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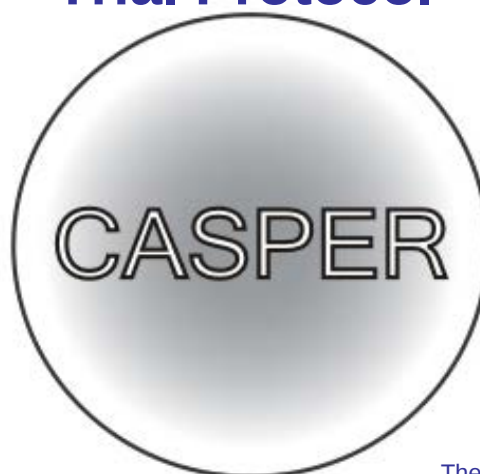
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Collaborative Care in Screen-Positive Elders – The CASPER Trial



Trial Protocol



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Summary

Depression accounts for the greatest burden of disease among all mental health problems, and is expected to become the second-highest amongst all general health problems by 2020. Efforts to ameliorate the burden of illness and personal suffering associated with depression in the elderly have focussed on those with more severe depressive syndromes. Less attention has been paid to those with mild disorders/sub-threshold depressive syndromes but these patients also suffer impairments in their quality of life and level of functioning. There is currently no clear evidence-based guidance regarding treatment for this patient group. The vast majority of depression in the elderly is managed entirely in primary care, without recourse to specialist mental health services[1, 2]. A range of individual treatments have been shown to be effective in the management of clinical depression in the elderly, including anti-depressants and psychosocial interventions. However, a repeated observation amongst those with depression has been the failure to integrate these effective elements of care into routine primary care services.

The current study brings together 3 established elements (screening for depression, collaborative care and low intensity psychological intervention) to see whether collaborative care reduces depression symptom severity in older adults in a cost-effective manner compared with older adults who are managed by usual GP care. This intervention does not involve the use of anti-depressants which are generally not effective in this group.

The study will randomly allocate 540 participants to receive either usual GP care alone or collaborative care plus usual GP care. We will assess depressive symptoms using the PHQ-9. We will recruit participants via their GP practice in 3 centres (York, Leeds and Hull). We will follow-up participants for 12 months.

Collaborative care and low intensity psychological intervention is currently not routinely offered, therefore it is unclear how acceptable this form of treatment is. The study will examine this issue and how it should be delivered, by discussions with participants and those delivering collaborative care.

1.0 Study Identifiers

1.1 Full title of trial

Collaborative care and active surveillance for screen-positive elders with sub-clinical depression: a pilot study and definitive and randomised evaluation.

1.2 Acronym

'CASPER' – **Coll**aborative Care in **S**creen-**P**ositive **E**lde**R**s

1.3 ISRCTN

ISRCTN02202951

1.4 HTA Reference

08-19-04

2.0 Study Background

2.1 Problem to be addressed

Depression accounts for the greatest burden of disease amongst all mental health problems, and is expected to become the second-highest amongst all general health problems by 2020[3]. Projected demographic changes mean that population strategies to tackle depression will increasingly have to address the specific needs of the elderly[2]. Amongst older people, depressive syndromes often affect people with chronic medical illnesses[4], cognitive impairment, social isolation or disability. Beyond personal suffering and family disruption, depression worsens the outcomes of many medical disorders and promotes disability[5]. Recently published National Institute for Health and Clinical Excellence (NICE) guidelines have acknowledged the symbiosis of physical health problems and depression[6, 7]. The impairments in quality of life associated with depression are comparable to those of major physical illness[8].

Amongst the elderly, a clinical diagnosis of major depression is the strongest predictor for impaired quality of life (QoL)[8]. The focus has been on identifying and treating those with more severe depressive syndromes as set down in classificatory systems such as DSM IV[9] major depressive disorder

or ICD 10[10] moderate/severe depressive disorder[2]. UK policies under the Quality and Outcomes Framework (QOF) advocate screening for these threshold-level disorders amongst those with chronic physical health problems such as heart disease and diabetes[11]. Once detected, evidence-supported guidelines advocate the prescription of anti-depressant drugs and appropriate provision of psychological care[1, 6, 7].

Less attention has been paid to those with mild disorders/sub-threshold depressive syndromes or those who give positive responses to screening questions but do not have sufficient levels of depressive symptoms to meet diagnostic criteria[1]. A recent large cross-sectional study conducted over 20 countries[8] showed that even relatively minor levels of depression are associated with a significant decrement in all QOL domains and with a pattern of negative attitudes toward ageing. Sub-threshold depression is also a clear risk factor for progression and the development of more severe depressive syndromes[12]. The focus of the current study will be in a population of screen-positive sub-threshold older adults.

2.2 The need for a trial

Primary care services have increased their focus on screening for depression in the elderly. This screening programme has enabled primary care providers to identify and treat those with severe depressive syndromes. However, the screening programme also identifies those with sub-threshold depression. There is currently no clear evidence-based guidance regarding treatment for this patient group. NICE[6, 7] have recently developed guidelines for patients with physical health problems and have acknowledged that patients with sub-threshold depression need to be provided for but evidence of what works is needed. The rationale for screening for depression in the elderly is clear, since a substantial portion of those with depression go unrecognised and untreated[1].

2.2.1 A new method for providing care

The vast majority of depression in the elderly is managed entirely in primary care, without recourse to specialist mental health services[1, 2]. A range of

individual treatments has been shown to be effective in the management of clinical depression in the elderly, including anti-depressants and psychosocial interventions[1]. However, a repeated observation amongst those with depression has been the failure to integrate these effective elements of care into routine primary care services[13]. Additionally, the implementation of any form of care will require a strategy which is both low intensity and offered within primary care[14].

A new model of care has been introduced called Collaborative Care[15]. Collaborative care borrows much from chronic disease management and ensures the delivery of effective forms of treatment (such as pharmacotherapy and/or brief psychological therapy) and involves augmenting the role of non-medical specialists in primary care. The ubiquity of depression in primary care settings and the poor integration and co-ordination of care have led to the development and use of this model of care.

In a recent review of 36 trials (12,000 participants), collaborative care was shown to be effective in the short and medium term in alleviating depressive symptoms and improving quality of life[16]. Moreover, there is evidence to suggest that collaborative care can be cost effective by reducing healthcare utilisation and improving overall quality of life[17].

The United States IMPACT study, by Unützer and colleagues[18], of collaborative care in older adults (those aged over 60) found at 12 months almost half the participants in the intervention group were at least 50% improved from baseline, compared with only one in five of those receiving usual care. The only UK trial of collaborative care in elderly participants showed some positive results, but focussed on more severe depression - meeting a diagnostic threshold[19]. A smaller US trial has used a collaborative care model in low severity depression (DSM-IV minor depression and dysthymia), and has shown good clinical improvements at 12 months (OR 5.21; 95%CI 2.01-13.49)[20].

In addition to the provision of collaborative care low intensity psychological interventions, such as Behavioural Activation (BA) may benefit individuals experiencing depressive symptoms. BA focuses on the behavioural deficits common amongst those with depression and reintroduces positive reinforcement and reduces avoidance. Such interventions manipulate the behavioural consequence of a trigger (environmental or cognitive) rather than directly interpret or restructure cognitions[21]. BA is about helping patients to '*act their way out*' of depression rather than wait until they are ready to '*think their way out*'. The effectiveness of this psychological approach is now well demonstrated[22]. BA can be readily delivered either over the phone by a trained case manager or face to face for those who experience difficulty using or accessing phone-based therapy[23]

2.2.2 Limitations of previous trials

The major limitations of previous trials are two-fold. First, previous trials have generally included those with above threshold-level depression and have not looked exclusively at sub-threshold depression. Second, a key component of collaborative care is 'medication management' (encouragement of compliance and guideline-concordant prescription of anti-depressants) but anti-depressants are not indicated in those with screen-positive sub-threshold depression[1, 6, 7].

2.2.3 Identifying depressive symptoms and validating measures of depression

Two depression tools have been in regular use in primary care: the Whooley Questions[24], a brief 2 item depression questionnaire which has been used as a screening tool (the Whooley questions are detailed in Figure 1); and the Patient Health Questionnaire 9 (PHQ-9)[25] to measure depression severity once treatment is initiated. Both these tools have been adopted to fulfil QOF objectives (QOF DEP 1 and QOF DEP 2 respectively)[26].

Question 1: 'Over the past month, have you been bothered by feeling down, depressed or hopeless?'

Question 2: 'Over the past month, have you been bothered by having little interest or pleasure in doing things?'

Figure 1: Whooley questions

have been validated, it has been against above-threshold depression and in non-elderly/non-UK primary care groups[27] or non-primary care populations[24]. Secondly, little is known about the ability of these instruments to identify less severe or sub-threshold levels of depression. Additionally, little is known about the significance of those who respond with positive answers to screening questions but do not have levels of depression that meet diagnostic criteria. It is likely that these individuals with sub-threshold depression have decrements in their quality of life[8] and are at an increased risk of developing more severe depressive disorders in the future (necessitating pharmacological or high-intensity psychological intervention)[12]. Little is offered for this population in the UK, and this problem will increase with the uptake of greater levels of screening as a population-level strategy to combat depression.

