Title: **A tailored, cognitive behavioural approach intervention for mild to moderate anxiety and/or depression in people with chronic obstructive pulmonary disease (COPD): A randomised controlled trial**

STUDY COLLABORATORS

Full Title	A tailored, cognitive behavioural approach intervention for mild to moderate anxiety and/or depression in people with chronic obstructive pulmonary disease (COPD): A randomised controlled trial
Short Title/Acronym	TANDEM (Tailored intervention for ANxiety and Depression Management in COPD) trial
Sponsor	Queen Mary, University of London Contact person of the above sponsor organisations is: Dr Sally Burtles Director of Research Services and Business Development Queen Mary Innovation Centre Joint Research Management Office (JRMO) Lower Ground Floor, 5 Walden Street London E1 2EF Tel: 020 7882 7265 Fax: 020 7882 7276 (Internal: 13-7276) Email: sponsorsrep@bartshealth.nhs.uk
Sponsor's reference	**ReDA 011674**
REC Reference	17/LO/0095
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Trial registration	ISRCTN59537391
Date of registration	20/03/2017
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Committees

Steering committee comprises the co-investigators listed above.

Independent Trial Steering Committee (ITSC)

Data Management and Ethics Committee (DMEC)

Pilot trial sites

Research sites - Pulmonary rehabilitation (PR) services in NHS Trusts

(1) Community cardio-respiratory service, St Mary's Hospital, Imperial College Healthcare NHS Trust.

(2) Acute COPD Early Response Service (ACERS), Homerton University Hospital NHS Foundation Trust.

(3) Glenfield General Hospital, University Hospitals of Leicester NHS Trust

(4) Loughborough Hospital, Leicestershire Partnership NHS Trust (in principle)

Research sites - Clinical Commissioning Groups (CCGs)

(1) NHS Brent CCG, NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith & Fulham CCG, NHS Harrow CCG, NHS Hounslow CCG, NHS Hillingdon CCG, NHS West London CCG - Partners with Imperial NHS Trust

The CCGs in northwest London have formed two groupings:

(i) CWHHE collaborative: NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith & Fulham CCG, NHS Hounslow CCG, and NHS West London CCG

(ii) BHH federation: NHS Brent CCG, NHS Harrow CCG and NHS Hillingdon CCG

(2) Hackney and City CCG - Partner with Homerton Hospital NHS Trust -

(3) West Leicestershire CCG, Leicester City CCG, East Leicestershire and Rutland CCG - Partners with University Hospitals of Leicester NHS Trust

Main trial sites

Research sites - Pulmonary rehabilitation (PR) sites in NHS Trusts

(1) Guy's and St Thomas' NHS Foundation Trust

(2) Atrium Health Ltd, Centre for Exercise and Health, University Hospitals Coventry and Warwickshire NHS trust

(3) South Warwickshire Rehab service, South Warwickshire NHS Foundation Trust

(4) Community cardio-respiratory service, St Mary's Hospital, Imperial College Healthcare NHS Trust

(5) Glenfield General Hospital, University Hospitals of Leicester NHS Trust, Loughborough University (National Centre for Sport & Exercise Medicine (NCSEM)

Research sites- Clinical Commissioning Groups (CCGs).

(1) NHS Southwark CCG, NHS Lambeth CCG, NHS Wandsworth CCG - Partners with Guys and St Thomas NHS Trust

(2) Coventry and Rugby CCG - Partners with University Hospitals Coventry and Warwickshire NHS Trust

(3) South Warwickshire CCG - Partners with South Warwickshire NHS Foundation Trust

(4) NHS Brent CCG, NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith & Fulham CCG, NHS Harrow CCG, NHS Hounslow CCG, NHS Hillingdon CCG, NHS West London CCG - Partners with Imperial NHS Trust

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(ii) BHH federation: NHS Brent CCG, NHS Harrow CCG and NHS Hillingdon CCG

(5) West Leicestershire CCG, Leicester City CCG, East Leicestershire - Partners with University Hospitals of Leicester NHS Trust

Clinical Research Networks

(1) CRN North Thames covers Homerton University Hospital NHS Foundation Trust.
Noclor Partners supports research in mental and community Trusts, Primary Care and CCGs. Partners are CRN North Thames,

