Community pHarmaciEs Mood Intervention STudy (CHEMIST): Feasibility Study and Pilot RCT

Trial Protocol

Amendment history:

List details of all protocol amendments here whenever a new version is produced

Amendment no.	Protocol version no.	Date issued	Author of change	Details of changes made
N/A	1.1	3rd Nov 2016	LL	Addition of procedure for recruitment of participants to qualitative studies (sections 6.18 & 7.14)
SA1	2.0	3th Jan 2017	LL	Revision to recruitment procedure (section 6.5 and flowchart). Minor revisions (updates and clarification).
MA1	2.1	10th May 2017	LL	Provision of study information with prescriptions of customers visiting pharmacy
MA2	2.2	25th May 2017	LL	Update Protocol & PIS (Feasibility) with contact details for CI.
SA3	3.0	6th July 2017	LL	Revision to recruitment procedure – conducting searches on pharmacy database systems to identify eligible customers to send study information pack.

SA4	3.1	19th July 2017	LL	Revision to recruitment procedure – to include study information pack with medication deliveries of eligible customers
SA5	3.2	7th Sept 2017	LL	Revision to procedure for conducting qualitative interviews.
SA7	4.0	6th Mar 2018	LL	Revisions for pilot RCT – recruitment procedure (handing out study information pack in first instance to customers visiting pharmacy), removal of PHQ-15 outcome measure, revisions to qualitative study, removal of reference to objective GP data collection.
SA8	4.1	7th Mar 2018	LL	Changes to consent procedure – ticks/crosses accepted as valid consent if participant has printed name, signed and dated the consent form accurately.
MA9	4.2		LL	Removal of postal code restriction on GP database search criteria.

CHEMIST
Mood Intervention Study

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1. Key information

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1.3. Study Identifiers

Full title of trial:	Community pHarmaciEs Mood Intervention STudy (CHEMIST): Feasibility Study and external Pilot randomised controlled trial
Acronym:	CHEMIST
ISRCTN:	ISRCTN11290592
Funder:	National Institute of Health Research Public Health Research (NIHR-PHR)
NIHR reference:	14/186/11
Sponsor:	Tees, Esk and Wear Valleys NHS Foundation Trust
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1.4. Abstract

1.4.1. Feasibility study

Objectives:

a) Refine a bespoke Enhanced Support Intervention (ESI) (including self-help materials, intervention manual and training) for implementation by community pharmacy (CP) staff to people with subthreshold depression and Long Term Conditions (LTCs) based upon evidence supported interventions in primary care.
b) Develop and refine study procedures (CP recruitment strategies and set up, screening, participant recruitment, assessment, suitability of outcome measures and data collection procedures) for testing in the pilot study phase.

Design: A before and after observational/qualitative study.

Setting: UK community pharmacies (Durham/Teesside).

Population: Adults with long term health conditions who screen-positive for depression but who do not reach the threshold for DSM IV Moderate Depressive disorder.

Intervention: Enhanced Support Intervention (ESI) delivered by an appropriately trained community pharmacy team member of 4-6 sessions over 4 months. ESI is a modified form of the intervention within the collaborative care framework for sub-threshold depression validated in previous studies in UK primary care, which appears suitable for implementation in community settings. Defining features are a brief psychosocial intervention (behavioural activation based on goal orientated activity scheduling) using facilitated self-help developed and tested in previous studies in comparable populations. Previously developed training, intervention and self-help materials (developed by co-investigators) will be adapted for use in community pharmacies in consultation with PPI and stakeholder groups.

Sample size: 20-30 participants

Outcomes: As we are assessing feasibility, we will assess study implementation (recruitment and attrition rates), quality of data collection at baseline and 4 months and ESI adherence (number of contacts, DNA and drop out) as per objectives 1a/b.

Qualitative Evaluation: Semi-structured interviews with up to 10 participants and ESI facilitators and focus group(s) (range of pharmacy staff n=8-10) will be conducted to explore acceptability of the intervention and feasibility of the study, training and study procedures. Findings will inform adaptations prior to the pilot trial.

1.4.2. External pilot study

Objectives:

a) Quantify the flow of participants (eligibility, recruitment and follow up rate) within the CHEMIST study.
b) Evaluate proposed recruitment, assessment and outcome measure collection methods within the CHEMIST study.

c) Examine the delivery of the Enhanced Support Intervention in a community pharmacy setting (intervention uptake, retention and dose) to inform process evaluation.
d) Process evaluation, using semi-structured interviews with participants across a range of socio-economic settings, and pharmacy staff to explore acceptability of the ESI within community pharmacy, elements of the intervention that were considered useful (or not) and appropriateness of study procedures.

Design: Pilot randomised controlled trial, including a prospective economic and qualitative evaluation.

Setting: As above incorporating North Yorkshire

Population: As above

Intervention: As above with adaptations post feasibility study

Comparator: Usual care

Sample size: 100 participants

Outcomes: Data will be used to estimate recruitment, intervention delivery and study completion rates as per objectives 2a-d. We will not make definitive estimates of the effectiveness of ESI.

Primary outcome: Depression severity (Patient Health Questionnaire 9) at 4 months.

Secondary outcomes: Patient acceptance, uptake and attrition. We will also measure ICD10 depression status; anxiety (GAD 7); health related quality of life (SF-12); health-state utility (EQ5D-3L); health service use (adapted Adult Service Use Schedule, AD-SUS) at 4 months.

Economic evaluation: The incremental cost per QALY will be calculated from both the NHS and societal perspective.

Process Evaluation: Using mixed methods we will examine potential mediators/moderators of the intervention, the acceptability (to participants and pharmacy staff), barriers and facilitators to the use of ESI in community pharmacy, and impact on usual practice. Semi-structured interviews with approximately 30 study participants, 20 pharmacy staff and 8 GPs near participating pharmacies will be conducted.

Health Inequalities: We will prospectively sample pharmacies from a range of socio-economic areas and explore potential benefit of the intervention though quantitative, economic and qualitative analysis.

1.5. Summary

About 30% of the UK population have long term physical health problems. In those that do, depression is 2-3 times more common than in the general population. Depression alongside long term physical health problems can worsen health outcomes, quality of life and double healthcare costs. People with these conditions are more likely to live in poorer areas, contributing significantly to health inequalities.

For most people with milder depression their symptoms will go undetected/untreated alongside physical health problems. This is disappointing as treatments can help and improve quality of life. One treatment, we recently tested in UK, in people over 65, with mild depression (most with long term health problems), called collaborative care, was acceptable and effective. It reduced depression symptoms at 4 and 12 months and nearly halved progression to major depression, compared to usual primary care. The intervention was delivered by people with no professional healthcare qualification, but who were trained/supported by experts in the approach. It included a psychological self-help treatment called behavioural activation supported by structured phone/face to face sessions, regular use of a mood measurement questionnaire and liaison with the person's GP if needed.

As nine out of 10 people live within 20 minutes' walk of a pharmacy, we think they may provide an excellent public health setting for such an intervention, having a strong presence in poorer communities. Pharmacies are well placed to offer opportunistic psychological support to people with long term physical problems who attend their pharmacy for a range of health related services. In CHEMIST we aim to adapt our intervention and see if it can be delivered by suitably trained community pharmacy staff to adults with mild depression and long term health problems. If beneficial in this setting the intervention could reach many people who remain untreated.

We plan to conduct two phases of research to test if a larger definitive study would be possible. In 'phase one' we will train a small number of pharmacy staff to test our proposed study recruitment, intervention and data collection processes. We plan to recruit 20-30 people via pharmacies, community settings or local GP practices. By using interviews with participants and staff and observing recruitment, intervention acceptance and data completion rates we will refine our research approaches/intervention. In 'Phase two' we will run a randomised controlled trial 'in miniature' with 100 people testing our intervention against 'usual care'. By observing how many people we need to approach, screen and assess to recruit this number and by observing how well we can treat people and collect those data we need, we will be able to decide if a larger study is possible. We will collect a range of questionnaires at the start and at 4 months. We will also conduct detailed interviews with participants and a range of staff to get an in depth understanding of our procedures. If we are successful in meeting our aims we will seek separate funding to run a larger study to reliably answer the question 'does enhanced support in pharmacies work for less severe depression, can it prevent progression to major depression and does it represent value for money'? Local pharmacy networks, pharmacy user groups and local authorities will ensure a fit for purpose intervention is developed.

2. Background

2.1. Introduction

Depression accounts for 4.3% of the global disease burden and causes 63 million disability adjusted life years annually. It is the largest cause of disease burden of all mental health problems and is set to become the highest amongst all health problems by 2030 (1). Two to three fold increase in the prevalence of depression is found across the range of Long term Conditions (LTCs) resulting in poorer outcomes, lower quality of life, a reduced ability to self-manage, substantial increased cost (2) and a significant contribution to health

inequalities.(3) Sub threshold depression, identified by a positive screen on the Whooley questions (4) and between two and four symptoms of depression is highly prevalent and a major risk factor for progression to major depression.(5) With comparable rates of associated excess mortality, (6) estimates of prevalence in community samples from 1.4% to 17.9% (7) and up to 20% in those with LTCs clinical guidelines recommend brief psychological support. (8) However psychological health care services struggle to meet demands of major depression/anxiety and over 80% of 'below threshold' conditions remain untreated in those settings. (9) Psychological interventions reduce depressive symptoms in this population and reduce the incidence of major depression (10) but are not commonly available. We need to move beyond traditional reliance on health services delivery and view sub threshold depression as a public health problem requiring new approaches to its management.