2.3 Research objectives

Screening for depression, collaborative care and low intensity psychological intervention represents a complex intervention. There is currently insufficient evidence and experience in identifying sub-threshold depression in older adults and the intervention would need to be refined for this particular patient group, therefore there will be two sets of objectives. The first set of objectives (1-3) will be set against a pilot trial. Upon successful achievement of the first three objectives, we will seamlessly progress into a 'definitive RCT' (objectives 4 & 5).

Pilot Study

1. To develop a low intensity collaborative care intervention based upon evidence-supported models of care for elderly people with screen-positive sub-threshold depression.
2. To establish the acceptability and uptake of this service by elderly people with screen-positive sub-threshold depression in primary and residential care settings.
3. To test the feasibility of conducting a successful trial of low intensity collaborative care intervention for elderly people with screen-positive sub-threshold depression.
4. Validating the Whooley questions in a UK elderly population

Main Study

5. To establish the clinical effectiveness of low intensity collaborative care intervention for elderly people with screen-positive sub-threshold depression.
6. To examine the cost effectiveness of a low intensity collaborative care intervention for elderly people with screen-positive sub-threshold depression across a range of health and social care costs.

3.0 Study Design

3.1 Trial outline

The CASPER study has been designed to assemble an epidemiological cohort of people over 65 years of age (the CASPER cohort), from which we will identify those eligible to participate in a trial of collaborative care for sub-threshold depression (the CASPER trial). Participants for the CASPER study will be identified via GP practices. All patients who have been identified by the GP practice as eligible for an invitation mailing will be sent an invitation pack (letter of invitation, Participant Information Sheet, consent form, decline form, background information form). Patients wishing to take part in the CASPER study will be asked to return completed consent and background information forms by post to the study centre. All consenting participants will then be asked to complete a baseline questionnaire. All participants who return valid baseline data will be included in the CASPER cohort (see 3.11). Inclusion in the CASPER trial is dependent on participants meeting the inclusion criteria and currently experiencing sub-threshold depression. This protocol describes the method for identifying and recruiting all participants for both parts of the CASPER study (the epidemiological cohort study and the trial) and, specifically, the methods employed for the CASPER trial. The key phases of the trial are shown in Appendix 1.

The trial has been designed as a multi-centre, unblinded, pragmatic randomised controlled trial lasting 45 months, comprising a 6 month 'pre-trial' period for refining the intervention, 12 month pilot trial period, 12 month

definitive trial period, 12 month follow-up period and a final 3 month analysis period.

CASPER involves screening for depression, collaborative care and a low intensity psychological intervention and therefore represents a complex health intervention. The study will adopt the stepwise MRC complex interventions framework[28, 29] to design and evaluate the effectiveness of collaborative care in screen-positive elders with sub-threshold depression. The primary research design will be a fully randomised pilot trial (**phase II**) and definitive (**phase III**) trial, informed by essential developmental work (**phase I**) (see Appendix 2).

All participants in the CASPER study will be followed up at 4 and 12 months with follow-up questionnaires; additionally primary care sources will be checked for depression prescribing. The primary outcome measure will be self-reported depression severity; a number of QoL measures will be used as secondary outcome measures. An economic analysis will be carried out to assess cost-effectiveness.

A qualitative evaluation will be carried out to examine the acceptability of collaborative care and BA for those over 65 and to ascertain the views of various stakeholders in order to assess the feasibility of delivering collaborative care and BA in the NHS.

3.1.1 Identifying sub-threshold participants

As mentioned previously (see 2.2.3), the Whooley[24] has not been validated in the UK elderly population. One of the aims during the pilot study is to validate the Whooley. During the pilot study, upon receipt of a valid baseline questionnaire all participants will be contacted by telephone to arrange a diagnostic interview; all diagnostic interviews will be carried out over the phone, by a trained researcher. The major depressive episode module of the Mini International Neuropsychiatric Interview (M.I.N.I.) will be used to ascertain the presence or absence of depressive symptoms and depressive disorders (sub-threshold depression and major depressive disorder) [30]. All

participants diagnosed with sub-threshold depression will be randomised to either the intervention or control arm (see Table 1 for the criteria used to ascertain either sub threshold or above threshold depression). Participants diagnosed as either below- or above-threshold will not be randomised; participants will be advised of the outcome of their diagnostic interview and will be encouraged to remain in the study as part of the CASPER cohort and will be encouraged to return follow-up questionnaires. Participants diagnosed as experiencing a ‘major depressive episode’ on the M.I.N.I. will be referred to their general practitioner.

Table 1: Diagnostic criteria for depression based on DSM-IV[30-32]

Based on the 9-item depression module from the MINI participants are classified in the following way:
• Major depressive episode: 5 or more symptoms, including one of the key symptoms • Sub-threshold depressive symptoms: 2-4 symptoms, may or may not include a key symptom • Non-depressed: 0-1 symptoms
Symptoms: 1. Depressed mood* 2. Loss of interest* 3. Significant weight loss or gain or decrease or increase in appetite 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive or inappropriate guilt 8. Diminished ability to think or concentrate, or indecisiveness 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan *key symptom

3.1.2 Phase I – Refinement of collaborative care/behavioural activation

The delivery of collaborative care and BA in working-age adults has been established and the necessary training package and manual already exists[23]. However, these have not been tailored for the use of case managers with older adults diagnosed with sub-threshold depression. During the refinement phase necessary changes will be made to the training package

and manual to account for differences that may exist in the older adult population.

3.1.3 Phase II – Pilot trial

The purpose of the pilot trial will be to:

1. Establish the feasibility of recruitment of people with sub-threshold depression
2. Test the delivery of collaborative care within the context of a trial
3. Test our ability to achieve follow up
4. Obtain preliminary estimates of the effect size of collaborative care
5. Validate Whooley questions as a screening tool

A total of 100 participants aged over 75 who have been diagnosed with sub-threshold depression will be included in the pilot trial. Participants will be randomised into one of two groups: (1) Collaborative Care with Behavioural Activation plus Usual GP care intervention, or (2) Usual GP care. Participants will be randomised by the York Trials Unit Randomisation Service.

Participants randomised to the collaborative care intervention group will be initially contacted by a case manager to arrange their first session of collaborative care with BA. Future sessions may be carried out either face to face or over the phone for a period of 8–10 weeks. Participants in the control group will receive “usual care” under their GP. We will not interfere with usual GP care in the control arm and no treatment will be denied to patients through participating in this trial.

3.1.4 Phase III – Fully powered RCT

If the pilot trial successfully meets the recruitment target (100 participants within 12 months) the study will move to Phase III where a fully powered trial will be conducted, where an additional 440 participants will be recruited. It is anticipated that the trial will move seamlessly from the pilot to full trial phase. The design of the full trial will mirror that of the pilot trial in terms of the content of the intervention, inclusion criteria, outcome measures and period of follow-up. The difference between pilot and full trial will be telephone contact for

diagnostic interview. Participants will be contacted by telephone for diagnostic interview only if they have answered positively to at least 1 Whooley question, either at the invitation stage or baseline questionnaire stage. Therefore not all participants will be contacted (i.e. participants with negative responses at either invitation or baseline questionnaire, will not be contacted for a diagnostic interview).

The number of recruiting sites will be increased in phase III to ensure the trial meets recruitment targets. Appendix 1 shows how a participant progresses through the trial.

3.2 Trial intervention

3.2.1 Intervention group: Collaborative care with behavioural activation

Participants randomised to the intervention group will receive low intensity collaborative care which has been designed specifically for those aged 65 or over with sub-threshold depression, over 8–10 weekly sessions. The defining features of collaborative care include a case manager working with the participant, with access to the GP and a mental health specialist (psychiatrist or psychologist). Collaborative care will be delivered by a case manager (a primary care mental health worker/Improving Access to Psychological Therapies – IAPT worker). If a case manager deems depression to have deteriorated (moving from sub-threshold to threshold) the participant will be referred back to their GP for appropriate management and will not be directly influenced by this trial; the participant will be provided with the option of continuing to receive collaborative care. The additional elements of collaborative care include: telephone support; symptom monitoring and active surveillance (facilitated by computerised case management systems (PC-MIS); low intensity psycho-social management (BA). This will be delivered according to an established protocol[23, 33]. Participants randomised to collaborative care will meet with a case manager for their first session, after this initial meeting subsequent sessions will be on a weekly basis either conducted face to face or by telephone according to patient preference.

3.2.2 Control group

Participants randomised to the control group will receive usual primary care management of sub-threshold depression offered by their GP, in line with NICE depression guidance as implemented by their GP and local service provision[6, 7].

3.3 Withdrawal

Withdrawal can occur at any point during the study at the request of the participant. If a participant indicates they wish to withdraw from the study, withdrawal will be clarified as to whether the withdrawal is from the intervention, from follow-up or all aspects of the study. Where withdrawal is only from the intervention then follow-up data will continue to be collected. Data will be retained for all participants up to the date of withdrawal, unless they specifically request for their details to be removed.

3.4 Duration of intervention period

Screening for sub-threshold depression involves up to two stages (positive response to Whooley questions at either invitation or baseline questionnaire and diagnostic interview) with up to two reminders at both questionnaire stages. The intervention for participants will be delivered over 8–10 weeks.

