with employing organisations and service providers to develop and maintain a database system to monitor the number of participants approached, and number of participants failed.
screening and those who refused to participate in order to quantify recruitment response rates.

**Baseline Assessments Outcome Measures**

Eligible consenting participants will be sent the questionnaires containing the outcome measures (see below). Participants will also be advised that they can complete these questionnaires by telephone with the MURT member if they prefer. If so a time and a date will be arranged to call the participant to conduct the baseline assessments. Some of the outcome measures (1-7) will be repeated approximately 3 months later when they have finished the intervention period. If participants drop out of the intervention before 3 months, they will be asked if they would still be willing to complete the measures and if they would be willing to give a reason or take part in a short interview about why they had withdrawn from the study. The following outcome measures are assessed by the MURT:

1. Clinical Outcomes in Routine Evaluation outcome measure (CORE-OM). The CORE-OM is a 34 item measure of psychological distress and comprises four dimensions: subjective wellbeing, symptoms, functioning, and risk.

2. 12 item Short Form Health Survey (SF12) (version 2) is a brief version of the well-known SF36. The scale uses 12 questions to measure functional health and wellbeing over the past 4 weeks.

3. Patient Health Questionnaire-9 (PHQ-9). This is a nine item scale recording core symptoms of depression.

4. Work and Social Adjustment Scale (WSAS) is a short, 5 item measure of impairment in functioning across 5 domains (work, home management, social leisure, private leisure, relationships).

5. Self-reported actual and effective working hours quantified by the World Health Organization Health and Work Performance Questionnaire.

6. Client health and social care utilisation from which demographic data will be collected.

7. EQ-5D-5L measure of health related quality of life will be included for cost effectiveness calculations. The 5 item scale covers mobility, self-care, usual activities, pain, anxiety and depression, each with five levels of severity and provides a utility value based on a population tariff.

8. Bayliss measure of multimorbidity will be used to assess the impact of physical symptoms and associated long-term conditions. The measure assesses the presence and impact of 22 common problems. This outcome measure will only be carried out at baseline assessment.
Ineligible and non-recruited participants

Standard conventional management will be offered to participants who are not eligible or failed screening and not recruited into the trial. Participants who withdraw from the trial will also be offered the standard Care as usual by the two organisations; OH Assist and Leicester Fit For Work.

Randomisation

We aim to recruit 100 participants over a 6 month period. Participants will be randomised by the research team via a central telephone based system provided by the MAHSC-CTU to avoid selection bias. The method of randomisation will be permuted block within strata with block sizes themselves varying randomly between pre-specified limits. There are two stratification factors: Partner organisation (OH Assist, Leicester Fit for Work) and baseline CORE-OM score (11 to 17.9, 18 to 23.9, 24 to 40).

Following the screening interview, when eligibility for trial entry has been confirmed, consent to participate in the trial has been obtained; the participants will be randomised. A member of MURT will contact MAHSC-CTU randomisation line as follows:

THE MAHSC-CTU TRIALS RANDOMISATION LINE

Mon – Fri 9am to 5pm
Tel: 0161 446 3311

The following information will be required by the MAHSC-CTU before randomising a participant:

- Password for the trial (password given during training)
- Name of the person randomising the participant
- Confirmation that the participant has passed all screening evaluations
- Participant’s initials
- Participant month and year of birth
- Participant’s Screening Log ID
- CORE-OM Score

Following randomisation, a confirmation email will be sent to the member of staff who randomised the patient and specified members of the team who had been
nominated to be informed of the randomisation. The e-mail provides a brief summary of the information provided, the trial ID and allocation to one of the two arms of the trial. The trial ID should be used in all correspondence and on all relevant trial documentation. Only MURT will be able to randomise participants. MURT will send a letter to each participant to inform them about the trial arm allocation they have been assigned to. At the same time MURT will notify the two centres about allocation of participants in the CCM group only.