2.2. Rationale for current study

Community pharmacies are ideally placed to offer opportunistic support to people with a range of health problems including low mood. (11) The Healthy Living Pharmacy programme is an example of extending roles (i.e. smoking cessation, weight management) of counter staff through new innovative training programmes. These programmes lend support to the NHS and Public Health England's Five Year Forward View Plan (12) calling for a radical upgrade in public health including new partnerships that "break down barriers" to support people with multiple health problems. The Marmot Review on Health Inequalities (13) recommended a focus on mental health of people with long term health problems due to the uneven socio-economic distribution and impact of such co-morbidities. The content of behavioural change/management approaches to sub threshold depression share much with other public health interventions such as smoking cessation or weight management (goal setting, facilitated self-help, and diary keeping). Therefore these interventions targeted at sub threshold depression may also be suited to delivery by those staff delivering other public health behavioural change programmes. Ninety percent of people live within 20 mins walk of their local pharmacy especially within areas of high social deprivation (14) and with high rates of 'footfall' of people with LTCs they have a unique position to offer enhanced support for any co morbid sub threshold depression alongside other health promotion activities. We have found strong PPI and Stakeholder support for this approach; however high quality evidence is needed to inform the design and delivery of such services. This has led us to our primary public health research question for the CHEMIST Study;

> *'What is the clinical/cost effectiveness and acceptability of enhanced support for sub threshold depression in community pharmacies in adults with long term health problems?'*

Our recently completed study '**C**oll**A**borative care for **S**creen **P**ositive **E**lde**R**s (CASPER)' has provided a fully developed effective intervention for people with sub-threshold depression suited to delivery by non-mental health specialists. To establish the suitability and effectiveness of these interventions as a public health initiative further research is needed to evaluate their utilisation beyond traditional health care settings. Our proposal is to adapt our existing experience of 'what works' for sub threshold depression in primary care and examine if this can be translated to the important public health setting of

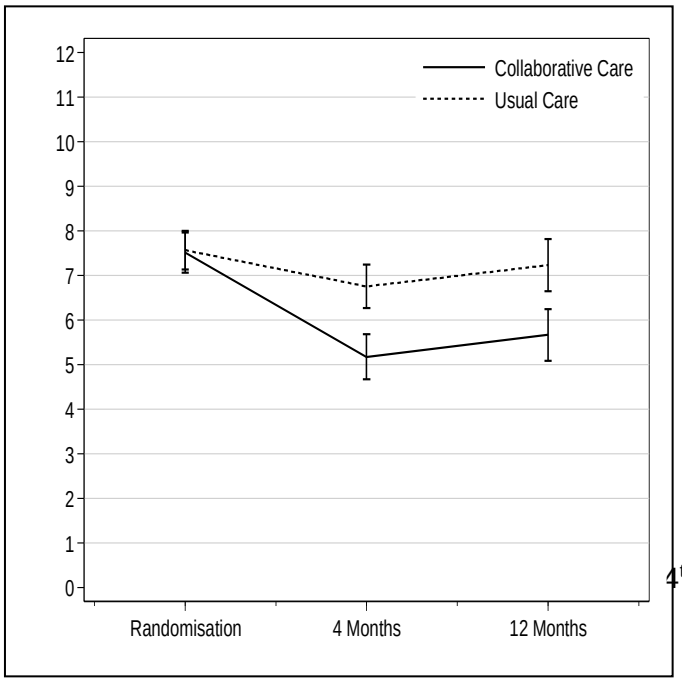
community pharmacy. The current proposal is to conduct a feasibility and pilot study to inform a fully powered evaluation of clinical and cost effectiveness. This will provide new knowledge to inform potential public health agendas related to the national policy push to expand the Community Pharmacy staff role. The main study will also examine the depression prevention value of the intervention, which is of particular benefit to the individual, healthcare system and society (15). Owing to the contribution long term conditions and depression make to health inequalities we will also focus on examining associations between socio economic status and outcomes.

2.3. Enhanced support/collaborative care

Collaborative care ensures delivery of effective forms of treatment (16) and is recommended for depression in people with LTCs by NICE. (8, 17) Members of the CHEMIST research group have contributed to the evidence base of collaborative care for depression via definitive reviews, (18-20) including non-MH specialist services and co morbid LTC (21) and controlled trials (22, 23). The intervention is effective in the short and medium term (24). Most studies however included major depression and anti-depressant support, not indicated in those with sub-threshold depression as a first line treatment (25, 26). Hence the collaborative care framework requires adjustment with a focus on a low intensity psychosocial intervention (termed 'Enhanced Support Intervention', ESI, in this protocol) for sub threshold depression.

2.4. The CASPER study

Our recent NIHR HTA study CollAborative Care for Screen Positive ElderRs (CASPER), (23) tested one such intervention in older adults with sub threshold depression. The intervention consisted of the elements of collaborative care using predominantly a facilitated self-help based upon behavioural activation supported over the phone by non-specialist workers, compared to usual primary care. The study report is now submitted to NIHR HTA. In 586 patients (90% co morbid LTCs) a significant benefit was found in depression symptom level at 4 and 12 months, effect size of 0.30 (see fig) consistent with findings across the literature. (20)



Importantly at 12 months a significant difference was observed in progression to major depression in favour of the intervention,15.7% vs 27.8% (OR: 1.98, 95% CI: 1.21 to 3.25, p=.007). These findings are reflective of depression prevention literature (15) lend support to using the CASPER intervention to target at risk populations. The PHR highlight notice asked for research that utilises community pharmacies' unique position to offer opportunistic public health based interventions for mental health. It is in the context of our findings and this highlight notice that we seek to develop our research beyond primary care, the CHEMIST study aims to test our well-developed enhanced support intervention in a new public health setting of community pharmacy.

2.5. Existing research

In preparation for the CHEMIST study we have conducted extensive searches (Sept/Oct 2014) to identify any relevant existing or ongoing studies (PROSPERO ref CRD42014013517). We identified 18 potential relevant studies. None examined pharmacy counter staff support, public health interventions or sub threshold depression. Existing studies mainly investigate pharmacist medication support in major depression. (27, 28)

2.6. Implications/Why this research is needed now

As highlighted sub threshold depression can be seen as a major public health issue, particularly in those with LTCs. In national policy directives Community Pharmacy is increasingly identified as a potential provider of enhanced services and is uniquely placed to expand these to sub threshold depression. Results of the CHEMIST study will support Local Authority Public Health and policy makers with high quality evidence to inform decision making in relation to the development of extended roles.

3. Research Objectives

From our review of the literature we acknowledge the evidence is not sufficiently robust, or experience sufficiently developed, to propose a definitive trial at this stage in the evolution of this public health intervention. We therefore propose two sets of objectives. The first set of objectives to be met in our feasibility phase will be to refine our intervention and research procedures. Our second set of objectives to be met in our pilot phase will examine key uncertainties in relation to recruitment, acceptability and retention. Findings from these phases will inform the design of the main definitive trial for which separate funding will be sought when progression targets are met.

3.1. Feasibility study objectives

a) Refine the bespoke Enhanced Support Intervention (ESI) (including self-help materials, intervention manual and training) for implementation by community pharmacy (CP) staff to people with sub-threshold depression and LTCs based upon evidence supported interventions in primary care.
b) Develop and refine study procedures (CP recruitment strategies and set up, screening, participant recruitment, assessment, suitability of outcome measures and data collection procedures) for testing in the pilot study phase.

3.2. External pilot study objectives

a) Quantify the flow of participants (eligibility, recruitment and follow up rate) within the CHEMIST study.
b) Evaluate proposed recruitment, assessment and outcome measure collection methods within the CHEMIST study.
c) Examine the delivery of the ESI in a community pharmacy setting (intervention uptake, retention and dose) to inform process evaluation.
d) Process evaluation, using semi-structured interviews with participants, pharmacy staff and GPs across a range of socio-economic settings to explore acceptability of the ESI within CP, elements of the intervention that were considered useful (or not), and appropriateness of study procedures.

4. Progression Criteria

The below criteria will inform our TSC and the PHR funding bodies decision in relation to continuation of the study from feasibility to pilot phase. The pilot to definitive trial criteria is provided to support our TSC and PHR funding body in deciding if a fast track application is appropriate to maintain CHEMIST study momentum.

4.1. Feasibility to Pilot

I. Recruit five participants in each pharmacy by month six.
II. Eighty percent of participants receive two or more ESI support contacts in four month post recruitment.
III. Collect valid primary outcome measure on eighty percent of recruited participants at four months post recruitment.
IV. A fidelity score of ‘acceptable’ (3) or above to be achieved in at least 90% of assessed audio recorded enhanced support sessions.

4.2. Pilot to definitive trial

I. Recruit and randomise 100 participants across 5-6 recruitment sites by month 20.
II. 80% of participants randomised to EIS intervention receive two or more ESI support contacts in four months post recruitment.
III. Collect valid primary outcome measure on 80% participants at four months post randomisation.

5. Research Design

We will undertake a mixed methods feasibility study incorporating qualitative and observational methods. This will be followed by an external pilot randomised controlled trial (RCT) examining clinical and economic data collection with a nested qualitative process evaluation. The theoretical and empirical evidence to justify our intervention choice has been highlighted in previous sections. Both phases of the study will further refine our understanding of the delivery of our intervention and conducting an RCT in this population in community pharmacy settings. This will allow the full trial, if funded to focus on how the intervention is effective as well as if it is effective.