3.5 Inclusion and exclusion criteria

Eligible participants will be identified from GP practice lists. The following eligibility criteria will be used:

Inclusion:

- Aged over 65
- Screen positive to at least 1 of the Whooley[24, 27] questions and is classed as experiencing sub-threshold depression during diagnostic interview based on the M.I.N.I. (Mini-International Neuropsychiatric Interview)[30]

Exclusion:

- Screen positive but suffering with above threshold depression (Major Depressive Disorder) based on the M.I.N.I.[30]

- Known alcohol dependency (as recorded on GP records)
- Any known co-morbidity that would in the GP's opinion make entry to the trial inadvisable (e.g. recent evidence of self-harm, known current thoughts of self harm, significant cognitive impairment)
- Other factors that would make an invitation to participate in the trial inappropriate (e.g. recent bereavement; terminal malignancy)
- Known to be experiencing psychotic symptoms (as recorded on GP records)

3.6 Sample size calculation

Our pilot study will recruit at least 100 people with sub-threshold depression (50 in each group). This sample size exceeds recommendations for pilot trials and will be sufficiently large to provide clear estimates of recruitment and follow up.

To detect a minimum effect size of 0.3, with 80% power and a two-sided 5% significance level would require 352 patients (176 in each group). Although this is an individually-randomised trial, there may be potential clustering at the level of each collaborative care case manager and hence we need to inflate the sample size to account for this. Based upon an ICC=0.02 and a caseload size of 20, the design effect would be $1.38 (1 + (20 - 1) \times 0.02)$ and we would require 486 patients (243 in each group). Allowing for a potential loss to follow-up of 10% the final sample size needed is 540 patients (270 in each group).

3.7 Recruitment

This is a new and innovative study. In light of this, recruitment may need additional effort to achieve recruitment rates, for two reasons. First, the motivation amongst people with even sub-threshold depression is lower than in the general population, and there might be a high refusal rate amongst those we approach. Second, this is an intervention predicated upon population screening. Elderly people with low severity depression identified by

screening might not see themselves as in need of help from a healthcare professional, and therefore might be reluctant to participate.

Recruitment will take place through primary care. GP Practices will be recruited to the study after a member of the study team has provided the practice with written information and visited the practice to explain the study and what participation would entail.

Participants who meet the initial inclusion criteria of being a registered patient at participating practice and aged over 65 years will be identified by GP practices. The practice will be asked, at this stage, to screen out all patients who have known alcohol dependency, other co-morbidities, psychotic symptoms, or any other issue which would make participation inappropriate. All eligible patients will be sent a letter of invitation by the practice, signed by GPs with an information sheet about the study. All identifiable information will be held in the NHS until written consent has been obtained from participants. All patients sent an invitation will be given the opportunity to decline participation but still provide some demographic information and reason for declining, in order to provide comparison information with those who are participating. During this consenting stage, potential participants will be informed of the possibility of participating in other related studies (e.g. qualitative studies). Consenting participants will be asked to indicate (by ticking a box on the consent form) if they would prefer not to be approached about these studies. All patients who consent to take part in the CASPER study at this stage will be part of the CASPER cohort.

3.8 Randomisation

Participants with sub-threshold depression who meet the inclusion criteria and have provided written consent will be eligible for randomisation into the trial. Randomisation will be carried out once all relevant data are collected and entered into the study database. Randomisation will be carried out by the York Trials Unit Randomisation Service. Participants will be randomised on a 1:1 basis to either the intervention group or control group. Participants who meet the inclusion criteria but have below- or above-threshold depression will not

be randomised. These participants will form the cohort group and will be followed-up with questionnaires at 4 and 12 months post-assessment.

3.9 Blinding

Blinding of the participants will not be feasible, nor is blinding of all members of the study team who are actively involved in the administration of the study. However, members of the study team responsible for the statistical analysis will be kept blind to group allocation.

3.10 Follow-up

Follow-up will be for a minimum of 12 months post-randomisation for those participants who were eligible to participate in the trial or 12 months post-assessment for cohort participants. Follow-up for all participants is expected to be longer should further funding be available for future follow-up.

There are likely to be some cases of loss to follow-up due to death, this is likely to be below 8.2% *per annum* (calculated from national mortality rates for this age group). Loss to follow-up due to migration is unlikely as this group tends to be geographically stable and initial follow-up is only for 12 months. Where a participant has been lost to follow-up their data will be included in the main analysis up to where they have been lost to follow-up. Where a participant is lost to follow-up, efforts will be made to contact the participant.

3.11 CASPER epidemiological cohort

All eligible patients identified by a GP practice will be sent an invitation to participate in the CASPER programme of research. Participants who return a completed consent form and baseline questionnaire will be eligible for inclusion in the CASPER cohort. This design has been termed the "cohort multiple randomised controlled trial (cmRCT)",[34] with the following design features: (I) Recruitment of a large observational cohort of patients with the condition of interest; (II) Regular measurement of outcomes for the whole cohort; (III) Capacity for multiple randomised controlled trials over time. Therefore, the design has the following advantages: ongoing information as to the natural history of the condition and to treatment as usual; and a facility for

multiple randomised controlled trials. In this case, we are interested in following the natural history of depressive symptoms amongst older people; comparing health outcomes for older people with and without depressive symptoms and potentially in the future, using this cohort to recruit for future trials in this age group.

Once a completed baseline questionnaire is returned researchers will assess for participant eligibility. Participants who are either not experiencing depression or are experiencing above-threshold depression will not be eligible to participate in the trial. Participants will be informed of this outcome and encouraged to complete follow-up questionnaires as part of the CASPER epidemiological cohort. This cohort will be sent questionnaires at similar times to participants in the trial. The questionnaires will be the same as those used for the trial follow-up questionnaires. Participants can withdraw at any point during the study. If a participant indicates they wish to withdraw from the study, withdrawal will be clarified as to whether this includes objective data collection. Data will be retained for all participants up to the date of withdrawal, unless they specifically request for their details to be removed.

3.12 Qualitative study

There has been little previous qualitative work exploring issues of effectiveness and acceptability of collaborative care amongst an older population with sub-threshold depression. An in depth appreciation of these issues will be essential in the implementation of collaborative care. A qualitative evaluation will be carried out to examine the acceptability of collaborative care and BA for those over 65. Additionally, the views of case managers will be obtained in order to assess the acceptability of collaborative care and BA by older adults and the feasibility of delivering collaborative care and BA in the NHS.

The qualitative aspect of the CASPER study has been designed to capture issues around acceptability, adherence, and utility in collaborative care. Different stakeholders will be used[35]. Through the triangulation of data from multiple sources of evidence this type of design can provide an in-depth

analysis of how collaborative care may be used in primary care to support older people with differing needs. Having different (embedded) units of analysis recognises that different stakeholders associated with the introduction and use collaborative care in older people may hold very different perspectives. We intend to explore the interaction between case managers, patients and the intervention.

Issues for qualitative evaluation:

Issues relating to elders

- Acceptability of screening
- Acceptability of intervention
- Adherence to intervention
- Mode of delivery
- Characteristics of group

Issues relating to case managers

- Intensity and duration
- Acceptability of intervention
- Adherence to delivery protocols
- Mode of delivery
- Characteristics of group

Additionally, data will be collected on the trial process itself in order to explore the acceptability of the treatment options, the randomisation procedure and the methods of data collection.

The qualitative study is embedded in the CASPER trial. Participants who have indicated on their CASPER Study consent form that they are willing to be contacted about any related studies will be eligible for contact (See 3.7 for recruitment strategy). Participants indicating a willingness to be contacted will be sent a separate information pack about the qualitative study. The pack will contain an invitation letter, participant information sheet, and a consent form.

Participants will be purposively selected on the following criteria:

- sub-threshold depression levels
- geographical area
- education
- gender

This is in order to obtain a maximum variation sample.

All case managers will be invited to participate in the qualitative study. They will be provided with an information pack containing an invitation letter, Participant Information Sheet, and a consent form.

The qualitative study will be conducted during the pilot and definitive trial phases. During the pilot trial approximately 30 participants will be consented to participate in the qualitative study. We will collect more in-depth data for approximately 10 participants (audio recordings of all contact sessions, up to 3 face to face interviews with participant and case manager, case manager diary data), and carry out face to face interviews with the remaining participants. During the definitive trial period approximately 20 additional participants will be consented to participate in the qualitative study for face to face interviews. It is anticipated these interviews will be carried out around the time of final follow-up in the trial. Withdrawal from the qualitative study can occur at any point at the request of the participant. Data will be retained for all participants up to the date of withdrawal, unless they specifically request for their details to be removed.

4.0 Data Collection and Analysis

4.1 Quantitative data collection and analysis

Data collection will initially occur at five time points, additional data collection may occur subject to additional funding being secured. Data will be collected at invitation, baseline (pre-randomisation/pre-assessment), diagnostic interview for participants entering the trial (pre-randomisation), at 4 months post-randomisation/post-assessment and 12 months post-randomisation/post-assessment for trial and cohort participants. A data collection schedule is shown in Appendix 3.

Diagnostic interviews will be carried out by telephone. Participants will be sent questionnaires by post at follow-up in order to collect self-report depression, quality of life, psychological anxiety and medication data.

There has been little previous qualitative work exploring issues of effectiveness and acceptability of collaborative care amongst an older population with sub-threshold depression. An in depth appreciation of these issues will be essential in the implementation of collaborative care. A qualitative evaluation will be conducted to examine current experience and views of case managers in order to assess feasibility of delivering collaborative care in the NHS and acceptability of collaborative care by older persons.

4.1.1 Invitation and baseline data collection

Eligible patients identified by GP practices will be sent an invitation letter by the practice with a detailed Patient Information Sheet. Patients will be asked to complete and return a consent form and demographic questionnaire which will include the Whooley questions. A baseline questionnaire will be sent to all participants who have returned a completed consent form.