**Interventions**

**Collaborative case management**- The intervention will involve core aspects of published ‘collaborative care’ models, including a 60 minute client-centred assessment, collaborative goal setting (to agree what support is needed), and choice of evidence based low intensity interventions (such as behavioural activation, problem solving, cognitive restructuring), as well as effective liaison and information sharing with key health care personnel such as general practitioners and other primary care providers (where appropriate, and with patient consent). These are elements core to all effective collaborative care interventions and the principles of effective chronic disease management. Employees will receive four to five, 45 minute sessions to assess progress and solve problems that may arise in achieving their goals. To maximise the ‘reach’ of the intervention, we expect that most sessions will be delivered by telephone, although we will explore the importance of face to face sessions in the intervention development phase. The intervention will also involve workplace interventions, where the case manager (with client agreement) mediates between employer and employee to identify barriers to return to work. Sharing of information and confidentiality will be crucial and we will ensure that there is agreement between employee and case manager about what information can be shared.

The Case Managers will remain free to give the best suitable forms of interventions as described above. However, if the Case Manager feels it would be in the best interest of the participant to use another form of intervention outside those mentioned in this protocol, they are free to do so provided the reason for doing so is recorded. If the other intervention clashes with any of the inclusion criteria, the participant will stop trial treatment but remain in the trial for follow-up and data analysis. Similarly, the participant will remain free to withdraw at any time from the trial intervention without giving reasons and without prejudicing his/her further intervention/assistance scheme.

**Care as usual**- The intervention will be assessed against ‘care as usual’ in the organisations where we are recruiting. There is likely to be significant variation in care as usual, depending on the type of organisation (large, SME-small and medium sized enterprises, public and private). Although such variation in the trial will reflect
usual practice, we will assess the care received by participants in this arm using a structured questionnaire developed in a previous trial of ‘collaborative care’ in an occupational context. We are unable to control interventions received outside of the occupational context through the NHS. We will collect detailed data on the nature of usual care for description and costing, and of other services accessed via traditional healthcare routes.

**Follow Up**

MURT will follow up all participants including those allocated to Care as Usual at week 12 and will be asked to complete the Client Satisfaction Questionnaire (CSQ8) which is an another outcome measure consisting of eight items scored using a four point Likert scale, in addition to outcome measures 1-7 (see page 16).

**Participant reimbursement**

The primary outcomes will be participant well-being as measured by the CORE outcome measure and return-to-work. If participants drop out of the intervention before 3 months, they will be asked if they would still be willing to complete the measures and if they would be willing to give a reason/take part in a short interview about why they had withdrawn from the study.

All participants will be sent a £20 gift voucher (such as a 'Love to Shop' voucher which can be used in a wide range of shops) to reimburse their time for completing the baseline outcome measures and a further £20 voucher if they complete the follow-up outcome measures. Completing these measures is a fairly lengthy process for which their time will be reimbursed. The vouchers are for this purpose and not an incentive for recruitment.

**Trial Data**

The relevant data will be recorded on the CAMEOS case report forms (CRFs) provided by the MAHSC-CTU. All entries on the CRF, including corrections, must be made by an authorised member of trial staff. The majority of screening and follow up data is collected by the research team directly on to the CRF and will therefore be treated as source data. Some aspects of the CRF are transcribed from source data elsewhere.

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Participant completed questionnaires will also be treated as source data. The research team will submit the CRFs and participant completed questionnaires to MAHSC-CTU, and retain a copy.

Data provided to the MAHSC-CTU will be checked for errors, inconsistencies and omissions. If missing or questionable data are identified, the MAHSC-CTU will request that the data be clarified. All aspects of data collection and handling throughout the life cycle of the trial will be described in trial specific documents. Upon completion of relevant data management processes prior to any final analysis the trial data will be passed to the trial statistician for analysis. All data handling and analysis will be conducted in line with GCP-ICH (the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) and Research Governance Framework for Health and Social Care (2005) guidelines and the Data Protection Act 1998.