6. Methods - Feasibility study

6.1. Design
An observational study with nested qualitative evaluation.

6.2. Setting
Community pharmacies in the NE of the UK.

6.3. Study population
Inclusion criteria: Adults (18+) with sub threshold depression (screen positive with 2-4 symptoms confirmed by diagnostic assessment tool) and one or more long term condition(s). We use the Department of Health (DoH) definition of LTC 'a condition that cannot, at present be cured; but can be controlled by medication and other therapies'. For the purpose of the CHEMIST study we focus on a range of exemplar conditions linked to pharmacy extended services (New Medicines Service NMS, Medicines Use Review MUR): Arthritis, Cancer, Cardiovascular Conditions, Diabetes, Respiratory Conditions and Stroke.

Exclusion criteria; given the pragmatic nature of the CHEMIST study there will be few exclusion criteria. People who have alcohol or drug dependence, or cognitive impairment, have a bipolar disorder/psychosis/psychotic symptoms, or are acutely suicidal, ascertained by baseline research interviews; and those currently in receipt of psychological therapy.

6.4. Feasibility Recruitment
The PHR highlight notice emphasised the use of opportunistic support to people with mental health problems. It is of note however that recruitment to sub-threshold depression studies within community pharmacy is untested in the UK. Therefore, a key objective of the feasibility study will be to refine potential recruitment approaches to test in the external pilot study. We propose three approaches.

Our first approach will be to use the opportunities to approach potential participants when they use a pharmacy for services associated with LTCs. In preparation for this study we reviewed data gathered across 30 community pharmacies in one year. An average 6522 items (2549-12,241) were prescribed monthly per pharmacy linked with the New Medicines Service (NMS). Assuming half were linked to LTCs included in the CHEMIST study (as NMS is primarily linked to LTC medications) 3261 prescriptions per pharmacy per month, 39,132 year, could be screened. If half of those prescriptions were multiple (19566) and we use a prevalence of sub threshold depression in this population of 10% (midway conservative assumption) this would provide 1957 potential participants per year per pharmacy. In previous studies we identified post screening an eligibility rate of 37%, of those 29% had sub threshold depression and were recruited (N=723 and 209 respectively).

Our second approach will be to advertise the CHEMIST study in pharmacies, General practices and local community support services often used by people with LTCs (guided by our stakeholder and PPI groups). We will provide a central contact point/website for potential participants to self-refer into the study.

Our third approach is to utilise 'catchment' GP practices. GP database searches are commonly used in primary care studies. We are a team experienced in recruiting to target in

a number of large randomised controlled trials for depression in primary care and time such as CASPER (N=780), COBRA (N=440), CADET (N=581), REEACT (N=691), MIR (N=480). While the CHEMIST study is 'public health' focussed the inclusion of this approach in our feasibility and pilot phases will allow benchmarking recruitment approaches 1 and 2 against current best practice in primary care depression studies (3). This will provide useful data for the planning of recruitment in the phase III definitive study.

6.5. Recruitment procedure

It is expected that in most cases, pharmacists or their staff will opportunistically identify eligible patients within the New Medicines Service (NMS) and Medicines Use Review (MUR) service. Additionally, the patient medication record (PMR) can highlight eligibility (see appendix for example list of 'flag' medicines). We intend to mirror this established procedure to identify potential participants to screen in the CHEMIST study. People using study pharmacies for a service associated with our list of LTCs will be informed the pharmacy is involved in the research and provided with a brief CHEMIST study information sheet to review while they wait for their prescription, or to read at home. This information will include the 2 short Whooley depression case-finding questions (29) recommended by NICE (8, 30). A positive answer to one or both questions (screen positive) indicates suitability for further assessment of depression symptoms. This information sheet will inform potential participants that if their response to either/both questions is positive they may be suitable for inclusion in the study. They will be offered a study recruitment pack to take away and read which will include an invitation letter, a participant information sheet, background information questionnaire and a study consent form with a stamped addressed envelope for return to the study team. In addition, each participating pharmacy will have a secure box to deposit forms if the person would prefer this method. For everyone that takes the recruitment pack a verbal "request not to be contacted" or a "permission to contact" will be recorded by the pharmacy staff. The "permission to contact" is a verbal agreement for a member of the research team to contact them to enquire if they have any questions regarding the study. This is not consent to participate. The participant can at this point state they do not want to be contacted and still take a recruitment pack. After a minimum period of 48 hours all those that have given a permission to contact will be followed up with a phone call and asked if they are interested in participating. If they are not or no permission to contact was given no further contact will be made. If they do want to participate they will be asked to return their consent form in the manner described above. Eligible people who receive their pharmacy prescriptions via home delivery services will receive a study recruitment pack with their delivered prescriptions. Interested participants will then need to complete the consent form and return this directly to the study team.

To support the opportunistic identification of eligible patients as described above, we will also conduct searches on pharmacy databases/systems. Such searches will be conducted to identify people with LTCs involved in CHEMIST and will utilise existing pharmacy systems and services, such as the NMS and MUR. Lists of eligible patients will be reviewed by appropriately trained pharmacy staff for exclusion of any patients who it would be inappropriate to invite. Patients who have previously been approached about the study (as recorded on their PMR) via one of the methods described above will be excluded. As per

our approaches when inviting patients via GP database searches (see below), the pharmacy will post study recruitment packs with a pharmacy letter-headed invite letter to potential participants. This will include a postage paid return envelope for potential participants to return a completed consent form and background information sheet to the study team. This method will allow us to determine the response rate to this type of pharmacy-based recruitment method and will also act as a comparator to database searches conducted in GP practices (see below).

On receipt of the consent form the study administrator will record the participant on the study database. A researcher will then contact the participant to arrange to conduct a telephone diagnostic interview (see section 6.6) and check eligibility. A baseline questionnaire pack will then be posted to all eligible participants to complete and return to the study team. On receipt of a completed baseline questionnaire, participants will be randomised (randomisation undertaken in the pilot phase only). There will be a telephone contact point for the study team to answer any potential questions from participants. Information leaflets/letter/consent forms have been produced using the current guidelines on the HRA website and feedback from our PPI stakeholder groups.

The website will include the information sheet and Whooley Questions as per the approach above. Alternatively, this information will be posted to participants who contact the study team by phone. If potential participants make further contact with the study team they will be posted the study recruitment pack and the subsequent procedure will be as per pharmacy recruitment above.

Database searches on GP practice systems will be conducted for people with our LTCs (as per QoF coding systems). These will be refined to postal codes within two miles of the participating pharmacy to ensure suitability of access and lists reviewed by practice staff for exclusion of any patients who it would be inappropriate to invite. As per our approaches used in previously successful primary care studies, the GP practice will then post study recruitment packs with a GP letter headed invite letter to potential participants. This will include a postage paid return envelope to the study team. On receipt of consent we will then follow procedures outlined above.

These procedures will be refined in the feasibility phase to facilitate use and evaluation in the pilot study.

6.6. Diagnostic Confirmation

The presence or absence of depression will be established through a standardised diagnostic interview at baseline conducted according to internationally recognised criteria (DSM IV/ICD10). We will use the Mini International Neuropsychiatric Interview (M.I.N.I) (31) to establish the presence or absence of depression symptoms and disorder (sub threshold/Major). Interviews will be carried out by a trained researcher over the phone. All those screen-positive who have sub threshold depression (2-4 symptoms) will be included in the study (and proceed to randomisation in the pilot phase). All those with screen-positive depression who have major depression will not be included and a letter sent to their general practitioner informing them of the probable presence of depression and a suggestion that

further assessment/treatment should be offered. This process is adapted from those used in previous our primary care studies, considered acceptable to participants and that recruited to target on time.

6.7. Planned interventions

No treatment will be withheld for participants in the CHEMIST study. Enhanced support intervention (ESI); designed and delivered specifically for those with sub threshold depression and long term conditions over 4-6 sessions in a 4 month period delivered via phone or face to face in the privacy of pharmacy consulting rooms. ESI will be adapted from training/treatment materials which have undergone extensive development exploring theoretical framework, acceptability and validity in previous multi centre randomised trials. ESI consists of 4 main elements.

1. Behavioural Activation focussed self-help support. A simple psychological approach focussed upon identifying life changes that have a detrimental impact on psychologically healthy activities, and scheduling to stay well.
2. Proactive follow up. Participants would be supplied with the BA self-help manual and the pharmacy team member would phone/meet the patients at regular intervals to support its use.
3. Symptom monitoring. The pharmacy support staff will monitor symptoms using the depression scale from the Depression Anxiety Stress Scale (DASS) widely used/validated in a UK community context (32). It is brief; simple to score with clear clinical cut off scores (non/mild/moderate severe).
4. Decision supported signposting. Scores on the DASS will be used to guide decision making by pharmacy staff, guided by supervision delivered by co applicants (DE/DM). Where risk or significant clinical deterioration is noted the patient would be supported to access more formal healthcare interventions.

We as a study team have extensive experience in training and supporting non-specialists in this approach. Supervision will be provided via the phone on regular basis (DE, DM). Patient materials will be reviewed to ensure suitability for use in areas of high social deprivation and staff trained to manage delivery when low levels of literacy block use. Our proposed intervention has been reviewed by PPI and stakeholder groups with a broad consensus of suitability for delivery in this community setting.

6.8. Who will deliver the intervention?

In the CHEMIST study the enhanced support intervention will be delivered by pharmacy support staff experienced in delivery of extended roles (such as smoking cessation behavioural change approaches) and/or training to Royal Society of Public Health standard (Understanding Health Improvement Level 2). Support time will be scheduled alongside other public health behavioural change duties and carried out face to face or on the phone in private consultation rooms which will be available in all CHEMIST identified pharmacies. Ongoing collaboration with Local Pharmacy Networks/LPCs will guide staff training standards.