4.1.2 Efficacy outcome measures

The following measures will be collected:

Primary outcome:

- Depression severity and symptomatology at four months.

Secondary outcome:

- Depression severity and symptomatology
- Quality of life measures
- Psychological anxiety
- Medication
- Mortality

Self-reported data will be captured from the following:

- Demographic details at invitation
- Whooley questions[24, 27] at invitation and baseline
- Questions about physical health problems at baseline
- SF-12[36] at baseline and follow-up

- EQ-5D[37] at baseline and follow-up
- GAD-7[38] at baseline and follow-up
- Questions about falls at baseline and follow-up
- PHQ-9[39] at baseline, diagnostic interview and follow-up
- PHQ-15[40] at baseline and follow-up
- CD-RISC2[41] at baseline and follow-up

NHS numbers for each participant will be obtained at the outset for all consenting participants. This is to enable the study team to follow participants up if they move to a different address, move to different GP practice or follow-up any hospital admissions.

Depression severity will be assessed by the PHQ-9. Quality of life will be assessed using the SF-12 and EQ-5D questionnaires. Psychological anxiety will be assessed using the GAD-7. All the above measures are completed by the participant; additionally, all participants will be asked if they have been diagnosed with any physical health problems. Depression medication data will be captured by self-report and directly from GP records, data will start to be collected from baseline onwards. Mortality will be established by flagging all randomised participants to the NHS Information Centre at regular intervals.

4.1.3 Analysis for validation of Whooley questions

The sensitivity, specificity and predictive values of the Whooley questions will be calculated with two-by-two contingency tables with the clinical diagnostic interview as the gold standard. Associated 95% confidence intervals will also be calculated for each estimate.

4.1.4 Efficacy data analysis

There will be no interim analysis of phase II data if the study proceeds to phase III, and the data will be considered as one single trial. Data will be analysed on an intention to treat basis, including all randomised patients in the groups to which they were randomised. Analyses will be conducted in Stata version 10, using 2-sided significance tests at the 5% significance level. The

statistician conducting the analyses will remain blind to treatment group until all data summaries and results are finalised.

A logistic regression model will be used to compare collaborative care with usual care on the primary outcome adjusted for baseline depression severity (as measured by the PHQ-9) and physical/functional limitations (as measured by the SF-12 physical functioning scale). Odd ratios and corresponding 95% confidence intervals will be obtained from this model. To explore the potential clustering within collaborative care case managers the primary analysis will be repeated adjusting for the clustering using the Huber-White standard estimator (robust standard errors).

All secondary analyses will be conducted using linear or logistic regression, depending on the outcome measure, adjusting for similar covariates to the primary analysis. In addition, for each outcome measure the number of non-responders will be calculated for each treatment group and response rates compared. Appropriate sensitivity analyses will be used to examine the effects of missing data on outcomes.

4.2 Qualitative data collection and analysis

The qualitative study will be conducted during the pilot and definitive trial phases.

4.2.1 Pilot trial phase qualitative data collection

The purpose of collecting qualitative data during the pilot trial is to assess the practical, acceptability, and refinement issues surrounding collaborative care. We aim to recruit approximately 30 randomised participants and all case managers. Data will be primarily collected through semi-structured interviews. All interviews will be conducted using a topic guide to ensure consistency across participants, however, the format will be flexible in order to allow participants to generate naturalistic data. All interviews will be audio recorded and transcribed verbatim. Those who have been randomised to the intervention group will be interviewed prior to receiving their intervention and again after their final contact with their case manager. We will collect more in-

depth data for approximately 10 participants (observation/audio recordings of all contact sessions, up to 3 face to face interviews with participant and case manager, case manager diary data). Case managers involved with the delivery of the intervention will be asked to complete a weekly reflective diary, to note any issues/observations regarding service provision. They will also be asked to record any relevant details where an intervention participant has been withdrawn from treatment. Semi-structured interviews will also be carried out with case managers, again a topic guide will be used.

4.2.2 Definitive trial phase qualitative data collection

The purpose of collecting qualitative data during the definitive trial is to assess the experience of participating in a trial and the experience of receiving collaborative care. The method of identifying participants and data collection will be the same as those used during the pilot trial. We aim to recruit approximately 20 randomised participants (10 intervention and 10 usual care participants). It is anticipated these interviews will be carried out around the time of final follow-up in the trial. Case managers will again be asked to complete a reflective diary and record details of intervention participants who have been withdrawn from treatment.

4.2.3 Qualitative data analysis

The computer package ATLAS-ti will be used to manage the data. The data will be analysed using thematic content analysis[42]. This approach is inductive (themes emerge from the data and are not imposed upon it by the researcher) and iterative (data collection and analysis occur simultaneously). Data will be coded and classified according to themes which arise out of the interview data. Comparative analysis will also be carried out; this method allows data from different participants to be compared and contrasted. Deviant cases will be actively sought throughout the analysis and emerging ideas and themes modified in response[43].

4.3 Economic analysis

Incremental cost-effectiveness analysis will be undertaken from a health and personal social services perspective following NICE guidance[44]. The

economic analysis will estimate the value for money afforded by the diet and activity intervention over and above the control. QALYs will be estimated using the EQ-5D. This approach enables comparisons to be made across different health interventions and provides extra information for decision makers. QALYs will be estimated by measuring the area under the curve[45] which joins baseline and follow up EQ-5D utility scores derived from population based values.

Costs of the intervention, control and the total health care costs during the treatment and follow up period will be assessed. Individual take-up of depression management and control interventions will be measured and costs will be estimated using a bottom-up approach. Various methods of collecting costs, e.g. self report questionnaires, and medical record checks will also be examined. Wider health and social service use will be measured using a service use questionnaire which has been used in previous trials by the investigators, with national unit costs applied to quantities of resources utilised[46, 47]. Costs of the intervention, total health care costs and changes in outcome measures in the RCT will be combined to calculate the incremental cost-effectiveness ratios. The sensitivity of the cost-effectiveness ratio to different threshold values for a QALY will be demonstrated using cost-acceptability curves[48].

5.0 Ethical Issues

We are aware that older people with sub-threshold depression represent a vulnerable group. However, we do not anticipate any major ethical issues since we will only offer interventions recommended in recent guidance issued by NICE. Where participation in the trial is felt to be detrimental to health and wellbeing, we will not make an approach to participate. Participants will not be denied any form of care that is currently available in the NHS by participating in the trial, since participants allocated to usual care will still have full access to NICE recommended treatments, subject to local provision of services.

5.1 Anticipated risks and benefits

The trial does not involve new medicinal products or any invasive/potentially harmful procedures and is therefore considered low risk for participants.

All participants will receive usual GP care, and therefore no treatment will be withheld by participating in this trial. This trial may in fact benefit individual participants, since collaborative care is not routinely offered to our target group (screen-positive sub-threshold depression). By participating in this trial, participants will also receive a more intensive level of monitoring than that normally received in primary care. Participants who become more depressed or become suicidal will be more readily identified and directed to appropriate care.

5.2 Informing participants of anticipated risks and benefits

The Patient Information Sheet will provide potential participants with information about the possible benefits and anticipated risks of taking part in the study either as a participant in the epidemiological cohort or additionally in the trial. Participants will be given the opportunity to discuss this issue with their GP or trial co-ordinator prior to consenting to participate. The trial co-ordinator will inform the participant if new information comes to light that may affect the participant's willingness to participate in the trial.

5.3 Obtaining consent

Potential participants will receive an information pack about the trial. The pack will contain an invitation letter, Patient Information Sheet, a consent and a decline form and demographic questionnaire. The Patient Information Sheet will be produced using the current guidelines for researchers on writing information sheets and consent forms, posted on the NRES website.

5.4 Retention of study documentation

All data will be stored for a minimum of 5 years after the end of final analysis of the study and will be accessed by the Trial Statistician. All paper records will be stored in secure storage facilities. Personal identifiable paper records

will be stored separately from anonymised paper records. All electronic records will be stored on a password protected server within York Trials Unit.

6.0 Service User Involvement

Service user input into the conduct and dissemination of the CASPER study comes from Michael Beckett. Michael is the director of the York and District Mind. Mind is a national charity, which aims to provide information, support and advice to those have mental health problems and their carers. Michael will be part of the Trial Steering Committee. The CASPER research group will follow good practice in terms of ensuring service user representation will be able to contribute to discussions relating to the study. We will also work with our service user representative to ensure that our dissemination strategies are inclusive and accessible to service users.

7.0 Research Governance

The trial will be conducted to protect the human rights and dignity of the participant as reflected in the 1996 version of the Helsinki Declaration. Patients will not receive any financial inducement to participate. In order to protect the trial participants the following provisions will be made/upheld; the trial has been designed to minimise pain, discomfort and fear and any foreseeable risk in relation to the treatments involved; the explicit wishes of the participant will be respected including the right to withdraw from the trial at any time; the interest of the patient will prevail over those of science and society; provision will be made for indemnity by the investigator and sponsor.

7.1 Monitoring and adverse events

This study is non-CTIMP (Clinical Trial of an Investigational Medicinal Product) and is therefore not subject to any additional restrictions. Decisions regarding prescription of medications will made by the participant in conjunction with their GP; participation in the study will have no bearing on this process. If a participant asks a member of the CASPER study team for an opinion on medication issues, they will be strongly encouraged to seek advice from their GP.