**Quantitative Analysis**

To meet the aims and objectives of the proposed internal pilot, the main analyses will be descriptive, and will involve assessment of:

a) Total recruitment, including rates over time and response rates (i.e. the proportion of clients responding to invitations to participate).

b) Engagement with collaborative case management, including rates of attendance at initial and follow up sessions, and qualitative and quantitative data on acceptability and satisfaction with management.

c) Exploratory analyses of the effectiveness of the intervention, looking at return-to-work rates and comparing mean CORE-OM scores at 3 month follow up between intervention and control groups, controlling for relevant and predefined baseline covariates.

**Interviews**

A sub-sample of employees, employers and case managers will be interviewed after the intervention. Twenty (20) employees in the treatment arm, and who indicated on the trial consent form that they would be willing to take part in an interview, will be purposively sampled on length of absence, problem type and employment type. Interviews will be audio recorded with participant consent. The interviews (largely conducted by telephone) will explore experiences of the study (to assess issues of feasibility, and barriers to recruitment), of the intervention, and of possible barriers to acceptance and implementation. We will also try to conduct exit interviews with a
proportion of employees who are randomised but fail to engage with the intervention (maximum n=6), if we are able to secure interviews with this subsample.

**Qualitative analysis**

The interviews will be transcribed verbatim and analysed according to the Framework approach an applied, health services research model. Although essentially a deductive enterprise one of the main strengths of the framework approach is that it remains grounded in the data, making use of emergent as well as a priori analytic categories. In common with other qualitative methods, framework analysis is an iterative process that facilitates the development and refinement of concepts and categories based on the analyst's interpretation and reinterpretation of raw data. Framework analysis typically follows these stages: familiarisation, development of a thematic framework, indexing, and mapping and interpretation. Analysis will be conducted by researchers of different professional backgrounds so increasing trustworthiness of analysis.

We will also assess whether the eligibility criteria and outcome measures are appropriate. This assessment will be based on the rates of exclusion of employees, views of the providers concerning the appropriateness of employees for the collaborative case management intervention, and assessment of the responses to the scales (missing data, participant burden, ceiling and floor effects, and change over time).

**Safety Monitoring and Reporting**

**Definitions**

The definition of an adverse event (AE) within the context of the current trial is:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any relevant deterioration in the scores of the health and wellbeing outcome measures

A serious adverse event (SAE) as defined in general as an untoward event which:

- is fatal or life threatening
- requires or prolongs hospitalisation
- is significantly or permanently disabling or incapacitating
- may jeopardise participation in the trial and may require intervention to prevent one of the outcomes listed above.
The cause of AEs or SAEs in the context of the interventions provided in the current trial is divided into the following:

- AEs/SAEs caused by one part or combination of different elements of collaborative case management intervention
- AE/SAEs caused by inappropriate use of one or more elements of collaborative case management intervention
- AE/SAEs caused by the participant characteristics which may render the intervention harmful.

SAEs or AEs may be expected or unexpected. Unexpected AEs/SAEs are those types of events which are not listed in the protocol as expected occurrences. AEs or SAEs of interest are defined as those that result in sustained deterioration caused by the intervention.30

The following AEs or SAEs may be reported via one of the following routes:

**a) Adverse Events reported by the participant:**

1. Increase in symptoms or development of new symptoms associated with underlying conditions: Clinical features that influence safety such as increase in pain, anxiety and depression will be communicated to the GP. Monitoring will be done at intervals recommended by the Case Manager and discussed with the patient’s GP. Further monitoring will be done by the patient’s GP.

2. Behavioural or mental state deterioration associated with intention to self-harm and suicide: If a participant discloses thoughts of self-harm or suicide during Intervention, these will be explored in the session. Following the session, the findings will be discussed with the GP. Case Managers may refer the patient for urgent psychiatric assessment or referral centre for management of the current crisis.