6.9. Fidelity

Fidelity will be supported by facilitator manuals and training adapted from those used in previous studies. In addition, we will use a bespoke competency assessment, again based upon experience from previous studies at the end of training to ensure facilitators are able to support the intervention. Audio recording will be undertaken of telephone support sessions in the feasibility stage. A random selection of recordings (10-20%) across the different phases of the intervention (early/late) will be collected from each facilitator of the intervention and independently reviewed. We will adapt a fidelity assessment tool used in previous supported self-help studies (NIHR OCTET study) to score recordings on Likert scales (1=unacceptable, 3=average, 5=excellent). Based upon previous experience we would expect scores to be above 3 to indicate community pharmacy staff's ability to deliver our intervention (see feasibility to pilot progression criteria iv).

6.10. Outcome measures

Primary outcome measure depression severity: Self-reported depression severity (as measured by the Patient Health Questionnaire 9 PHQ9 (33). Widely used in clinical trials and settings the PHQ9 provides excellent internal and external validity. Members of the CHEMIST team have established PHQ9 specificity/sensitivity in a UK population (34).

6.11. Secondary outcome measures

Prevention of depression: Binary Depression Severity (PHQ9), using scores ≥ 10 to designate moderate depression caseness at follow up (measuring the preventive aspects of the intervention in their ability to prevent progression of depression). Our previous CASPER study identified a significant reduction in depression at 1 year in the intervention group. This is an outcome of particular public health interest if replicated in community pharmacies. This measure is included to mirror procedures to be undertaken in the main study if funded.

Anxiety: General Anxiety Disorder scale (GAD7) (35) is widely used in clinical trials. Anxiety commonly co-occurs with sub threshold depression and with LTCs. We found reduction in anxiety in previous studies and if replicated in community pharmacy will be an important secondary outcome.

Quality of life: Health related quality of life will be collected on (SF-12v2) (36); health-state utility (EQ5D-3L) (37).

Health service use/Economic Outcomes: Participants' use of enhanced support will be collected from pharmacy electronic records e.g. Pharm-Outcomes and directly from therapist records. Other health and social care services used, including productivity losses will be collected via an adapted version of the Adult Service Use Schedule (AD-SUS). For further details see health economics section below

Process measures: Moderators; depression severity (PHQ9), age of onset (MINI), number of episodes (MINI), long term condition and socio economic status will be collected at baseline interview. The socio-economic status of participants will be established using the participant's postcode which directly maps to small area level geography (also known as lower layer super output area, or simply LSOA) in England. Then using the national database of Index of Multiple Deprivation for all small areas in England, we will establish the deprivation level of each participant.

Mediators; number of contacts, level of activation Behavioural Activation for Depression Scale (BADS) collected at treatment sessions (38)

Baseline Demographic Measures: DOB, ethnicity, education level, socio economic status, sex.

6.12. Assessment and Follow up

Clinical, demographic and economic measures will be collected at invitation, baseline and four months (see table 1 appendix for schedule of data collection).

Invitation. Demographic questionnaire, Whooley questions, physical health conditions.

Phone based diagnostic interview: The major depressive episode module of the Mini International Neuropsychiatric Interview (MINI).

Baseline measure pack (post and telephone interview): PHQ9 depression symptom level, GAD7 anxiety, Whooley Questions and Socio-Demographic details and physical health problems (PHQ 15) (39). Quality of life measures (SF12v2 and EQ5D-3L). Medication use and service use data will be collected on a health resource questionnaire (modified ADSUS).

Four Months post baseline (post and telephone interview): PHQ9 depression symptom level (primary outcome), GAD7 anxiety. Quality of life measures (SF12v2 and EQ5D-3L), Medication use and service use data will be collected on a health resource questionnaire (modified ADSUS).

NHS numbers for each participant will be obtained at the outset for all consenting participants to enable the study team to follow participants who move address. All above measures are completed by the participant; (Except MINI). We will adopt a combination of postal/telephone data collection in line with the NIHR carbon reduction policy and cost efficiency. This approach is adapted from successful procedures in the CASPER study (83% follow up at 4 months).

6.13. Assessment of Harms

Adverse events will be monitored as per the trial Standard Operating Procedures and Good Clinical Practice guidelines approved by our DMEC/TSC and sponsor. Assessment of adverse events will be taken at each outcome point by trained researchers. In addition, CHEMIST pharmacy staff will monitor and report adverse events (see study governance arrangements).

6.14. Sample Size

No formal sample size calculation has been undertaken for the feasibility study. A sample size of 20-30 participants recruited will be sufficient to meet feasibility phase objectives.

6.15. Outcomes and data analysis.

As we are assessing feasibility we will assess study implementation (recruitment and attrition rates, quality of data collection) at baseline and 4 months and ESI adherence

(number of contacts, DNA and drop out) as per objectives. Rates will be reported descriptively.

6.16. Qualitative Study

In-depth interviews will be conducted with up to ten patient participants (purposively sampled across pharmacy location and with a mix of LTCs, from different areas of deprivation and up to 10 ESI facilitators. Additional focus groups will be conducted with pharmacy staff to explore the feasibility and acceptability of the training, intervention and study procedures. Existing literature will be used to develop topic guides, which will be amended in light of the findings from previous interviews. The Normalisation Process Theory (NPT) approach (40) will be used to develop topic guides, and provide a framework for analysis and interpretation of data in order to identify the barriers and facilitators to implementation. This approach has been used in previous studies by members of the CHEMIST team (41).

Analysis will inform adaptations to the intervention materials, training and study procedures for the pilot study. By month 12 we will have an ESI intervention and study procedures amenable to evaluation in a clinical trial.

6.17. Qualitative study recruitment

Recruitment of patient participants for qualitative interviews will be included in the process outlined in section 6.5.

Staff involved in CHEMIST (particularly those staff involved in the delivery of the interventions) will be contacted directly by the study team by letter and provided with the staff participant information sheet and consent form. They will be provided with pre paid envelopes to return the documentation directly to the study team. This process will be carried out independently of the pharmacy to ensure it is free from coercion from employers or co workers. All data collected will be anonymised by the qualitative research team prior to reporting to ensure confidentiality of participants

7. Methods External Pilot Study

7.1. Design

An external pilot Randomised Controlled Trial including nested process evaluation and economic evaluation.

7.2. Setting

Six Community Pharmacies in NE UK sampled across quintiles of area level deprivation.

7.3. Population

As Above.

7.4. Recruitment procedures

We will use recruitment procedures as detailed in 6.5 above but with the following refinements based on evaluation of recruitment procedures in the feasibility study

People using pharmacy services who are identified as having one of the study LTCs will be informed the pharmacy is involved in the research. However, rather than being provided with a brief CHEMIST study information sheet in the first instance as described in the feasibility phase, eligible people will instead be provided with the study recruitment pack to take away and read from the outset. The invitation letter will still include the 2 short Whooley depression case-finding questions (29). Consent forms will be accepted as valid if participants place a tick/cross (rather than their initials) in the consent statement boxes, provided that they have printed their name, and signed and dated the form.

The procedure for conducting database searches on GP practice systems will be adapted. Searches will not be refined to postal codes within two miles of the participating pharmacy to promote feasibility of conducting searches for GP practice staff. The invitation letter accompanying GP mail outs will be individualised to the participating pharmacy. Lists of eligible patients will still be reviewed by practice staff for exclusion of any patients who it would be inappropriate to invite.

Remaining recruitment processes and procedures are as detailed in 6.5 above.

Documents used via each recruitment approach will include relevant coding for identification and subsequent evaluation of recruitment yield.

7.5. Assessment and follow up

As detailed above. Information about somatic symptoms (PHQ-15) will not be collected.

Participants will be offered the option of completing baseline and follow-up questionnaires over the telephone or via post.

7.6. Intervention

As above with adaptations post feasibility study.

7.7. Comparator

The control group will be usual primary care management of sub threshold depression offered by their GP and other local community provision.

7.8. Outcome measures

As above

7.9. Sample size

This will be an external feasibility trial of a complex public health intervention where the primary purpose is to test the feasibility of the new intervention and the methods of recruitment, randomisation and follow up for a full trial in this population. Sample size calculations are based on estimating attrition and standard deviation of the primary outcome. Assuming 20% of participants are lost to follow up (17% in the CASPER trial) with a sample size of 100, then the 95% confidence interval for this level of attrition will be

the observed difference ±8 percentage points (i.e. between 12% and 28%)(42). Hence, an external pilot trial of 100 participants should ensure robust estimates of recruitment and follow-up in this population. Furthermore, an external feasibility study of 80 measured subjects will provide robust estimates of the standard deviation of the outcome measure in this population to inform the sample size calculation for the subsequent larger definitive fully powered trial (43).

7.10. Randomisation and allocation concealment

Individual independent randomisation (York CTU, NIHR reg 40) is to be used. We feel the risks of contamination are minimal in this study and the disadvantages of clustering outweigh these. Randomisation will be carried out by York Trials Unit online Randomisation Service (URL:www.yorkrand.com/) independently of the trial team. One hundred participants will be randomised into the trial on a 1:1 basis to either the intervention group (50) or control group (50) following the completion of the diagnostic interview. Post randomisation participants will be contacted informing them of their group allocation, if ESI the pharmacy worker will be informed and initiate contact. The participant's GP will be informed that the patient was eligible to take part in the CHEMIST study specifying allocation. This approach is established within the YTU and successfully used in previous studies.