(2) CRN North West London covers Imperial College Healthcare NHS Trust

(3) CRN East Midlands covers University Hospitals of Leicester NHS Trust

(4) CRN South London covers Guy's and St Thomas' NHS Foundation Trust

(5) CRN West Midlands covers University Hospitals Coventry and Warwickshire NHS trust and South Warwickshire NHS Foundation Trust

Contents Page

1. GLOSSARY of Terms and Abbreviations

AE	Adverse Event
AOB	Any other business
AR	Adverse Reaction
ARNS	Association of Respiratory Nurse Specialists
ASR	Annual Safety Report
BAI	Becks Anxiety Inventory
BELLA	Better living with long term airways disease study
BDI-II	Becks Depression Inventory
B-IPQ	Brief Illness Perception Questionnaire
CA	Competent Authority
CAT	COPD Assessment Test
CBA	Cognitive Behavioural Approach
CBT	Cognitive Behavioural Therapy
CCQ	Clinical COPD questionnaire
CI	Chief Investigator
CLAHRC	Collaboration for Leadership in Applied Health Research Care
COPD	Chronic Obstructive Pulmonary Disease
COPERS	Coping with persistent pain, effectiveness research into self-management study
CPCPH	Centre for Primary Care and Public Health
CRF	Case Report Form
CRO	Contract Research Organisation
CRN	Clinical Research Network
CRQ-SAS	Self-administered Chronic Respiratory Questionnaire-
CRQ-SR	Chronic Respiratory Questionnaire-Self Reported
DAFS	Data abstraction forms
DM	Data Management
DMEC	Data Monitoring and Ethics Committee
EC	European Commission
EQ-5D-5L	is a standardised instrument for use as a measure of health outcome

GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GP	General Practice
HADS	Hospital Anxiety and Depression Scale
HCP	Health Care Professional
HE	Health economics
HES	Hospital Episode Statistics
heiQ	Health Education Impact Questionnaire
HSCIC	Health and Social Care Information Centre
HRA	Health Research Authority
HTA	Health Technology Assessment funding body
ICF	Informed Consent Form
IG	Information Governance
IPQ-R	Illness Perception Questionnaire Revised
IRAS	Integrated Research Application System
JRMO	Joint Research Management Office
mMRC	Modified Medical Research Council
MRC	Medical Research Council
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
ONS	Office of National Statistics
Participant	An individual who takes part in a clinical trial
PA	Personal Assistant
PCTU	Pragmatic Clinical Trials Unit
PFSDQ-M	Pulmonary function related activity questionnaire
PI	Principal Investigator
PIS	Participant Information Sheet
PHQ	Patient Health Questionnaire
PPI	Patient and Public Involvement
PR	Pulmonary rehabilitation
QA	Quality Assurance
QC	Quality Control
QMUL	Queen Mary University of London
RCT	Randomised Controlled Trial
REC	Research Ethics Committee

RNS	Respiratory Nurse Specialist
RSD	Requirements Specification Document
SAE	Serious Adverse Event
SDV	Source Document Verification
SGRQ	St George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials checklist
SSA	Site Specific Assessment
STAI	State-Trait Anxiety Inventory
TIDieR	Template for Intervention Description and Replication checklist
TMG	Trial Management Group
TSC	Trial Steering Committee
TSU	Time Use Survey
UCL	University College London
VAS	Visual Analogue Scale
VOLUME	Volunteering in Mental Health Care for People with Psychosis
WEMWBS	Warwick-Edinburgh mental Wellbeing Scale
YCB	Yvonne Carter Building
ZBI	Zarit Burden Interview

2. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 1.2, dated 21 December 2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Professor Stephanie Taylor

Chief Investigator Site: Queen Mary University of London

Stephanie Taylor

Signature and Date: 21 Dec **2016**

Co - Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 1.2, dated 21 December 2016)** or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Professor Hilary Pinnock

Chief Investigator Site: Queen Mary University of London / University of Edinburgh

Hilary J Pinnock

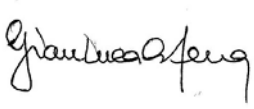
Signature and Date: **21 Dec 2016**

Statistician sign-off

The clinical study as detailed within this research protocol **(Version 1.2, dated 21 December 2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Statistician Name: Dr Gian Luca di Tanna