3. In the case of problematic relationships between participants and case managers, such as increased dependency, emotional attachment or signs of hostility or aggression,

4. The centres will take appropriate steps (in house SOP) to manage the relationship between the participant and the Case Manager and will discuss with the CI if withdrawal from the trial is the most appropriate course of action. A record will be made of any such event.

5.

These events have to be assessed in conjunction with the causal relationship to Collaborative Case Management. Only trained site investigators at each
participating centre would report the adverse events and causality will be determined by the CI.

b) Adverse Events reported by other and affecting others:
Spouse or partner or Case Manager may report any of the above mentioned conditions. Adverse events will be treated with sensitivity and the Case Manager will discuss the most appropriate course of action with the CI in consultation with the participant’s clinician if available or GP.

Causality to the Case Management Intervention

The causality to intervention may be classified into the following categories as outlined in Table 2.0:

Table 2.0: Causality assignment to adverse events

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Description</th>
<th>Event Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>There is no evidence of any causal relationship</td>
<td>SAE</td>
</tr>
<tr>
<td>Unlikely</td>
<td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time frame after start of the trial intervention). There is another reasonable explanation for the event (e.g. the patient’s physical or mental condition, other concomitant treatment).</td>
<td>SAE</td>
</tr>
<tr>
<td>Possible</td>
<td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time frame after the start of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the patient’s physical or mental condition, other concomitant treatments).</td>
<td>SAR</td>
</tr>
<tr>
<td>Probable</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
<td>SAR</td>
</tr>
<tr>
<td>Definitely</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
<td>SAR</td>
</tr>
</tbody>
</table>

Regulatory Reporting Procedures

All reportable adverse events that occur between the date the intervention has started and the date of the completion of the study per individual participant (not the end of the trial), must be recorded in the participant notes at the University site.
Centre staff reporting an AE or SAE will pass the information to the MURT who will collect all relevant information and related AE data will be collected in the CRF.

AEs meeting the definition of a Serious Adverse Event (SAE) must also be reported to the MAHSC-CTU using the trial specific SAE Report Form within 24 hours of observing or learning about the event.

Expected AE/SAEs – not reportable

In this patient population on long term sickness due to variety of long term underlying conditions the following are expected and not reported:

- New medical problems as complication of existing conditions
- New medical problem not associated with the current conditions
- Deterioration of existing medical problems not related to intervention.

Expected AEs/SAEs – standard reporting

The following AEs and SAEs are not expected to have been caused by the trial intervention within the study population. They will be reported by MURT team between the date the intervention has started and the 24th week following the start of the intervention using standard CRFs.

- Death (SAE)
- Hospital admissions and re-admissions for any reason in relation to self harm, overdose, intention to harm self or others (SAE)
- Patients referred to acute psychiatric units or secure hospitals or specialised institutions due to reported deterioration in mental health state
- Treatment on an emergency outpatient basis.

The above mentioned states are not inherent consequence of the study intervention but cannot be entirely ruled out and therefore should be reported to MAHSC-CTU. In recognition of this, events fulfilling the definition of an adverse event except for those conditions mentioned in the section of “Expected AE/SAEs – not reported” will be reported to MAHSC-CTU.

Unexpected and related SAEs – expedited reporting

All related/unexpected SAEs occurring to the participant from the date intervention has started to the 24th week post start of the intervention must be recorded on the related/unexpected Serious Adverse Event Form and faxed to the MAHSC-CTU within 24 hours of the MURT becoming aware of the event. The original form should be retained at the University Site File.

All SAEs must be reported by faxing a completed SAE Report Form within 24 hours of becoming aware of the event to the CAMEOs Trial Manager by Fax: 0161 446 8148

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On receipt of the SAE Report Form, an acknowledgement of the SAE/ SAR will be sent to the relevant members MURT. This acknowledgement will include an SAE reference number which should be included on all future correspondence regarding the SAE.

The TM will then liaise with the CI and treatment group lead to evaluate the event for seriousness, causality and expectedness to determine whether or not the case qualifies for expedited reporting (i.e. as a USAR).