7.11. Outcome and data analysis

The flow of participants through the trial will be detailed in a CONSORT flow diagram (see appendix). The number of people screened, randomly assigned, receiving the intervention, completing the study protocol and providing outcome data will be summarised overall and by trial arm. The number of individuals withdrawing from the intervention and/or the trial and any reasons for withdrawal will be summarised by trial arm. To quantify the acceptability of the intervention the number of sessions attended will also be summarised.

While the main aim of this study is to establish practicality, feasibility, recruitment rates and key parameters for the sample size in order to inform a full-scale trial, and although it is unlikely that the small sample size will result in effectiveness being established, we will none the less test the primary outcome to mimic practice for full-scale trial. We must emphasise that results from this analysis will be treated as unreliable and interpreted with caution. (44, 45)

The two treatment groups will be compared for the primary outcome (PHQ-9 at 4 month follow up) using linear regression with adjustment for important baseline covariates. Estimates from the model and 95% CI will be presented. We may also explore the impact of pharmacy effects. The potential impact of 'pharmacy effects' will be quantified using ICC estimates with 95% confidence intervals and the average caseload per pharmacist. All secondary outcomes will be summarised descriptively by treatment arm using mean, SD, 95% confidence intervals, median, 25th and 75th percentiles for continuous outcomes; and the number of events and percentages for categorical data.

7.12. Health economics

The economic analysis will evaluate the feasibility of collecting resource use and health-related quality of life (HRQoL) data in people with long term health conditions and sub threshold depression. It will enable us to identify relevant resource use categories for the cost-effectiveness analysis and evaluate feasibility and challenges of measuring costs and outcomes in the study population. Feasibility of collecting resource use data will be evaluated using an adapted version of the Adult Service Use Schedule (AD-SUS) previously established in depression studies (46, 47). Using this adapted instrument, the following data will be collected at individual-level:

I. Use of primary and secondary health care resource use, including visits to/consultations with GP, nurse, pharmacy (excluding study-related visits), psychotherapist, psychologists, psychiatrists and counsellors; also, medication use and hospital admissions will also be recorded.
II. Use of social care, including visits by/consultations with social worker, family support worker and family therapist.
III. Use of advice services (e.g. Citizen's Advice Bureau) or helplines (e.g. Samaritans).
IV. Lost work and productivity (including full and partial days of work lost).

We will also assess the feasibility of collecting intervention costs and acquiring unit cost data for all resource use categories. Unit costs will be searched in reference cost databases, including Unit Costs of Health and Social Care report (produced by Personal and Social Services Resource Unit, PSSRU), NHS Reference Costs database and British National Formulary unit costs.

To assess HRQoL, EQ-5D and SF-12 questionnaires will be used. The EQ-5D instrument assesses quality of life today in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression (48). The SF-12 instrument assesses health during the past 4 weeks and is usually presented in terms of physical and mental health domains (49). Both measures are psychometrically valid instruments (50). While both instruments are commonly used in mental health trials, the literature indicates that they may provide different health-related utility scores and may produce different cost-utility estimates. We will also compare changes in HRQoL based on these instruments with changes in PHQ-9 responses.

Our primary analysis will focus on questionnaire completion rates and item-level rates of missing data at each time point for both resource use questionnaire and quality of life instruments. Also, the level of resource use and utility levels (and quality-adjusted life years) will be presented for each group.

We will also evaluate the feasibility of conducting a cost-effectiveness analysis using resource use and quality of life instruments data. We will conduct a cost-utility analysis using the EQ-5D and SF-12 responses which will be converted into utility scores using UK population algorithms. Then we will use the area under the curve approach to calculate quality-adjusted life years (QALYs) for both groups. To estimate the incremental difference in costs and QALYs, we will use regression approach which will control for baseline characteristics of patients, particularly baseline utility. The regression coefficient will provide the estimate of the incremental difference in QALYs and costs between the treatment and

control arms. We will use bootstrap approach to get confidence interval around the incremental cost-effectiveness ratio. The results will be presented on cost-effectiveness plane and as cost-effectiveness acceptability curve to evaluate the probability of being cost-effective against the commonly used willingness-to-pay threshold in the UK.

For our inequalities analysis, we will evaluate the distribution of uptake rate of screening and health benefits of the intervention (measured using EQ-5D) by socioeconomic quintiles. This will inform whether the intervention is more or less likely to benefit certain socioeconomic groups. This preliminary analysis will also allow us to understand the feasibility of extending our economic evaluation approach to conduct a distributional cost-effectiveness analysis if a full study is conducted.

7.13. Process evaluation

As per UK MRC recommendations in our full study (if funded) we will use a mixed methods approach to process evaluation (51) to consider fidelity, implementation, mechanisms and context. Descriptive statistics will be used to describe elements of the intervention (participants, dose and intervention content). Moderational analysis will examine baseline variables that may moderate outcomes such as age, depression onset age, number of episodes and socio economic status. Mediational analysis will investigate hypothesised mechanisms of change such as number of sessions, content of scheduled contacts (from pharmacy staff records) and changes in activation (BADS) using established methodology (52). In the external pilot we would be considerably underpowered to undertake these evaluations so data will be summarised and used to refine process evaluation design in the full study.

A process evaluation using qualitative methods will be used to explore acceptability and important elements of the intervention from the perspective of the participants. A purposive sample of approximately15 participants who completed the intervention will be invited to participate in a semi-structured interview (recruitment and data collection will continue until category saturation has been achieved). Sampling will ensure that participants with a range of age and gender are sampled, and from a range of socio-economic groups. The interviews will explore acceptability of case-finding for sub threshold depression, receiving the ESI intervention within a community pharmacy setting, impact on relationship with general practice and research procedures. A sample of participants who dropped out (had less than 2 sessions) will also be invited to participate in a semi-structured interview to explore reasons for drop out. It is likely that approximately15 interviews will be needed to achieve data saturation (53).

We will ensure sampling, in areas of higher deprivation (i.e. bottom two quintiles of IMD) to enable us to explore perspectives of people particularly from lower SES. We will ensure that we explore perceptions of the appropriateness of the intervention for people with poor health literacy and from lower SES. All interviewees will be interviewed at a time and place convenient to them (e.g. at home, in the pharmacy, GP surgery, or by telephone).

Interviews with patient participants will be conducted after the primary outcome data has been collected.

Interviews with approximately20 pharmacy staff (across a broad range of pharmacy roles) will examine acceptability and important elements of the intervention, training and supervision, barriers/ facilitators to participation and implementation, and impact on pharmacy practice.

Interviews with approximately8 local GPs will explore knowledge and perspectives of the intervention, impact on routine practice and how this intervention might be implemented in practice.

We will explore differences in data from participants with different social economic status (SES) and area-level deprivation.

Semi-structured interviews offer opportunities to cover in-depth, a range of topics relevant to the research questions, whilst also allowing for exploration and probing of additional issues raised during the interview. Interviews topic guides will vary by group; these may be amended iteratively as interviews progress but will contain core questions highlighted in the feasibility phase of the study. Interviews will last up to an hour and will be digitally recorded with consent and transcribed verbatim, the transcripts forming the data for analysis. Coding will be undertaken independently by members of the qualitative research team with meetings to ensure emerging codes remain grounded in the original data. Initial analysis will use the principles of constant comparison, which will allow modification of the topic guides, and analysis across the data sets (52). Further analysis will use the principles of framework analysis and NTP (40). CCG is experienced in this approach and will lead the qualitative evaluation, supervising the qualitative researcher.

7.14 Recruitment Pilot Qualitative Evaluation

As outlined in section 6.17 patient participants will be recruited for qualitative interviews as per the study recruitment procedure.

Pharmacy staff will be contacted directly by the study team independent of the pharmacy management structures. Those staff involved in the delivery of the intervention will be provided with the staff participant information sheet and consent form upon completion of their intervention training. Remaining pharmacy staff will be contacted by letter and provided with the same study information. All pharmacy staff will be provided with pre-paid envelopes to return the consent form directly to the study team. A reminder letter will be sent once the intervention delivery has commenced in each participating pharmacy. Consent forms will be accepted as valid if participants place a tick/cross (rather than their initials) in the consent statement boxes, provided that they have printed their name, and signed and dated the form. Processes will ensure participation is confidential and free from any coercion by employers or co workers.

GPs of recruited participants and GPs in participant identification sites will be contacted by letter and invited to take part. They will be provided with PIS, consent form and pre paid envelope to return to the study team.

8. Health Inequalities

8.1. Rationale

A key secondary outcome of the CHEMIST study is to assess how the effects of the intervention might vary by SES. The Marmot Review of Health Inequalities in England (2010) task group 8 on 'priority public health conditions' (54) recommended that the mental health care of people with physical health problems be improved to enhance public health and reduce health inequalities given the uneven socio-economic distribution of such co-morbidities. Community pharmacies are very accessible: 99.8% of those living in deprived areas have a pharmacy within a twenty minute walk (14). A concern for differential effects of the CHEMIST intervention by socio-economic status will therefore be embedded across all elements of the study, sampling frame, analysis of effectiveness, health economics and process evaluation. In the external pilot we will model this approach in miniature in preparation for the full study exploring data completion rates in association with Index of Multiple Deprivation (IMD).

8.2. Sampling

The IMD is the basis for our sampling frame, with pharmacies recruited from across all quintiles of area-level deprivation. We will use our Fuse Geohealthcare database which has the geographical location of all pharmacies in England, matched to the IMD score of the ward in which they are located to achieve this socio-economically diverse sample (14).