Statistician Site: Queen Mary University of London

Signature and Date:  **21 Dec 2016**

3. SUMMARY/SYNOPSIS

Short Title	TANDEM (Tailored intervention for ANxiety and DEpression Management in COPD)
Public title	Working together against COPD
Health condition(s) or problem(s) studied	Mild to moderate anxiety and /or depression in people with moderate or severe chronic obstructive pulmonary disease (COPD)
Primary registry and trial identifying number	In progress
Countries of recruitment	England
Research Sites	**PHASE II - INTERNAL PILOT & FEASIBILITY STUDY** **Pulmonary rehabilitation sites within NHS Trusts** **(1)** Community cardio-respiratory service, St Mary's Hospital, Imperial College Healthcare NHS Trust. **(2)** Acute COPD Early Response Service (ACERS), Homerton University Hospital NHS Foundation Trust. **(3)** Glenfield General Hospital, University Hospitals of Leicester NHS Trust **(4)** Loughborough Hospital, Leicestershire Partnership NHS Trust (in principle) **Clinical Commissioning Groups (CCGs)** **(1)** NHS Brent CCG, NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith & Fulham CCG, NHS Harrow CCG, NHS Hounslow CCG, NHS Hillingdon CCG, NHS West London CCG - Partners with Imperial NHS Trust The CCGs in northwest London have formed two groupings: **(i)** CWHHE collaborative: NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith & Fulham CCG, NHS Hounslow CCG, and NHS West London CCG **(ii)** BHH federation: NHS Brent CCG, NHS Harrow CCG and NHS Hillingdon CCG **(2)** Hackney and City CCG - Partner with Homerton Hospital NHS Trust -

	(3) West Leicestershire CCG, Leicester City CCG, East Leicestershire and Rutland CCG - Partners with University Hospitals of Leicester NHS Trust **PHASE III - MAIN TRIAL** **Pulmonary rehabilitation (PR) sites in NHS Trusts** **(1)** Guy's and St Thomas' NHS Foundation Trust **(2)** Atrium Health Ltd, Centre for Exercise and Health, University Hospitals Coventry and Warwickshire NHS trust **(3)** South Warwickshire Rehab service, South Warwickshire NHS Foundation Trust **(4)** Community cardio-respiratory service, St Mary's Hospital, Imperial College Healthcare NHS Trust **(5)** Glenfield General Hospital, University Hospitals of Leicester NHS Trust, Loughborough University (National Centre for Sport & Exercise Medicine (NCSEM) **Clinical Commissioning Groups (CCGs)** **(1)** NHS Southwark CCG, NHS Lambeth CCG, NHS Wandsworth CCG - Partners with Guys and St Thomas NHS Trust **(2)** Coventry and Rugby CCG - Partners with University Hospitals Coventry and Warwickshire NHS Trust **(3)** South Warwickshire CCG - Partners with South Warwickshire NHS Foundation Trust **(4)** NHS Brent CCG, NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith & Fulham CCG, NHS Harrow CCG, NHS Hounslow CCG, NHS Hillingdon CCG, NHS West London CCG - Partners with Imperial NHS Trust The CCGs in northwest London have formed two groupings: **(i)** CWHHE collaborative: NHS Central London CCG, NHS Ealing CCG, NHS Hammersmith & Fulham CCG, NHS Hounslow CCG, and NHS West London CCG **(ii)** BHH federation: NHS Brent CCG, NHS Harrow CCG and NHS Hillingdon CCG **(5)** West Leicestershire CCG, Leicester City CCG, East Leicestershire - Partners with University Hospitals of Leicester NHS Trust
Objectives/Aims	To refine, pilot and evaluate a tailored, psychological cognitive behavioural approach intervention, which links