This study will record details of any Serious Adverse Events (SAEs) that are required to be reported to the Research Ethics Committee (REC) under the terms of the Standard Operating Procedures for RECs [49].

An SAE is defined as a **'related'*** and **'unexpected'**** untoward occurrence that:

- (a) Results in death;
- (b) Is life threatening;
- (c) Requires hospitalisation or prolongation of existing hospitalisation;
- (d) Results in persistent or significant disability or incapacity;
- (e) Consists of a congenital anomaly or birth defect; or
- (f) Is otherwise considered medically significant by the investigator.

* **'related'** is defined as: resulting from the administration of any research procedures.

** **'unexpected'** is defined as: a type of event not listed in the protocol as an expected occurrence.

In the context of the current study, an occurrence of the type listed in (a) to (f) above will be reported as an SAE only if:

- It is suspected to be related to an aspect of the research procedures (e.g. completion of follow-up questionnaires, participation in qualitative sub-studies, telephone contact).
- or
- It is an unexpected occurrence.

Hospitalisations, disabling / incapacitating / life-threatening conditions and deaths are expected in the study population due to the age of the cohort, they will therefore only be reported as SAEs if they appear to be related to an aspect of taking part in the study. The Trial Manager should be informed of the SAE by telephone. The Trial Manager will inform the Chief Investigator (CI) and 2 members of the Trial Management Group (TMG) who will jointly decide if the event should be reported to the main REC as an SAE. Related and unexpected SAEs will be reported to the main REC within 15 days of the

CI becoming aware of the event. A SAE Form will be completed and a copy stored in the participant's records.

The occurrence of adverse events during the trial will be monitored by an independent Data Monitoring Ethics Committee (DMEC) and the Trial Steering Committee (TSC). The DMEC/TSC will immediately see all SAEs thought to be treatment related and they will see SAEs not thought to be treatment related by the Trial Management Group at the next scheduled meeting.

7.2 Suicide and self-harm

Inherent in the nature of the condition under scrutiny is the risk of suicide and deliberate self-harm. All participants will be subject to usual GP care, and their GP will be responsible for the day to day management of sub-threshold depression – and will ultimately be responsible for all patient level treatment / management decisions – including prescribing, referral and assessment of risk. This arrangement is made clear to all clinicians and GP practices who participate in the study. The pragmatic nature of this trial means that we will not seek to influence this arrangement. However, we will follow good clinical practice in monitoring for suicide risk during all encounters with participants. Where any risk to patients due to expressed thoughts of self-harm is encountered, we will follow the trial suicide protocol (see Appendices 4 - 4.3).

8.0 Trial Management

8.1 Sponsorship

The University of York will act as a sponsor for the CASPER Trial.

Sue Final

Intellectual Property Manager

University of York

Enterprise & Innovation Office

Innovation Centre

York Science Park

York

YO10 5DG

8.2 Indemnity

Normal NHS Indemnity procedures will apply. The University of York will also provide relevant cover.

8.3 Funding

Research funding has been secured from the National Institute of Health Research – Health Technology Assessment programme (reference: 08/19/04).

The main cost implication for the NHS is GP time. This is classed as a Service Support Cost. From 2008/09 service support costs have been met via the UKCRN Clinical Research Network Portfolio. It is anticipated that service support costs for CASPER will be met via this route once it has been adopted as a portfolio study.

8.4 Trial Steering Committee (TSC)

A TSC will be set up and will include an independent chair and at least two other independent members, along with the lead investigator and the other study collaborators. They will meet at least annually (See Appendix 5 for details).

8.5 Data Monitoring and Ethics Committee (DMEC)

A DMEC committee will be set up and will comprise of an independent statistician and clinician (primary care physician and mental health professional). The role of the DMEC is to immediately see all SAEs thought to be treatment related and unexpected; they will also review outcome data. They will meet at least annually. (See Appendix 5 for details).

8.6 Recruiting centres

Two centres (York and Leeds) will be co-ordinating the recruitment of participants to the study (epidemiological cohort and trial). Each study centre will utilise one or more primary care trusts for recruitment.

8.7 Day to day management of the trial

The chief investigator (Simon Gilbody) will be in charge of the overall management of the trial. The York-based trial manager (Natasha Mitchell) will be responsible for the co-ordination of the study between sites. A trial co-ordinator and trial secretary will carry out the day to day activities involved in running the trial at each site. Delivery of collaborative care will be carried out by a dedicated & skilled case manager (one per site in the pilot trial; two per site in the full trial). A research fellow will be responsible for the qualitative components of the study.

A local trial management group will be formed at each study centre and regular meetings will be held.

8.8 Responsibilities of the applicants

Simon Gilbody will act as the Chief Investigator with overall responsibility for the study and also act as the study mental health specialist. There will be a Principal Investigator at each site, Simon Gilbody (York) and John Holmes (Leeds), responsible for the local running of the trial and the provision of methodological input. Catherine Hewitt will be the lead trial statistician. Christine Godfrey will lead the economic evaluation. David Torgerson will provide methodological advice about trial design and contribute to the economic evaluation. Joy Adamson and Karen Spilsbury will lead the qualitative components of the study. Helen Lester will be the lead primary care academic. Dean McMillan, David Eckers, and David Richards will provide input to for the collaborative care and behavioural activation aspects of the study.

8.9 Dissemination

We will publish papers relating to this trial that will include (as a minimum) the results of the clinical and cost effectiveness comparisons and the results of

the qualitative analysis. Professor Gilbody is an editor of the Cochrane Depression, Anxiety and Neurosis Group and can thus ensure that the results of this trial are incorporated in relevant Cochrane reviews. We will also publish in professional journals to ensure that clinicians have prompt access to our findings. We will produce a short summary of the results that can be distributed to all trial participants, participating GP practices, as well as relevant patient and other interest groups. Finally, we will aim to ensure coverage of our findings in the wider media by issuing a press release. This will serve to bring the public and clinicians' attention to our findings.