9. Managing Bias

Trials in this field are methodologically challenging but are now informed by our experience completing CASPER and other trials. We will achieve high levels of participant retention, follow-up and completeness of data equally across arms by the use of postal questionnaires with telephone reminders. To maintain blindness researchers will remind patients not to discuss treatment in all contacts. The use of a registered trials unit to allocate and manage data ensures high quality study management using best practice standards. The study will closely monitor follow up rates and use multiple methods (phone, email, post) to maintain contact with participants and obtain follow up data. Missing data will be managed using the most up to date methods and outlined in the statistical analysis plan. Performance bias will be addressed by the use of treatment manuals, therapist records and supervision.

10. Ethical arrangements

We are aware that people with sub-clinical depression and health problems represent a vulnerable group. We do not anticipate any major ethical issues as we offer interventions recommended in guidance issued by NICE. (25) Where participation in this trial is felt to be detrimental to health and wellbeing, we will not make an approach to participate. The ethical aspects of the CHEMIST trial will be subject to full consideration by the University of York Department of Health Sciences Research Government Committee, the Health Research Authority (HRA) and the NHS REC system. Sponsor and local pharmacy governance arrangements will be complied with. Patients will not be denied any form of care that is currently available in the NHS by participating in the trial, subject to local provision of

services. Our key research question relates to the delivery of a public health based support intervention which will be offered in addition to 'usual NHS care'.

10.1. Risks and anticipated benefits for trial participants and society

All participants will receive usual GP care, and therefore no treatment will be withheld. This trial may in fact benefit individual participants, since enhanced support (or any other form of psycho-social care) is not routinely offered to our target group (screen-positive sub-threshold depression and LTC). By participating, participants will also receive a more intensive level of monitoring than that normally received. Our therapists and researchers will be trained in risk assessment with clear standard operating procedures relating to risk management and protection of participants. At all times a clinically qualified member of the study team will be on call to offer support and guidance. Patients who become more depressed or become suicidal will be more readily identified and directed to appropriate services.

10.2. Informing potential trial participants of possible benefits and known risks

The patient information leaflets will provide potential participants with information about the possible benefits and known risks of taking part in the trial. Participants will be given the opportunity to discuss this issue with their GP, health professional, pharmacist or trial coordinator prior to consenting to participate. The trial coordinator will inform the participant if new information comes to light that may affect the participant's willingness to participate in the trial.

10.3. Obtaining informed consent from participants

Potential participants will receive an information pack about the trial. The pack will contain an invitation letter, patient information leaflet(s), consent form(s) and baseline screening questionnaire. The information leaflets will be produced using the current guidelines for researchers on writing information sheets and consent forms, posted on the HRA website. Participants who wish to partake in the trial will return their completed consent to the study team. A contact point will be available to answer any questions. The researcher will contact the participant to arrange diagnostic interview and answer any questions. Written informed consent will be obtained prior to contact from the study team.

10.4. Withdrawal of participants

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

10.5. Proposed time period of retention of relevant trial documentation

Paper copies of the relevant trial documentation from the study will be held securely for a period of 10 years at York trials Unit whilst anonymised electronic copies will be held indefinitely in line with open access data policies.

11. Service User and stakeholder Involvement

The CHEMIST study has been developed in partnership with the University of Durham Pharmacy PPI group. Members of the group provided feedback on the study and intervention design and materials through face to face group discussions and follow up emails. In addition, the Tees Esk and Wear Valleys NHS FT service user research consultation group provided comment on study design and materials.

From initial consultations with these two PPI groups we have established an advisory group with who we will consult for the duration of the study. They will provide on study procedures and materials. The group will convene at least twice yearly. From this group we will appoint a member to join the study TMG to provide PPI input.

A special interest group made up of local public health specialists and community pharmacy staff (pharmacist and counter staff) has met on 3 occasions during the development of the CHEMIST study to advise on procedure and materials. In addition, regular meetings with the Local Pharmacy Committees and the Local Pharmacy Networks in the Durham, Tees and N Yorkshire area ensured processes within the study are realistic within the community pharmacy setting.

12. Governance arrangements

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.

12.1. Trial registration

This feasibility and pilot study will be added to the ISRCTN registry with details available relating to methods, outcome and analysis plan.

12.2. Trial sponsorship

Tees, Esk and Wear Valleys NHS foundation Trust (TEWV) has agreed to act as sponsor for the trial. Sponsor representative is Sarah Daniel.

12.3. Trial Management

The Chief Investigator (Dr David Ekers) will have oversight of the entire project and ensure timelines are adhered to and manage the team. The Trial Manager will oversee the day to day running of the trial including standard operating procedures. A Trial Management Group (TMG), composed of the grant applicants and Trial Manager, will meet at least every 6 months to discuss progress of the study.

12.4. Trial Oversight

A Data Monitoring & Ethics Committee (DMEC) and a Trial Steering Committee (TSC) will be set up to monitor the progress of the trial (in relation to recruitment and follow up) and review adverse events that are thought to be treatment related and look at outcome data regularly during data collection. The TSC/DMEC will be independent and include at minimum an academic chair, a clinician, a statistician and a health economist. Both the TSC/DMEC will meet at least once a year.

12.5. Monitoring adverse events and risk management

This trial is a non-CTIMP (Clinical Trial of an Investigational Medicinal Product) and is therefore not subject to any additional restrictions. Decisions regarding prescription medications will be made by the participant in conjunction with their GP; study participation will have no bearing on this.

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

Serious Adverse Event (SAE): an untoward occurrence (whether expected or not) that:-

- Results in death
- Is life-threatening (refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of congenital anomaly or birth defect
- Is otherwise considered medically significant by the Investigator

An SAE occurring to a research participant will be reported to the REC where in the opinion of the Chief Investigator the event was:

"Related" – that is, it resulted from administration of any of the research procedures, and

"Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted within **15 days** of the Chief Investigator becoming aware of the event, using the SAE report form for non- CTIMPs published on the HRA website:

http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

The Chief Investigator will include a report on the safety of participants in the annual progress report. The Chief Investigator will ensure Tees Esk and Wear Valleys NHS Foundation Trust, as Sponsor, is notified of any SAEs in accordance with local policy. Local investigators will report any SAEs as required to the local Research & Development Office. The Chief Investigator will establish how regularly the TSC/DMEC wishes to be updated with relation to SAEs and AEs at the initial TSC/DMEC meeting.

12.6. Suicide and self-harm risk management

Inherent in the nature of the population under scrutiny is the risk of suicide and deliberate self-harm. We will follow good clinical practice in monitoring for suicide risk during all encounters with trial participants. Where any risk to patients due to expressed thoughts of self-harm is encountered, we will report these directly to the GP (with the patients' expressed permission) or if an acute risk is present we will seek advice from the general practitioner immediately. If a risk develops into an event the procedures for reporting Serious Adverse Events will be used.

13. Monitoring, quality control and assurance

The trial will be managed in collaboration with York Trials Unit. The Chief Investigator will be responsible for the day-to-day study conduct at site. Quality control will be maintained through adherence to SOPs, study protocol, the principles of GCP, research governance and clinical trial regulations. This is a low risk trial and major safety data are not anticipated. Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by TEWV. The main areas of focus will include consent, serious adverse events and essential documents in study. All monitoring findings will be reported and followed up with the appropriate persons in a timely manner. The study may be subject to inspection and audit by TEWV under their remit as sponsor and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit study-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

14. Timetable and milestones

Project set up/intervention refinement meetings (months -6-2). Feasibility study recruitment and intervention delivery (months 2-8), analysis/write up (months 9-12). Pilot study site set up (months 10-12), recruitment/intervention delivery (months 12- 19), follow up (months 20-24) and analysis/write up (months 24-28).

15. Relevant Expertise/Contribution

Dr David Ekers (Chief Investigator) was a Senior Clinical Lecturer at Durham University School for Medicine Pharmacy and Health, a Nurse Consultant in primary care mental health with Tees Esk and Wear Valleys NHS Trust, and a Senior Visiting Research Fellow at the University of York. He is an experienced health services researcher and senior clinician, having led major sites on large multi-centre studies (CASPER/COBRA) and large clinical services. He is a leading researcher on the dissemination of Behavioural Activation and the psychiatric nurse representative on the NICE Depression Guideline development group. Professor Simon Gilbody is an experienced health services researcher/honorary consultant psychiatrist. He has led numerous multi-centre RCTs (CASPER/CASPER Plus, REEACT, SCIMITAR) and advises on NIHR funding panels (HTA, PGfAR), NICE guideline development groups. He will advise on intervention, trial management and mentor D Ekers in the CI role. Dr Dean McMillan is a Clinical Psychologist with further specialist training in Cognitive Behaviour Therapy and an experienced health services researcher. He is co-applicant on six NIHR-funded studies (BaBY PaNDA, CAMEOS, CASPER, CASPER PLUS,