	into, and optimises the benefits of routine pulmonary rehabilitation, with the aim of reducing mild/moderate anxiety and/or depression in people with moderate or severe COPD.
Interventions	The TANDEM intervention to optimise the potential synergy between the psychological one to one CBA intervention and PR. The CBA intervention will precede PR and target individuals' cognitions and behaviours associated with anxiety and depression to decrease psychological morbidity and increase self-efficacy (confidence) and motivation among patients with moderate to severe COPD to attend and complete PR
Main Inclusion and exclusion criteria	**Inclusion Criteria - Patients** • Adults with a confirmed diagnosis of COPD, post bronchodilator FEV1/FVC ratio <70% • Moderate or severe COPD severity on spirometry, FEV1 30-80% predicted. • Patients with probable mild or moderate anxiety as determined by the Hospital Anxiety and Depression Scale (ref85,86) Anxiety Subscale (HADS-A) scores ≥8 to ≤15; and/or probable mild or moderate depression as determined by Hospital Anxiety and Depression Scale – Depression Subscale (HADS-D) scores ≥8 to ≤15 • Eligible for attendance at their local pulmonary rehabilitation service at the ime of randomisation i.e.: 12 months have elapsed since last undertook PR or participant has another indication for PR referral (e.g. recent deterioration; recent hospitalisation with an acute exacerbation of COPD) **Exclusion Criteria - Patients** • Patients with both HADS-A score and a HADS-D score <8 (within normal range) • Unable to give valid consent • HADS depression or anxiety subscale score greater than 15 (suggestive of possible severe anxiety/depression) • Severe uncontrolled psychological or psychiatric disorder that would make them unsuitable for the intervention • Ineligible for pulmonary rehabilitation at their local PR service at the time of randomisation (typically if they had undertaken a course of PR in the last 12 months and there were no new clinical indications for PR ref41) NB. Patients who have been offered PR previously but declined the offer will not be excluded. • A co-morbidity so severe it would prevent the patient from engaging fully in the intervention/ control • Patients with moderate/severe cognitive impairment • In receipt of a psychological intervention primarily directed at helping to manage anxiety or depression in the last 6 months (NB those on antidepressants/ anxiolytics not

	excluded) • Patients currently involved in another clinical trial related to COPD (to reduce study participation burden on participants). • Not sufficiently fluent in English to be able to complete the questionnaires (NB the questionnaires are supervised self-complete, but can be read to participants if necessary, so poor literacy would not exclude individuals who are otherwise sufficiently fluent in English). **Inclusion Criteria – Carers** • Identified by a participant with COPD in the study as a 'particular family caregiver or friend who helps them' whom they would be happy for us to invite to join the study **Exclusion Criteria - Carers** • Unable to give valid consent • Not sufficiently fluent in English to be able to complete the questionnaires.
Methodology/Study type	**Phase II (internal pilot and feasibility study)** A pilot RCT with process evaluation. The intention is that this will be an internal pilot, unless significant changes to the intervention are necessitated making this inappropriate. **Phase III (main trial)** A randomised controlled trial. The study will also assess the cost-effectiveness of the intervention and we will conduct a parallel process evaluation
Date of first enrolment	Potentially 1st March 2017 (for Phase II - internal pilot and feasibility study)
Number of Participants/Patients/ Target sample size	**Phase II – Internal pilot and feasibility study** Target- 45 patients **Phase III – Main trial** Target – 430 patients
Primary outcome(s)	Depression and Anxiety
Key secondary outcome(s)	Depression and Anxiety Depression Anxiety Respiratory Health-related quality of life Illness perceptions about COPD Social engagement Functional/Social activity Carer Burden Interview Carer Mental Well-being
Statistical Methodology and	All analyses will be by intention-to-treat, and will include all participants for whom an outcome is available, and will

Analysis (if applicable)	analyse them according to the treatment group to which they were randomised. All analyses will account for clustering-by-therapist in the intervention arm, and each analysis will present a treatment effect (difference in means for continuous outcomes, odds ratios for binary outcomes) with a 95% confidence interval and a two-sided p-value. Outcomes at 6 and 12 months will be analysed using a mixed-effects regression model that will account for correlation within CBA facilitators, and correlation between outcomes at 6 and 12 months. This approach will provide unbiased estimates even if some participants only provide data at one of the two time points. Analyses will adjust for the outcome measured at baseline whenever possible.
Process evaluation data collection and analysis (Intervention fidelity and qualitative methodology, data collection and analysis)	The aim of the process evaluation is to examine the processes by which the intervention and trial is conducted and implemented and consider the effect of these on the outcomes of the study. Thus, informing implementation if the trial is successful or assisting interpretation of findings if not. A process evaluation will be conducted within both the pilot and main trials. For further details see Section 7 and 9.
Health economics data collection and analysis	The economic evaluation will be carried out as part of the main trial, with unit costs and instrumentation (i.e. the adapted Client Service Receipt Inventory) required for the measurement of resource use developed during the Phase II. The economic analysis will assess whether the addition of a tailored psychological intervention, combined with the availability of standard PR, is likely to be a cost-effective use of resources. For further details see Section 9.5.
Proposed Start Date	Internal pilot and feasibility study - 1st March 2017 Main trial (if internal pilot is successful) – 1st December 2017
Proposed End Date	Internal pilot and feasibility study - 30th November 2017 Main trial (if internal pilot is successful) – 31st Jan 2020
Study Duration	Internal pilot and feasibility study – 9 months Main trial (if internal pilot is successful) – 37 months