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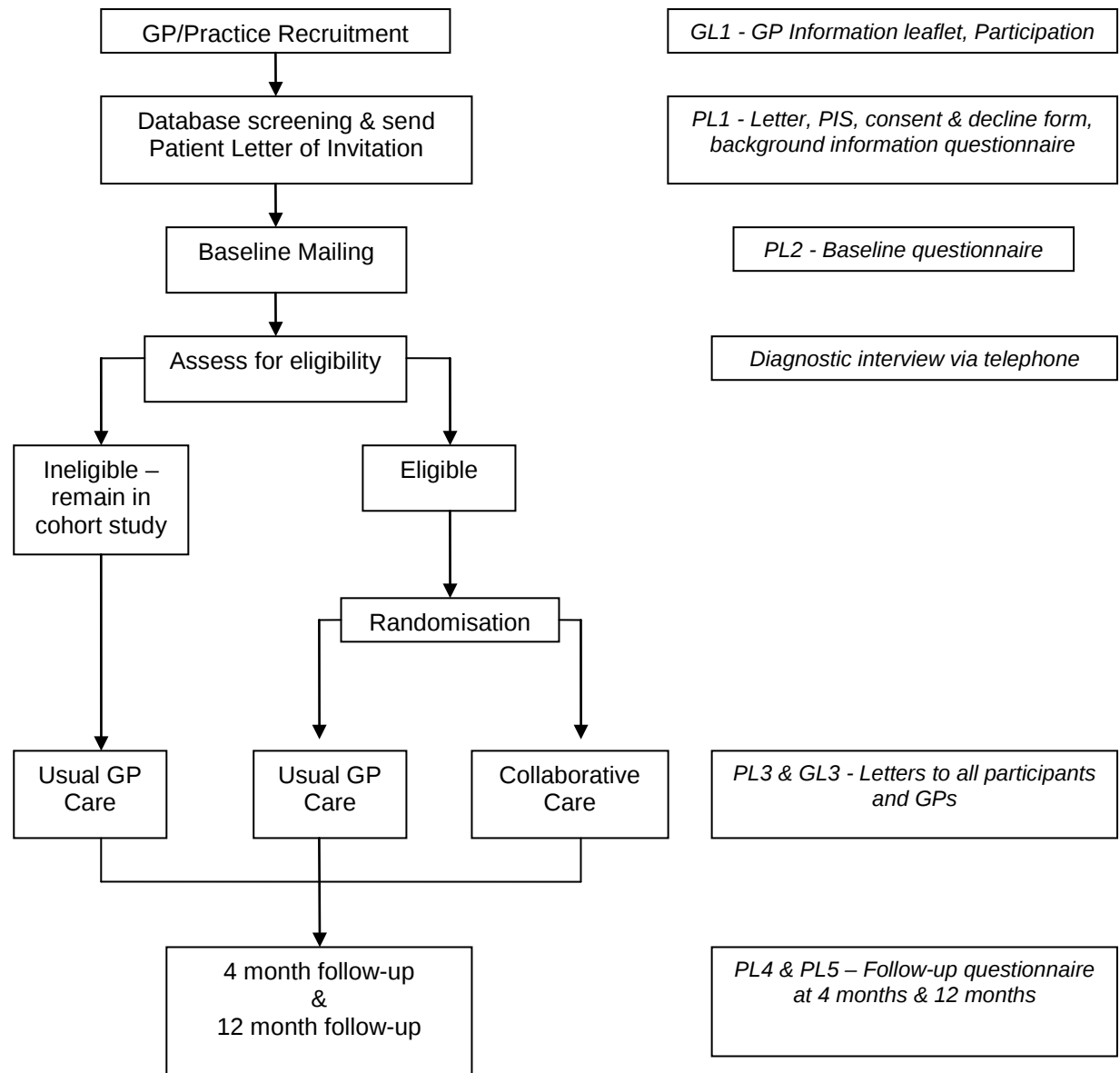
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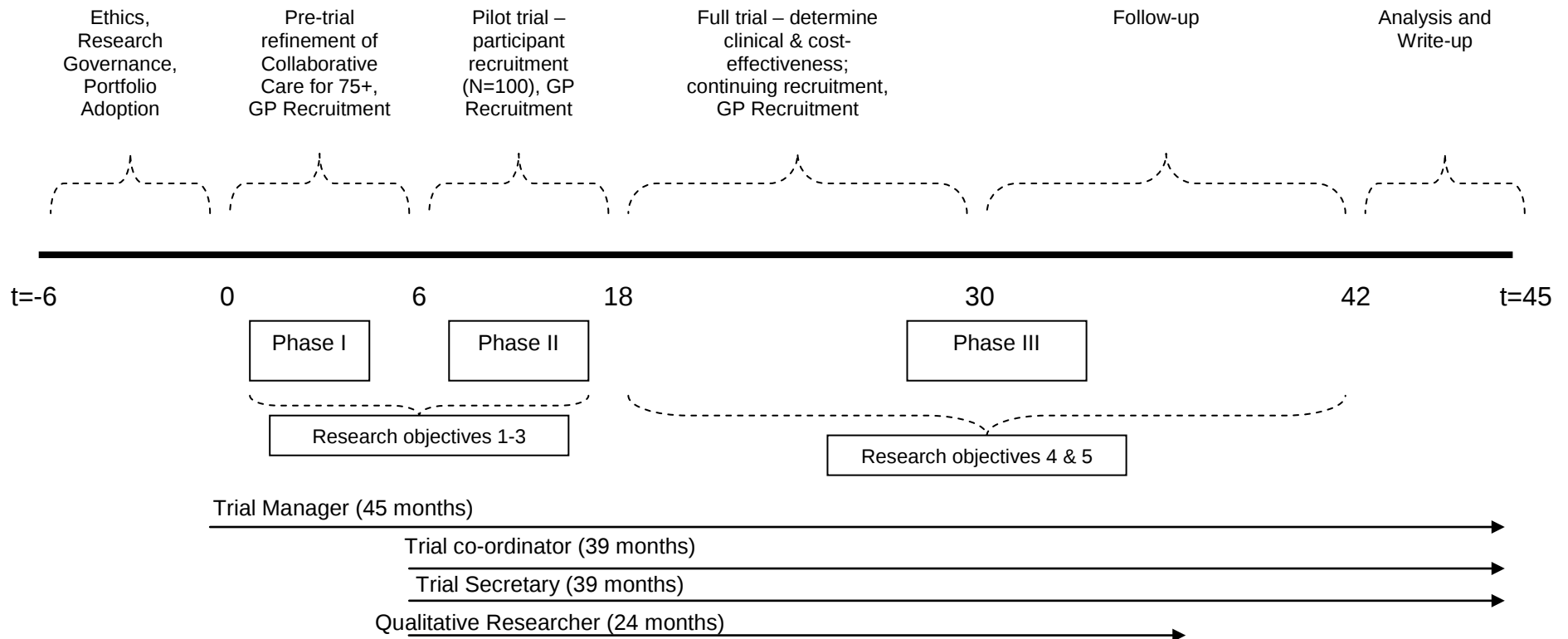
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Appendix 1: Summary of study activities and documentation



Appendix 2: Study Timeline

CASPER Study – overview of phased approach and timeline



Appendix 3: Data Collection Schedule

	Invitation	Baseline	Depression assessment	4 month follow-up	12 month follow-up
Consent/Decline form	•				
Demographic questionnaire	•				
Whooley questionnaire	•	•			
Physical health problems	•				
Falls questions	•				
PHQ-9		•	•	•	•
SF-12		•		•	•
EQ-5D		•		•	•
GAD-7		•		•	•
PHQ-15		•		•	•
CD-RISC2		•		•	•
Medication questionnaire		•		•	•
Diagnostic interview (MINI)			•		
Economic evaluation		•		•	•
Objective medication data		•		•	•

Appendix 4: CASPER Suicide Protocol



Suicide Protocol: For all participants of the CASPER Study

- This protocol has been devised to provide guidance in instances where a participant causes concern for the CASPER Study team regarding their mental wellbeing, specifically their risk of suicide or self-harm. Although there may be a risk of suicide or self-harm we do not anticipate this to be significant throughout the study. The suicide protocol would be implemented when the CASPER Study team become aware of this risk, i.e. as soon as the team are aware of the risk the protocol will be followed. For researchers, this could occur via data on returned questionnaires or during participant diagnostic interviews. For case managers, it could occur during a collaborative care session with one of their participants. All researchers and case managers working on CASPER will have received CASPER risk training. A set of flowcharts is provided with this protocol to provide an overview of the processes to be followed:
Suicide Intention Flowchart 1 – identified via questionnaires
 - **Suicide Intention Flowchart 2 – identified via diagnostic interviews**
 - **Suicide Intention Flowchart 3 – identified via collaborative care sessions**

Identifying participants as experiencing significant suicide risk from questionnaires

Data collection is based on the return of questionnaires at three time points (baseline, 4 months & 12 months), the PHQ-9 is on all questionnaires. It is anticipated that questionnaires will be opened each working day. Question 9 on the PHQ-9 will be used as the measure of significant suicide risk. Each returned questionnaire will be checked for validity of the primary outcome measure (PHQ-9). For the primary outcome measure to be marked as a 'valid' response all questions require a response. Where the primary outcome measure is 'invalid' the participant will be contacted. Additionally, the response to Question 9 will be checked. Flowchart 1 documents how to enact the suicide protocol in response to how question 9 is answered.

Identifying participants as experiencing significant suicide risk during diagnostic interview

Researchers conduct a diagnostic interview with participants once they have completed the baseline questionnaire. This includes the mini-international neuropsychiatric interview (MINI) and the PHQ-9. Question 3g of the MINI and question 9 of the PHQ-9 both ask about suicide ideation. Flowchart 2

documents how to enact the suicide protocol in response to how these two questions are answered.

Participants experiencing significant suicide risk expressed during collaborative care sessions with case manager

Participants who are randomised to the intervention group will receive collaborative care plus usual GP care. Collaborative care will be delivered by a case manager who will have contact with the participant during the delivery of the intervention. The intervention may be delivered face-to-face or over the phone. During these sessions the participant may communicate to the case manager thoughts of suicide or self-harm which may cause concern. If the case manager is concerned they must follow the suicide protocol documented in Flowchart 3. **Contact details**

YORK				
Title	Name	Landline	Mobile	Email
Chief Investigator				
Clinical Supervisor				
Study Manager				
Researcher				

DURHAM				
Title	Name	Landline	Mobile	Email
Principal Investigator / Clinical Supervisor				
Study Coordinator				

LEEDS				
Title	Name	Landline	Mobile	Email
Principal Investigator				
Clinical Supervisor				
Study Coordinator				

Documenting the procedure

If researchers identify suicide ideation during diagnostic interviews they will ask six Exploring Risk questions (see below) to try and determine level of intent before reporting to clinical lead. Where suicide ideation is identified on questionnaires, researchers will attempt to contact participant to ask Exploring Risk questions before speaking to clinical lead but will contact clinical lead even if they cannot reach participant. Once the procedure has been enacted (see flowchart 1 & flowchart 2), researchers will complete a suicide intention form (see Appendix4.1) as evidence of how the procedure was enacted which will remain with the participant's notes.

Exploring Risk questions

Plans	
1. Do you know how you would kill yourself? If Yes – details	Yes / No
2. Have you made any actual plans to end your life? If Yes – details	Yes / No
Actions	
3. Have you made any actual preparations to kill yourself? If Yes – details	Yes / No
4. Have you ever attempted suicide in the past? If Yes – details	Yes / No
Prevention	
5. Is there anything stopping you killing or harming yourself at the moment? If Yes – details	Yes / No
6. Do you feel that there is any immediate danger that you will harm or kill yourself? If Yes – details	Yes / No

Appendix 4.1: CASPER Participant Suicide Intention Form



Participant Suicide Intention Form

The participant below has expressed thoughts of suicidal intent / self-harm on the PHQ-9 of a questionnaire or during their diagnostic interview.

Participant ID code:



Risk of Suicide / Self-harm identified from

Question 9 of PHQ-9 on a questionnaire	3 (<i>nearly every day</i>)	☐
	2 (<i>more than half the days</i>)	☐
	1 (<i>several days</i>) Only if overall PHQ-9 score >20	☐
Question 9 of PHQ-9 during diagnostic interview	3 (<i>nearly every day</i>)	☐
	2 (<i>more than half the days</i>)	☐
	1 (<i>several days</i>)	☐
Question 3g of MINI during diagnostic interview	'Yes' to past two weeks (not to past episode)	☐

Summary of how procedure was enacted

(Which clinician gave advice, what advice was given, was risk judged as passive or active? If advised to contact GP – name of practice, name of GP spoken to, date etc.)