All related/unexpected SAEs will be reviewed by the Chief Investigator and for expedited reporting to the Sponsor and the REC by MAHSC-CTU on behalf of the Chief Investigator within 15 days. Events that are expected within the study population will not be subject to expedited reporting to the REC. They will however, be included in the annual safety report provided to the REC.

Any follow-up information should be faxed to MAHSC-CTU as soon as it is available and events will be followed up until the event has resolved or a final outcome has been reached.

In the event of differences in the opinion between the centre staff (from OH Assist or FFWS) and the CI giving rise to an event being classified as an SAE by the centre staff and as USAR by the MURT, the “worst-case” assessment is assumed i.e. it is classified as a USAR. Similarly, the information regarding the events provided by the centre staff to MURT regarding the seriousness / expectedness cannot be downgraded by the CI or MURT as the centre staff or patient’s local clinician for example participant’s GP is more familiar with the patient’s history, clinical condition than the CI. The CI may, however, upgrade the centre staff’s site assessment of causality after reviewing the data from relevant personnel’s in charge of the patient’s care.

Other Significant Safety Reporting

Pregnancy

If a trial participant becomes pregnant following recruitment, before intervention has started the state of the pregnancy must be recorded in the participants case notes and recorded on the CRF at baseline assessment. If the trial participant becomes pregnant during intervention the case managers will record the state of pregnancy in the participant’s case notes and complete the Pregnancy Notification Form and send it MURT. If the pregnancy is uneventful and not associated with maternal and /or
foetal complications, the trial participant can continue to remain in the trial at the discretion of the CI. In case of pregnancy associated complications and in those whose pregnancy has progressed to such a stage (e.g. >24 week) at the time of recruitment, intervention in the trial is deemed not practical due to the impending maternity leave; the participant will be either excluded or withdrawn from the trial at the discretion of the CI and by agreement with the participant. The pregnancy must be noted on the CRF as a cause for withdrawal from the study. We believe the risks associated with intervention in this trial are minimal and not expected to impact on maternal or foetal well being and therefore the pregnancy will not be followed up beyond the end of the follow up period as defined in this protocol to be the end of 24th week post start of the intervention.

**New Safety Findings**

If a new safety finding emerges from sources data analysis, the CI reviews the finding for its impact on the participants in the trial. If there is a potential impact on trial participant’s safety, the sponsor takes appropriate action in conjunction with the TM, CI and MURT. Appropriate reporting mechanisms are followed in the event of actions being taken.

**Annual Safety Reporting**

Annual Safety Report is submitted annually to REC in accordance with NREC requirements. These periodic reports will be circulated to the Sponsor.

All SAEs/SARs/USARs must be followed-up until resolution and the research team must provide follow-up SAE/USAR Reports if the SAE/USAR had not resolved at the time the initial report was submitted

**Trial Management and Monitoring**

**Trial Management**

There will be 3 committees set up:
The Trial Management Group (TMG) will include all applicants, the Research Associate, and CTU representatives. Face to face meetings for the TMG will be organised at the beginning of the project (to finalise intervention and trial protocol design) and at the end of the project (for interpretation of the results and planning of further applications, if indicated). The TMG will also have bi-monthly teleconference during the study to update on progress and troubleshoot issues that arise. Minutes will be taken at TMG meetings and copies of the minutes will be filed in the Trial CAMEOS Protocol_v3
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Master File. The trial manager and CI will ensure that all relevant issues and actions discussed during the meeting are followed up and resolved. Details of significant issues will be made available to participating sites and other relevant parties as appropriate.

We will set up two subgroups.

A. The first (Intervention) will have a Chair who will be responsible for development and delivery of the training, and assessment of fidelity to the model during Phase 2.

B. The second subgroup (Recruitment) will be chaired by the CI and will be responsible for development of recruitment materials, liaison with representatives from the organisations involved in the study, and recruitment and retention of participants.