4. INTRODUCTION

Background and rationale

Chronic obstructive pulmonary disease (COPD) is characterised by progressive, irreversible obstruction of the airways which, in the UK, is predominantly due to cigarette smoking.[1] It affects up to one in four adults by the age of 80 years,[2] and is a leading cause of death and disability in high-, middle- and low-income countries.[3, 4] COPD is a national priority clinical area,[5] with a call for action to improve quality of life and outcomes of patients with COPD. It is a common cause of emergency admissions and one of the most costly inpatient conditions to be treated by the NHS.[5] Death rates from COPD in the UK are almost double the EU average.[5]

The physical and psychological burden of COPD

Many people with COPD are affected by anxiety and/or depression.[5-7] The prevalence of depression increases with severity of COPD:[8] patients with severe COPD have 2.5 times the risk of developing depression compared to those with mild disease. Anxiety is reported across all ranges of COPD severity, with cited prevalence ranging from 10 to 50%.[9] It is associated with lower levels of self-efficacy, persistent smoking, impaired health status and worse physical functioning.[10, 11] Both anxiety and depression are associated with an increased likelihood of exacerbations, more frequent and longer hospital admissions, and reduced survival.[10, 12-15] Although depression is common in COPD it is widely reported as being under recognised and undertreated.[16, 17]

Pulmonary rehabilitation: an effective intervention (for those who attend)

A core function of pulmonary rehabilitation (PR) is to alleviate the disability associated with the disease, primarily through a package of exercise training and disease specific education, which attempts to break the cycle of physical disability with the associated anxiety, despondency, inactivity and isolation.[18, 19] PR results in a 'moderately large and clinically significant' relief of dyspnoea and fatigue, increase in exercise tolerance, improvement in emotional function and enhancement of the patients' sense of control over their condition,[19, 20] and a reduction in depression and anxiety.[21] However, there are reports of poor participation[22-25] and completion[22, 26, 27] from studies of PR - particularly amongst anxious and depressed people.[22, 28]

Psychological interventions in COPD

Management of psychological problems such as anxiety and depression in COPD remains poor. Key issues include health care professionals (HCPs) feeling ill equipped to deal with emotional difficulties resulting from physical illness, stigma relating to the use of psychiatric or psychological services, and interpretation by patients that referral from psychological help undermines the validity their symptoms. Guidelines for the management of anxiety and depression in those with physical health conditions recommend psychological treatment, pharmacological treatment or both in combination.[29, 30] Cognitive behavioural therapy (CBT) is an evidence based treatment which explores the links between situations thoughts, feelings, physical symptoms and behaviour. By developing new skills, unhelpful thoughts and behaviours can be challenged and changed. Once skills are acquired patients are empowered to use the techniques they have learnt in similar situations. CBT is

recommended for the treatment of many mental health problems including both anxiety and depression,[30] and it improves anxiety and depression in a number of physical conditions[31, 32] including COPD.[33-35]

Combining psychological interventions and pulmonary rehabilitation

A recent systematic review found evidence of possible benefit from interventions which combine exercise with psychological and lifestyle interventions in COPD,[36] and a small randomised trial (n=41) suggested that a course of CBT after PR reduced anxiety and panic.[37] NICE guidance for co-morbid mild/moderate depression in people with a chronic physical health problem recommends combined physical activity, individualised CBT and/or group psychoeducation.[29]

We aim to evaluate a cognitive behavioural approach (CBA) intervention that draws on self-regulation theory[38] and necessity-concerns framework.[39] It builds on the research team's experience of developing several evidence-based interventions:

- the cognitive behavioural intervention developed by Heslop-Marshall for anxiety in COPD,[40]
- our positive trial of training physiotherapists to deliver CBT-based interventions in low back pain,[31]
- our successful experience developing psychological support within a PR service,[41] and
- practical self-management advice drawn from the content of our successful SPACE manual;[42]

We will train respiratory HCPs with experience of managing individuals with COPD, to deliver the CBA intervention to address mild/moderate anxiety and/or depression in people with moderate to severe COPD who are eligible for a course of routine pulmonary rehabilitation (PR) at their local service. The TANDEM CBA intervention will thus precede and "bolt on to" the opportunity for the participant to attend routine pulmonary rehabilitation.