Researcher name:

Researcher signature:

Date:

Local clinical lead name:

Local clinical lead signature:

Date:



/ /

Day Month Year

Appendix 4.2: Suicide Intention Flowchart 1

Suicide Intention Flowchart 1: Identified via questionnaires (participants' response to question 9 of PHQ-9 on baseline, 4-month & 12-month questionnaires)

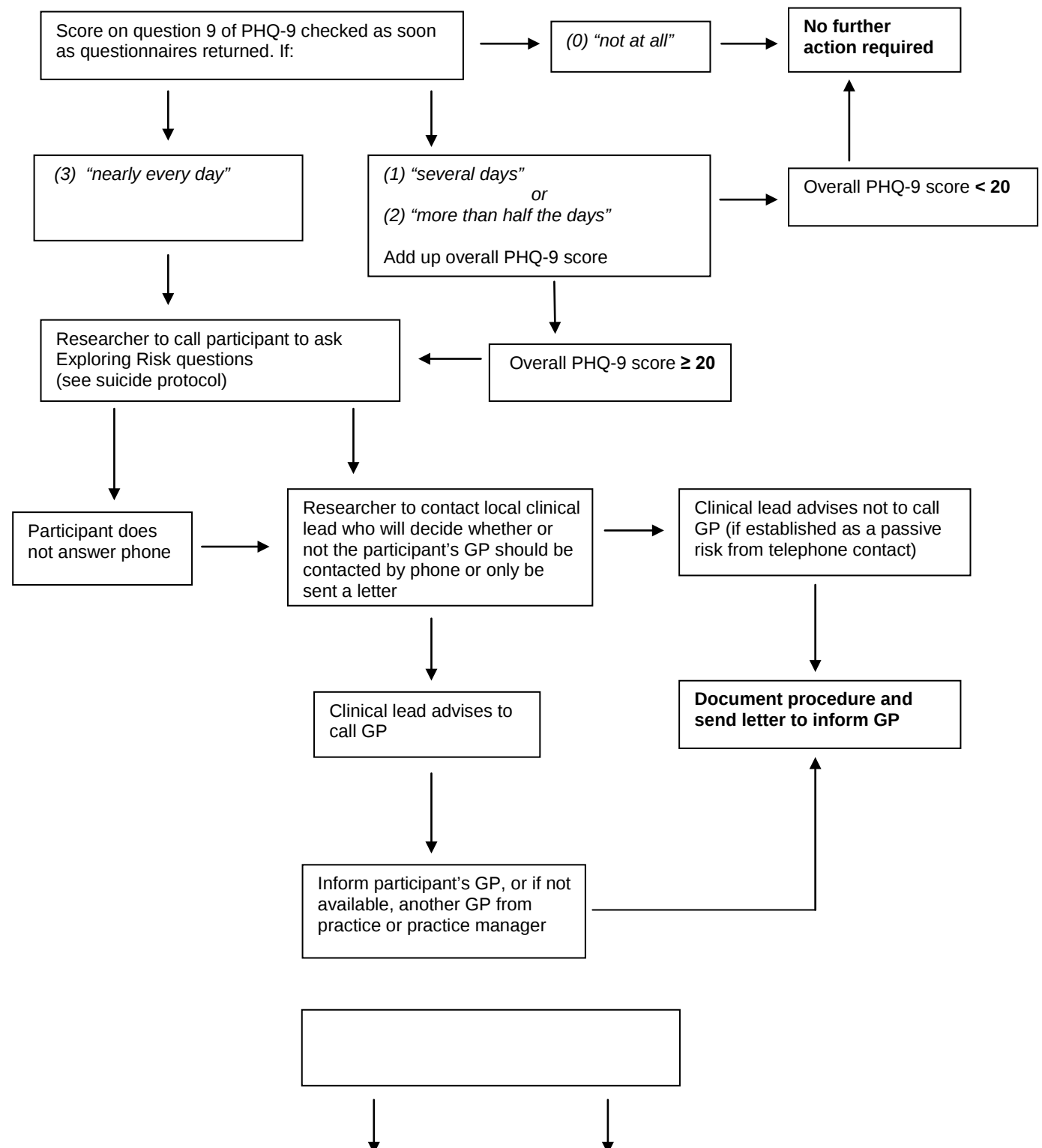
Q. 9 Thoughts that you would be better off dead, or of hurting yourself in some way? (PHQ-9)