• Annually, the TMG will be extended to invite an independent chair plus two additional independent members, a user representative and conducted as a Trial Steering Committee (TSC) meeting. This meeting would be used to assess the scientific integrity of the trial and to discuss any safety issues. If there are any reasons why independent advice is required at another time apart from the scheduled TSC meetings (e.g. safety issues, extensive amendments) then the independent members would be contacted and an interim TSC arranged.

• TSC meetings will be setup and the primary role of the Trial Steering Committee (TSC) is to monitor and supervise the progress of the trial towards its interim and overall objectives with the help of the Trial Management Group. This includes signing off the protocols for the trial and intervention, to receive reports on recruitment during Phase 2, and to make recommendations to the NIHR PHR about a definitive trial, after receiving reports from the TMG. TSC is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring overall conduct of the trial. The TSC will usually meet once ethics approval has been given and before the trial begins recruitment. Once the trial has started the TSC should meet at least annually to monitor the progress of the trial. Meetings of the TSC may be called more frequently if the Chairman or the CI thinks it is necessary.

• Minutes will be taken at TSC meetings and copies of the minutes will be filed in the Trial Master File. The CTPM and CI will ensure that all relevant issues and actions discussed during the meeting are followed up and resolved and details of significant issues will be made available to participating sites.
Minutes of all TSC meetings will be made available to relevant parties as appropriate.

- We will set up a separate Advisory Group, which will include client, employer and employee representatives, meeting twice during the study. At the first meeting (end of Phase 1), they will provide the Intervention subgroup with feedback on issues relating to the intervention, including ethics and confidentiality. At the end of Phase 2, they will also receive reports on recruitment and retention, acceptability of outcomes measures and the results of the qualitative data on the experience of participants. After their second meeting, they will be able to advise the TSC about issues which may be relevant to the TSC recommendations to the NIHR PHR Board.

**Trial Monitoring**

On-site monitoring will be based on a risk-based strategy and a thorough risk assessment will be completed by the MAHSC-CTU as part of the site set-up process to ascertain the frequency and intensity of monitoring visits required (although additional monitoring may be conducted if necessary). This risk assessment and associated monitoring plan will be stored at the MAHSC-CTU.

The purpose of these visits are:

- to verify that the rights and well-being of participants are protected
- to verify accuracy, completion and validity of reported trial data from the source documents
- to evaluate the conduct of the trial within the institution with regard to compliance with the currently approved protocol and with the applicable regulatory requirements

**Ethical and Regulatory Requirements**

The trial will be conducted in accordance with the principles of Research Governance Framework for Health and Social Care 2005 (updated 2010). The sponsor, CI and MAHSC-CTU will ensure that the trial protocol, Participant Information Sheet, Consent Form, GP letter and submitted supporting documents have been approved by the research ethics committee(s) prior to any participant recruitment. Any agreed substantial amendments will also be submitted for ethical approval prior to implementation. The study is being conducted under the well recognised ethical framework of Research Governance Framework.

The Chief Investigator will ensure local approvals have been secured at each of the collaborating centres. The sponsor and MAHSC-CTU will verify this, plus the presence of all other essential documentation (and potentially an initiation meeting)
before giving the site the “green light” to open the trial to recruitment. The CI is also responsible for ensuring that any subsequent amendments gain the necessary approvals.

**Sponsorship and Indemnity**

*Sponsor*

The University of Manchester will act as the sponsor for this trial. Delegated responsibilities will be assigned to the MAHSC-CTU in collaboration with the research team at the University of Manchester to manage the trial on behalf of the Sponsor and to the main two sites; OH Assist and FFW which are involved in recruiting participants to the trial and delivery of the study related intervention.

*Indemnity*

The two collaborative Centres will be liable for negligence and other negligent harm to participants taking part in the study and covered by the duty of care owed to them by the sites concerned. For participating sites that are part of the NHS, the NHS indemnity scheme will also apply. The University of Manchester indemnity will apply to any research related activity within the definition of the current trial at the University site and the two centres: OH Assist and LFFW.