Preliminary work

The TANDEM study is funded by the National Institute of Health Research Health Technology Assessment Programme (NIHR HTA) and comprises three phases.

In Phase I (completed and NOT the subject of this protocol) we developed the TANDEM CBA intervention manual; refined the intervention as a result of focus groups/individual interviews with patients, carers, and health care professionals (HCPs); and conducted a pre-pilot study in which the intervention was delivered to six patients with mild to moderate depression and/or anxiety and their carers followed by a qualitative evaluation among those who received the intervention and those who delivered the intervention.

Phase I also comprised liaising and confirming recruitment of PR sites, CCGs, GP practices and intermediate and secondary care for the main trial.

The findings of Phase I have informed the refined TANDEM CBA intervention (described in section 7.3.1) which will now undergo evaluation in the internal pilot and feasibility study (Phase II) and main randomised controlled trial (RCT) (Phase III). Phases II and III are the focus of this protocol.

The SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) 2013 Statement (http://www.spirit-statement.org/spirit-statement/) provides

recommendations for a minimum set of scientific, ethical, and administrative elements that should be addressed in a clinical trial protocol. This protocol has been written to comply with the SPIRIT checklist.

5. STUDY AIM AND OBJECTIVES

Study aim

To refine, pilot and evaluate a tailored, psychological cognitive behavioural approach intervention, which links into, and optimises the benefits of routine pulmonary rehabilitation, with the aim of reducing mild/moderate anxiety and/or depression in people with moderate or severe COPD.

Phase I – Pre-pilot study – completed as detailed in section 4.

Phase II (Internal pilot and feasibility study) - Aim & objectives

To undertake a feasibility study (consisting of an internal pilot RCT and a process evaluation) to inform: the feasibility of delivering the intervention, the trial processes, and progression to the main trial (Phase III), specifically studying the following:

a. Recruiting, training, standardising and assessing HCPs to deliver the psychological, one-to-one intervention
b. Identifying and recruiting eligible patients and their carers (where present)
c. Recruitment of GP practices and intermediate and secondary care
d. Intervention acceptability from patient, HCP and organisational perspectives
e. Patient intervention uptake, attendance, throughput and completion rates
f. Acceptability of standard pulmonary rehabilitation (PR) as the control intervention
g. Maintenance of intervention fidelity
h. Retention of HCPs delivering intervention
i. Acceptability of data collection from PROM (Patient Reported Outcome Measures)
j. Testing data collection for the cost-effectiveness analyses
k. Checking our sample size calculation assumptions
l. Informing whether intervention and/or trial adaptations are necessary and consequently whether the pilot should continue as an internal or external design
m. Refining the process evaluation for the main trial

Phase III (Main Trial) – Aim & objectives

To undertake a randomised controlled trial (and a process evaluation) to:

1) Examine the clinical effectiveness of the CBA intervention on clinical outcomes compared to usual care (the offer of pulmonary rehabilitation, PR, alone)
2) Examine the process outcomes
3) Examine the effect of the CBA intervention on carers (where appropriate)

4) Determine the cost effectiveness of the CBA intervention from an NHS and personal social services perspective
5) Conduct a process evaluation to inform the implementation of the CBA intervention if the trial is positive, or assist interpretation of findings if it is negative.

Research hypothesis

The TANDEM intervention will optimise the potential synergy between the psychological one to one CBA intervention and PR. The CBA intervention will precede PR and target individuals' cognitions and behaviours associated with anxiety and depression to decrease psychological morbidity and increase self-efficacy (confidence) and motivation among patients with moderate to severe COPD to attend and complete PR which in itself has a positive effect on anxiety and depression in addition to benefits on quality of life and exercise tolerance. The psychological and physical benefits of the TANDEM intervention and PR are synergistic but even participants who do not engage with PR following the TANDEM intervention will benefit from the CBA intervention.

6. STUDY DESIGN

Phase II

A pilot RCT with process evaluation. The intention is that this will be an internal pilot, unless significant changes to the intervention are necessitated making this inappropriate (further details given in Section 7.5.3).