COBRA, OCTET) and has expertise in the development and evaluation of brief psychosocial treatments and will support D Ekers in training and supervision. Professor Carolyn Chew-Graham is an academic GP with expertise in qualitative research methods and process evaluation of mental health interventions in primary care and will lead the qualitative evaluation. Professor Clare Bambra has expertise in health inequalities contributing to the Marmot Reviews of Health Inequalities in England/Europe, is health inequalities lead for the Centre for Translational Research in Public Health, is a co-Investigator on a NIHR SPHR grant into health inequalities and PI. She will advise on lead HI. Dr Adam Todd has experience implementing and evaluating public health interventions in community pharmacy especially accessibility in relation to social deprivation. He is a trained pharmacist and will support training/dissemination. Dr Cate Whittlesea is a Professor of Pharmacy Practice, leads a research group implementing alcohol interventions and has experience of NIHR HTA funded trial delivery of innovative interventions in community pharmacies. With links to the RPS and the Research Ready Pharmacy Scheme she will support the role out of the CHEMIST study. Ms Claire Jones is a Public Health Pharmacist with Durham County council and lead for Healthy Living Pharmacies. She will support intervention adaption, roll out and dissemination. Mr Jay Badenhorst is Superintendent Pharmacist at Whitworth Pharmacies and chair of Tees LPC. He will support intervention adaption and roll out and engagement with LPCs. Catherine Hewitt is Professor of Trials and Statistics and Deputy Director of York Trials Unit. She has 13 years' experience of designing and analysing trials across a spectrum of health and social sciences topic areas. CH was a co-applicant and senior statistician on the CASPER trial and will be leading the statistical aspects of the proposed evaluation/supervising the trial statistician. She will oversee YTU performance. Ada Keding has experience in the design and analysis of randomised controlled trials with emphasis in mental health and will be the trial statistician. Dr Shehzad Ali is health economist and a medical doctor with expertise in empirical methods used in applied health economics research. He will lead the cost effectiveness analysis. The York Trials Unit is embedded within the Department of Health Sciences, YTU undertake national, scientifically rigorous studies of the effectiveness and efficiency of existing or potential health care interventions. YTU primarily undertakes large pragmatic trials and has evaluated a wide range of health care interventions. The Unit has a strong methodological research interest and often undertakes evaluations of complex interventions. The research team have worked in partnership with the YTU to run a number of successful multi centre RCTs (CASPER, REEACT, OCTET).

16. References

1. World Health Organisation. The global burden of disease: 2004 update. Geneva: World Health Organisation, 2008.

2. Naylor C, Parsonage M, McDaid D, Knapp M, Fossey M, Galea A. Long Term Conditions and Mental Health: The cost of co-morbidities. The Kings Fund, 2012.

3. Mercer SW, Watt GCM. (2007). The Inverse Care Law: Clinical Primary Care Encounters in Deprived and Affluent Areas of Scotland. Annals of Family Medicine.5(6):503-10.

4. National Institute for Health and Clinical Excellence. Common mental health disorders: identification and pathways to care. London: NICE, 2011.

5. Cuijpers P, de Graaf R, van Dorsselaer S. (2004). Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. Journal of Affective Disorders. 79(1–3):71-9.

6. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. (2013). Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. The British Journal of Psychiatry. 202(1):22-7.

7. Rodriguez M, Nuevo R, Chatterji S, Ayuso-Mateos J. (2012).Definitions and factors associated with subthreshold depressive conditions: a systematic review. BMC psychiatry. 12(1):181.

8. National Institute for Health and Clinical Excellence. NICE clinical guideline 91:Depression in adults with a chronic physical health problem. London: NICE, 2009.

9. McManus S, Meltzer H, Brugha T, Bebbington P, Jenkins R. Adult psychiatric morbidity in England 2007: Results of a household survey. Leeds: 2009.

10. Cuijpers P, Koole SL, van Dijke A, Roca M, Li J, Reynolds CF, (2014) Psychotherapy for subclinical depression: meta-analysis. The British journal of psychiatry. 205(4):268-74.

11. NHS Confederation. Health on the high street: Rethinking the role of community pharmacy. 2013

12. NHS and Public Health England's Five Year Forward View Plan. http://www.england.nhs.uk/ourwork/futurenhs/5yfv-fore/ (accessed September 2, 2016)

13. Marmott M. The Marmot review final report: Fair society, healthy lives. 2010

14. Todd A, Copeland A, Husband A, Kasim A, Bambra C. (2014) The positive pharmacy care law: an area-level analysis of the relationship between community pharmacy distribution, urbanity and social deprivation in England. BMJ Open. 4(8).

15. van Zoonen K, Buntrock C, Ebert D, Smit F, Reynolds C, Beekman A, et al. (2014) Preventing the onset of major depressive disorder: A meta-analytic review of psychological interventions. International Journal of Epidemiology. 43(2):318-29.

16. Simon G. (2006) Collaborative care for depression. British Medical Journal. 332:249-50.

17. Chew-Graham C, Baldwin R, Burns A. (2004). Treating depression in later life. British Medical Journal. 329(7459):181-2.

18. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Archives of Internal Medicine. 166:2314-21.

19. Gilbody S, Whitty P, Grimshaw J, Thomas R.(2003). Educational and organizational interventions to improve the management of depression in primary care: a systematic review. JAMA. 289:3145-51.

20. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, et al. (2012).Collaborative care for depression and anxiety problems. Cochrane database of systematic reviews . 10.

21. Ekers D, Murphy R, Ebenezer C, Archer J, Kemp D, Gilbody S. (2013). Nurse-delivered collaborative care for depression and long-term physical conditions: a systematic review and meta-analysis. Journal of affective disorders. 149:14-22.

22. Richards D, Hill J, Gask L, Lovell K, Chew-Graham C, Bower P, et al. (2013) Clinical effectiveness of collaborative care for depression in UK primary care (CADET): cluster randomised controlled trial. BMJ. 347:f4913.

23. Mitchell N, Hewitt C, Adamson J, Parrott S, Torgerson D, Ekers D, et al. (2011) A randomised evaluation of CollAborative care and active surveillance for Screen-Positive ElderRs with sub-threshold depression (CASPER): study protocol for a randomized controlled trial. Trials. 12:225.

24. Gilbody S, Bower P, Whitty P. (2006) The costs and consequences of enhanced primary care for depression: a systematic review of randomised economic evaluations. British Journal of Psychiatry. 189:297-308.

25. National Institute for Clinical Excellence. Depression: core interventions in the management of depression in primary and secondary care. London: HMSO; 2004.

26. Baldwin RC, Anderson D, Black S, Evans S, Jones R, Wilson K, et al. (2003) Guideline for the management of late-life depression in primary care. International Journal of Geriatric Psychiatry. 8(9):829-38.

27. Rubio-Valera M, Serrano-Blanco A, Magdalena-Belio J, Fernandez A, Garcia-Campayo J, Pujol MM, et al. (2011) Effectiveness of pharmacist care in the improvement of adherence to antidepressants: a systematic review and meta-analysis. The Annals of pharmacotherapy. 45(1):39-48.

28. Al-Jumah KA, Qureshi NA. Impact of pharmacist interventions on patients' adherence to antidepressants and patient-reported outcomes: a systematic review. Patient preference and adherence. 6:87-100.

29. Whooley M, Avins A, Miranda J, Browner W. (1997) Case-finding instruments for depression: 2 questions are as good as many. J Gen Intern Med. 12:439 - 45.

30. National Institute of Clinical Excellence. Management of Depression in Primary and Secondary Care. London: NICE, 2009.

31. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry. 59 Suppl 20:22-33.

32. Henry JD, Crawford JR. (2005).The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. British Journal of Clinical Psychology. 44(2):227-39.

33. Kroenke K, Spitzer R, Williams J. PHQ9: (2001). Validity of a brief depression measure. Journal of General Internal Medicine. 16(9):606-13.

34. Gilbody S, Richards D, Barkham M. (2007) Diagnosing depression in primary care using self-completed instruments: UK validation of PHQ–9 and CORE–OM. British Journal of General Practice. 57. 650-2.

35. Spitzer R, Kroenke K, Williams J, Lowe B. (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166:1092 - 7.

36. Ware J, Kosinki M, Keller S. A (1996) 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Medical Care. 34(3):220-33.

37. EuroQol Group. EuroQol: (1990) A new Instrument for the measurement of Health Related Quality of Life. Health Policy. 16:199-208.

38. Manos RC, Kanter JW, Luo W. (2011) The Behavioral Activation for Depression Scale–Short Form: Development and Validation. Behavior Therapy. 42(4):726-39.

39. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a New Measure for Evaluating the Severity of Somatic Symptoms. Psychosom Med. 2002;64(2):258-66.

40. May, C, Finch, T. (2009) Implementing, embedding, and integrating practices: an outline of normalization process theory. Sociology. 43(3):535-554.

41. Coupe N, Anderson E, Gask L, Sykes P, Richards D, Chew-Graham C. (2014) Facilitating professional liaison in collaborative care for depression in UK primary care; a qualitative study utilising normalisation process theory. BMC Family Practice.;15(1):78.

42. Hertzog MA. (2008) Considerations in Determining Sample Size for Pilot Studies, Research in Nursing and Health 31:180-191.

43. Teare MD, Dimairo M, Shephard N, Hayman A, Whitehead A, Walters SJ. (2014) Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study, Trials. 15: 264.

44. Lancaster GA, Dodd S, Williamson PR (2004) Design and analysis of pilot studies: recommendations for good practice. Journal of Evaluation in Clinical Practice, 10, 307–312

45. Arain M, Campbell MJ , Cooper CL and Lancaster GA (2010) What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Medical Research Methodology, 10, 67

46. Barrett, B., Byford, S. (2007). Collecting service use data for economic evaluation in DSPD populations Development of the Secure Facilities Service Use Schedule. The British Journal of Psychiatry, 190(49), s75-s78.

47. Tyrer, P., Cooper, S., Salkovskis, P., Tyrer, H., Crawford, M., Byford, S. & Barrett, B. (2014). Clinical and cost-effectiveness of cognitive behaviour therapy for health anxiety in medical patients: a multicentre randomised controlled trial. The Lancet, 383(9913), 219-225.