The sites delivering the trial intervention have accepted limited liability related to the method and delivery of the trial intervention in accordance with the RGFHS and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the methodology and delivery of the case management intervention used as the trial treatment, but not where there is any modification to the prescribed case management intervention.

**Participant Confidentiality and Data Protection**

Participants will be assigned a unique trial ID via the MAHSC-CTU trials line which will be used throughout their participation in the trial (plus patient initials will be included on the CRF as an extra check). Any personal data recorded will be regarded as confidential, and any information which would allow individual participants to be identified will not be released into the public domain.

Each research team should keep a separate Trial ID and screening log of all participants consented and their screen status. The investigator must maintain this screening log and all other trial documents (including participant’s written consent forms) which are to be held at the participating centres, in strictest confidence. The investigator must ensure the participants’ confidentiality is maintained.
The MAHSC-CTU will maintain the confidentiality of all participants and will not reproduce or disclose any information by which participants could be identified. The Investigator and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial.

Representatives of the MAHSC-CTU and the regulatory authorities may require to have access to participant’s notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times. All Investigators and trial site staff involved with the trial must 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.

Participant notes and trial files at site must be kept in a secure storage area with limited access. 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 patients.

**Direct Access to Data**

By participating in the CAMEOS trial, the research team at each centre are confirming agreement with his/her local health/ social care authorities to ensure that:

- Sufficient data are recorded for all participating patients to enable accurate linkage between the participant Case identifier and CRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- Trial-related monitoring, audits, IRB/IEC review, are permitted and direct access to source data/documents is provided as required

**Trial Conduct**

**Protocol Amendments and Deviations**

Any changes in the research activity will be reviewed and approved by the Chief Investigator and submitted in writing to the Sponsor, the participating centre management team and appropriate REC for approval prior to enrolment into an amended protocol.

The regulations and guidance state that no deviation must be made from an approved trial protocol, unless it is an urgent safety measure taken to protect a
participant from immediate harm. The MURT are encouraged to contact the MAHSC-CTU if a potential protocol deviation has occurred (or if an event has occurred and it is unclear whether it should be classified as deviation and the MAHSC-CTU will advise the research team what information and actions are required.

**End of Trial**

The study end date is deemed to be the date of the last data capture. The CI and/or TSC have the right at any time to terminate the trial for clinical or administrative reasons.

The CI, MAHSC-CTU and sponsor will ensure that the ethics committee are notified that the trial has finished (either as expected or prematurely) within required timeframes with summary reports to be provided as required.

The end of the trial will be reported to the REC within the required timeframe if the trial is terminated prematurely. Investigators will inform participants of any premature termination of the trial and ensure that the appropriate follow up is arranged for all involved.

Following the end of the trial a summary report of the trial will be provided to the REC within one year from the end of the trial and a copy sent to the Sponsor: University of Manchester.

**Peer Review**
This protocol has been independently peer reviewed by NIHR Public Health Research Programme and MAHSC-CTU senior managers

**Publication Policy**

The main trial results will be published in the name of the trial in peer-reviewed journals, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the Trial Management Group, and high accruing academics and clinicians. All participating centres and investigators will be acknowledged in this publication together with staff from the MAHSC-CTU. All presentations and publications relating to the trial must be authorised by the TMG, on whose behalf publications should usually be made. Authorship of any secondary publications will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the CAMEOS trial without prior permission from the TMG and the Sponsor.

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**Trial Record Retention and Archiving**

Essential documents will be maintained at the MAHSC-CTU and at the University of Manchester site in a way that will facilitate the management of the trial, audit and inspection. Confidential information about the trial participants will be retained for a sufficient period (at least 10 years) for possible audit. Documents should be securely stored and access restricted to authorised personnel. Archiving instructions will be provided by the Sponsor in accordance with relevant SOPs.
References