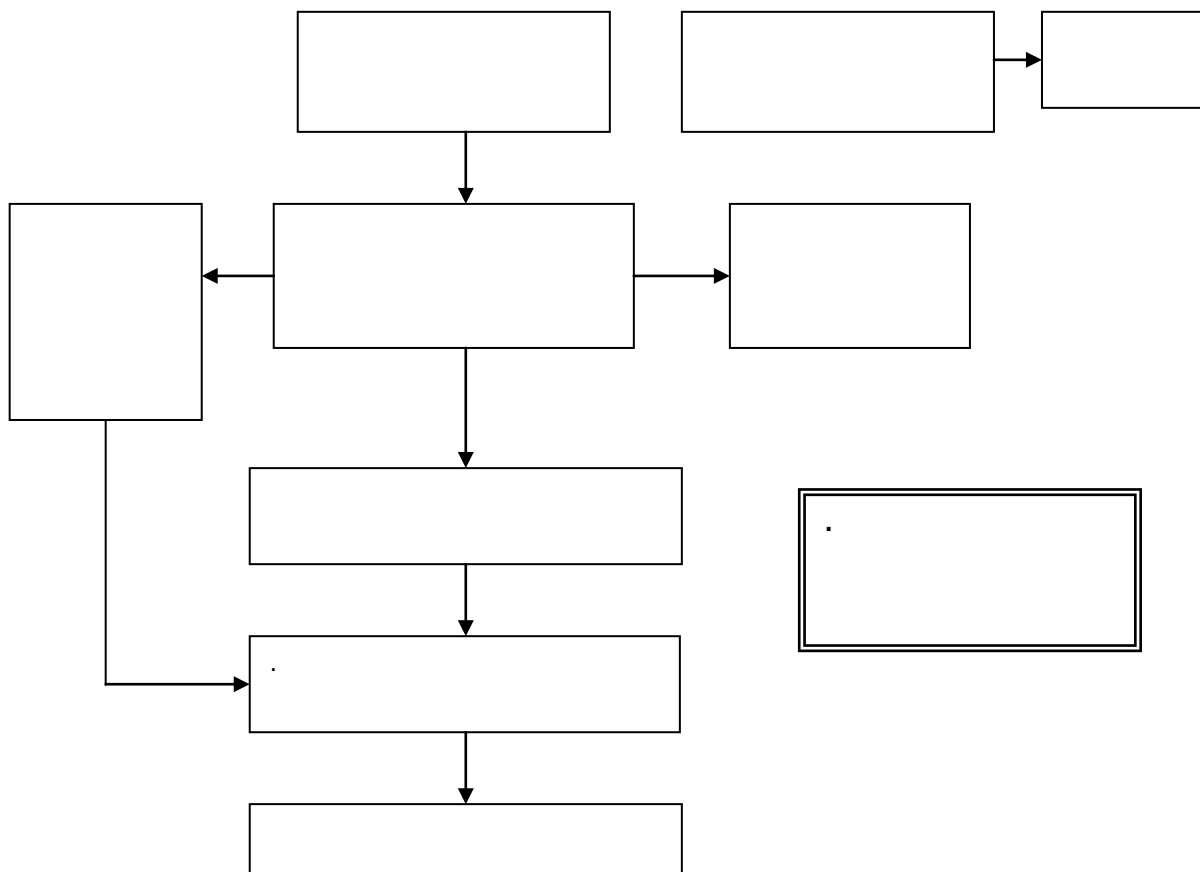
(0) *Not at all*

(1) *Several days*

(2) *More than half the days*

(3) *Nearly every day*





Appendix 4.3: Suicide Intention Flowchart 2

Suicide Intention Flowchart 2: Identified via diagnostic interviews

Q. 3g Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide? (MINI)

Past two weeks

Yes / No

Past episode

Yes / No

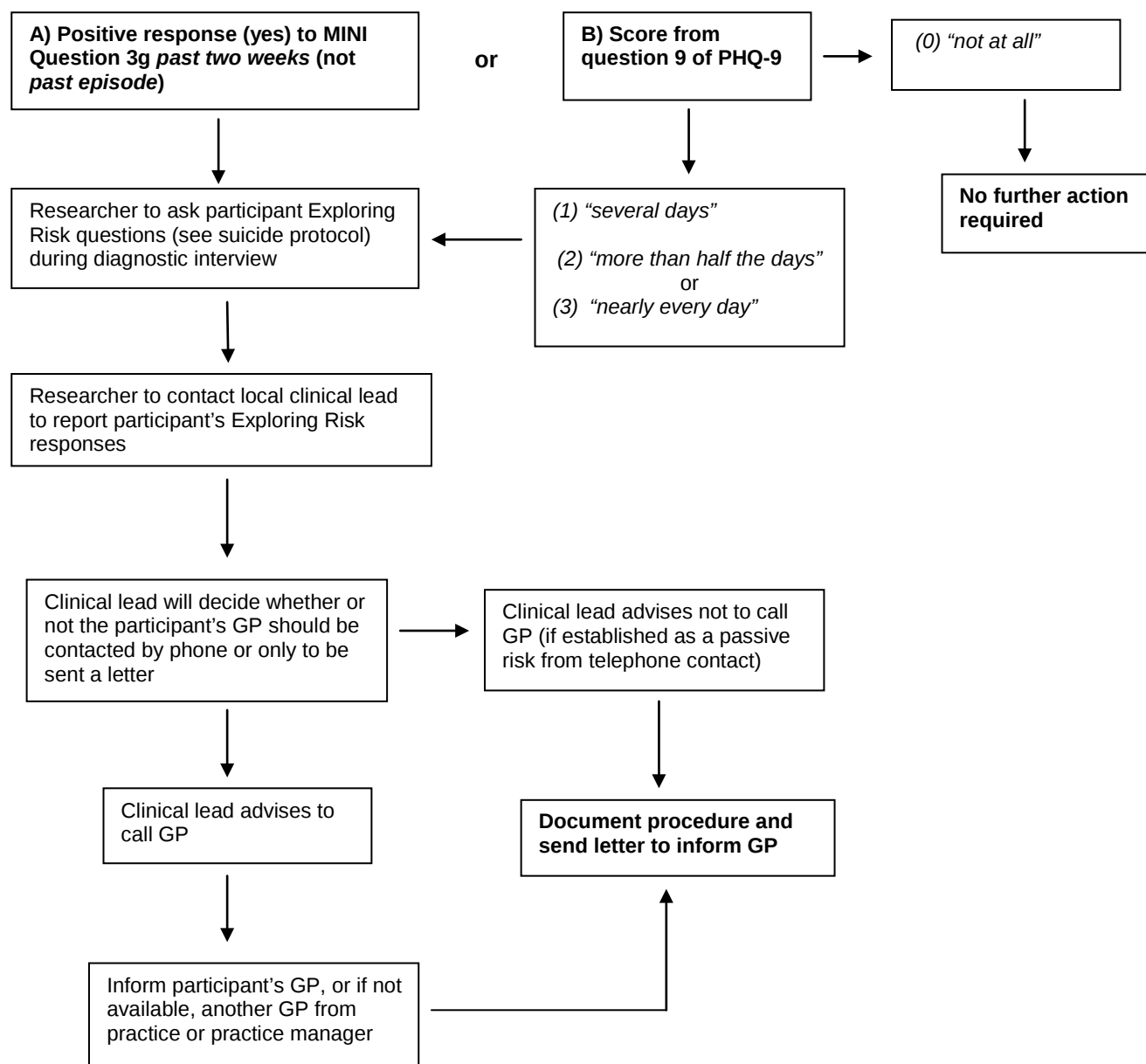
Q. 9 Thoughts that you would be better off dead, or of hurting yourself in some way? (PHQ-9)

(0) *Not at all*

(1) *Several days*

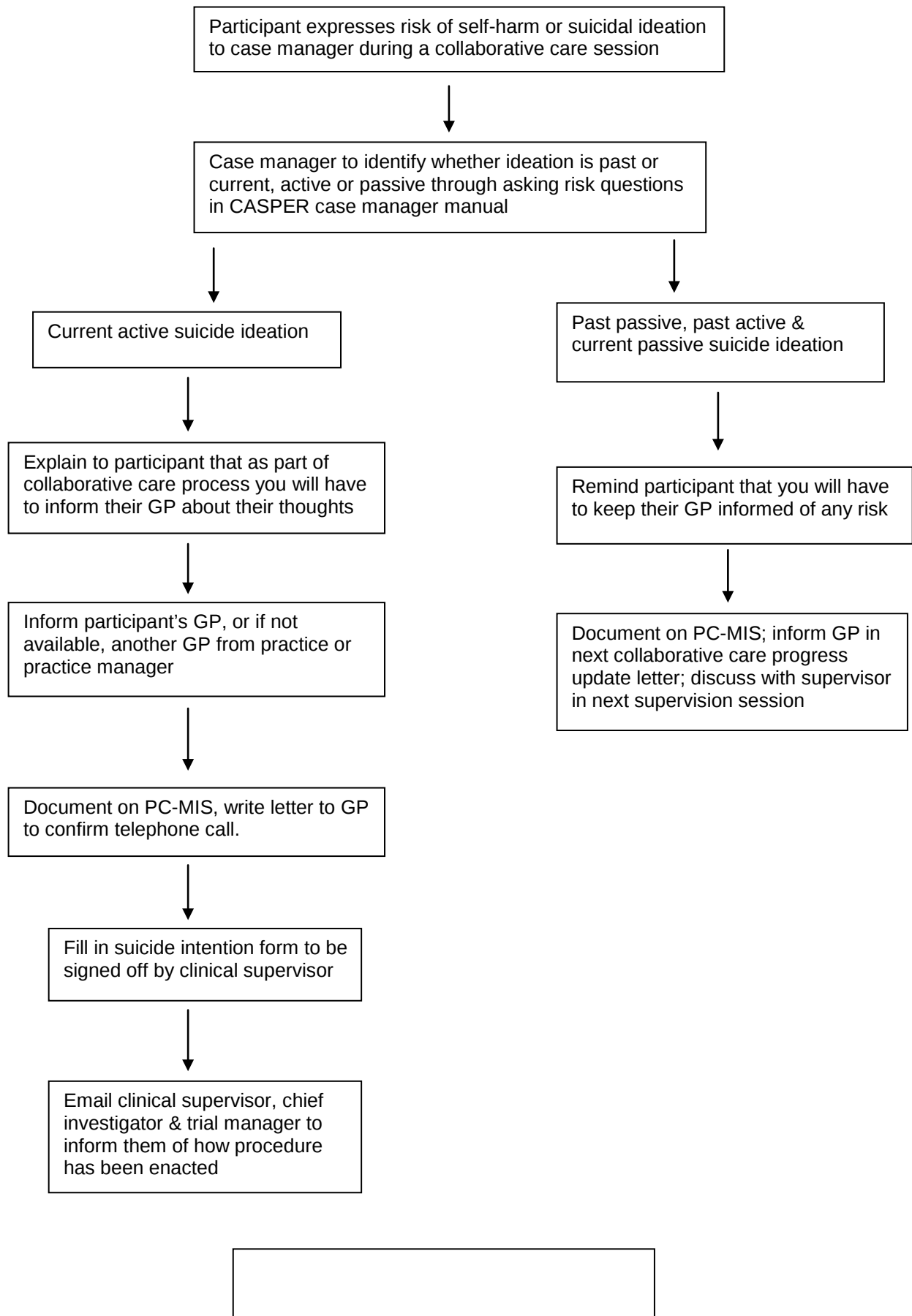
(2) *More than half the days*

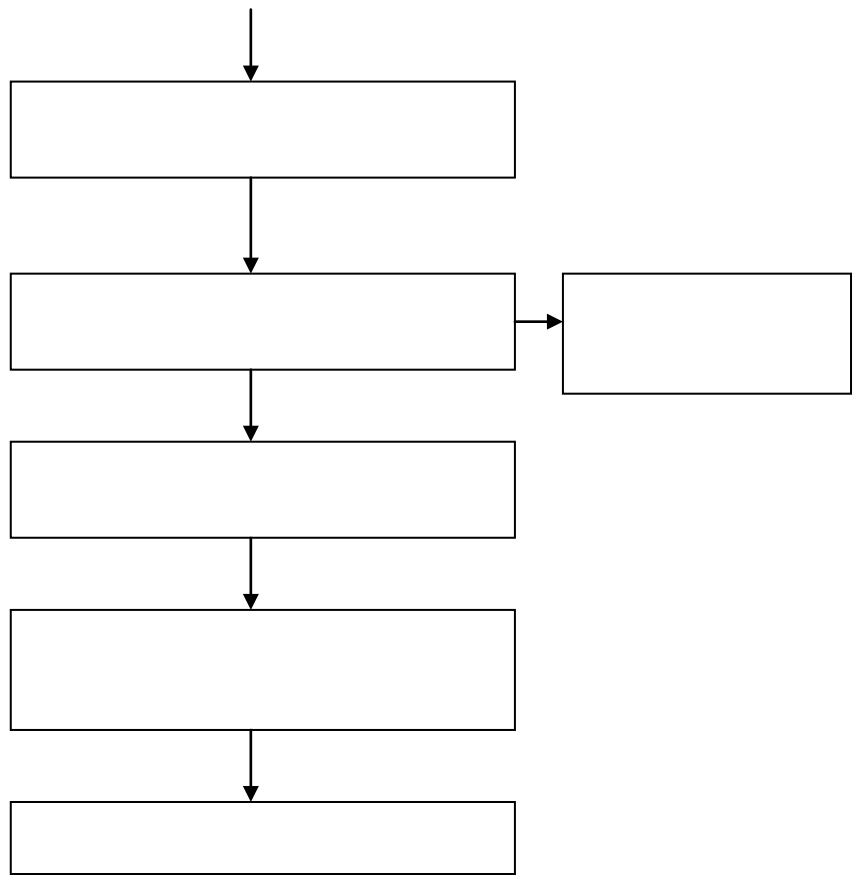
(3) *Nearly every day*



Appendix 4.4: Suicide Intention Flowchart 3

Suicide Intention Flowchart 3: Identified via case managers





Appendix 5: TSC and DMEC Membership

CASPER TSC Members

Mr Mike Beckett	Director of York MIND (patient representative) Email: mike@yorkmind.org.uk
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Plus members of the CASPER co-investigators	

CASPER DMEC Members

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Ms Judy Leibowitz	Primary Care Mental Health Development Coordinator, Camden PCT Email: judy.leibowitz@camdenpct.nhs.uk
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