48. Dolan, P. (1997). Modeling valuations for EuroQol health states. Medical care,35(11), 1095-1108.

49. Brazier, J. Roberts, J. (2004). The estimation of a preference-based measure of health from the SF-12. Medical care, 42(9), 851-859.

50. Mulhern, B., Mukuria, C., Barkham, M., Knapp, M., Byford, S., Soeteman, D., Brazier, J. (2014). Using generic preference-based measures in mental health: psychometric validity of the EQ-5D and SF-6D. The British Journal of Psychiatry, 205(3), 236-243.

51. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. (2015) Process evaluation of complex interventions: Medical Research Council Guidance 16:21:29.

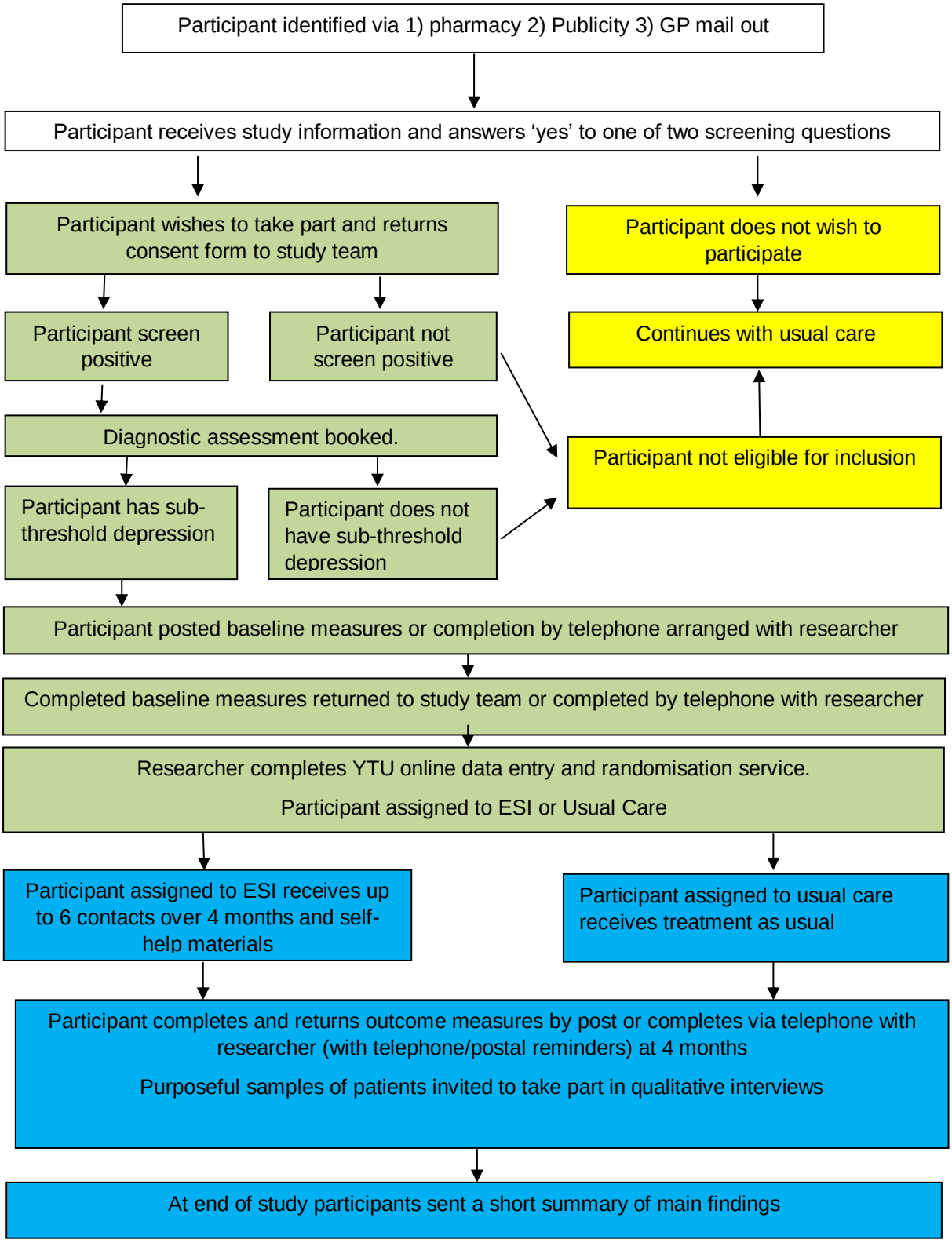
52. Kraemer H, Wilson G, Fairburn CG, Agras W. (2002) Mediators and moderators of treatment effects in randomized clinical trials. Archives of General Psychiatry. 59(10):877-83.

53. Silverman D. (1997) Qualitative Research: Theory, Method and Practice. London: Sage.

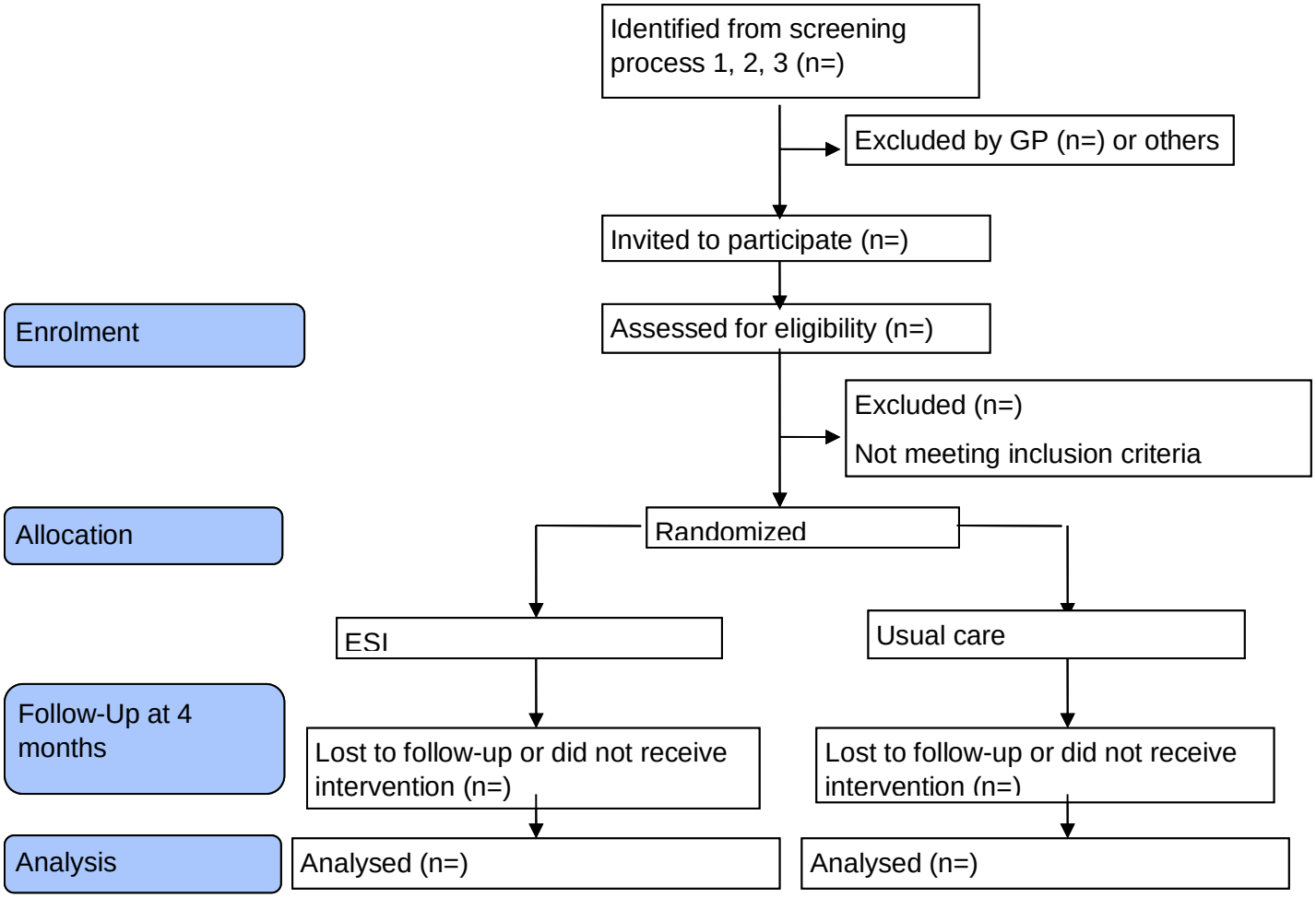
54. Bambra C, Joyce K, Maryon-Davies A Priority health conditions –Task Group 8 Report to the Strategic Review of Health Inequalities in England post-2010. 2010.

CHEMIST study participant process flow chart

NB in feasibility no randomisation process is conducted



CHEMIST pilot study consort flow chart



	Approach	Invitation & Recruitment Pack	Baseline Questionnaires	Diagnostic interview	Randomisation	4 month follow-up	Data collection schedule
Permission to contact	•						
Two Whooley questions		•		•		•	
Consent/Decline		•	• (re-checked)	• (re-checked)		• (re-checked)	
Demographic questionnaire		•				•	
Physical Health Condition/s		•		•	•		
PHQ-9			•			•	
SF-12			•			•	
EQ-5D			•			•	
GAD-7			•			•	
Adapted ADSUS (Medication questionnaire & Service use)			•			•	
M.I.N.I.				•			