Phase III

A randomised controlled trial. Patients will be randomised to the TANDEM intervention or usual care using minimisation with a random element: this will be done in order to minimise potential imbalances at baseline for anxiety (HADS-A), depression (HADS-D), dyspnoea (mMRC) and smoking.
The randomisation will be at the individual patient level with 1.25:1 allocation ratio.

7. METHODS: Participants, intervention outcomes

7.1 Study setting

Participants will be recruited from primary and secondary care, and from PR services. The intervention will be delivered in participant's own homes, or at a convenient local (usually NHS) facility, and over the phone.

7.2 Eligibility criteria

7.2.1 Inclusion Criteria - Patients

- Adults with a confirmed diagnosis of COPD, post bronchodilator FEV_1/FVC ratio <70%,[1]
- Moderate or severe COPD severity on spirometry, FEV_1 30-80% predicted.[1]
- Patients with probable mild or moderate anxiety as determined by the Hospital Anxiety and Depression Scale[43, 44] Anxiety Subscale (HADS-A) scores ≥8 to ≤15; and/or probable mild or moderate depression as determined by

Hospital Anxiety and Depression Scale – Depression Subscale (HADS-D) scores ≥8 to ≤15

- Eligible for attendance at their local pulmonary rehabilitation service at the time of randomisation i.e. 12 months have elapsed since last undertook PR or participant has another indication for PR referral (e.g. recent deterioration; recent hospitalisation with an acute exacerbation of COPD)[19]

7.2.2 Exclusion Criteria - Patients

- Patients with both HADS-A score and a HADS-D score <8 (within normal range)
- Unable to give valid consent
- HADS depression or anxiety subscale score greater than 15 (suggestive of possible severe anxiety/depression)
- Severe uncontrolled psychological or psychiatric disorder that would make them unsuitable for the intervention
- Ineligible for pulmonary rehabilitation at their local PR service at the time of randomisation (typically if they had undertaken a course of PR in the last 12 months and there were no new clinical indications for PR[19] NB. Patients who have been offered PR previously but declined the offer will not be excluded.
- A co-morbidity so severe it would prevent the patient from engaging fully in the intervention/ control
- Patients with moderate/severe cognitive impairment
- In receipt of a psychological intervention primarily directed at helping to manage anxiety or depression in the last 6 months (NB those on antidepressants/ anxiolytics not excluded)
- Patients currently involved in another clinical trial related to COPD (to reduce study participation burden on participants).
- Not sufficiently fluent in English to be able to complete the intervention, questionnaires (NB the questionnaires are supervised self-complete, but can be read to participants if necessary, so poor literacy would not exclude individuals who are otherwise sufficiently fluent in English).

7.2.3 Inclusion Criteria – Carers

- Identified by a participant with COPD in the study as a 'particular family caregiver or friend who helps them' whom they would be happy for us to invite to join the study

7.2.4 Exclusion Criteria - Carers

- Unable to give valid consent
- Not sufficiently fluent in English to be able to complete the questionnaires.

7.3 Interventions

7.3.1 TANDEM intervention

The intervention is described below using the Template for Intervention Description and Replication (TIDieR) checklist.[45]

Item 1. Brief name: Provide the name or a phrase that describes the intervention	Tailored ANxiety and DEpression Management in COPD (TANDEM)
Item 2. Why: Describe any rationale, theory, or goal of the elements essential to the intervention	See pages 19-20. Briefly: CBT is an evidence based treatment often used for managing anxiety and/ or depression The current cognitive behavioural approach (CBA) intervention draws on the principles of CBT as well as practical self-management skills drawn from the SPACE COPD manual which then links into PR with additional telephone support. The intervention is delivered by respiratory health care professionals experienced in working with people with COPD who will be trained and supervised in delivery of the cognitive behavioural skills needed for the intervention.
Item 3. What (materials): Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed	Materials for CBA facilitators - TANDEM manual, - Intervention work sheets – hot cross bun, breathlessness spider diagram, - Videos of CBA skills Materials for Patient participants: British Lung Foundation (BLF) DVD and Booklets http://shop.blf.org.uk/collections/copd - Living well with COPD - First steps to living with COPD booklet (code BK31) - Pulmonary rehabilitation and exercise booklet (code BK27) - TANDEM hand-outs on mood & COPD, anxiety & depression and COPD. SPACE hand-out on managing breathlessness Patients may also be given the following according to their needs - Sex and breathlessness (code FL22) - Going on Holiday with a lung condition (code BK6) - Get self-help leaflets for psychosocial difficulties Carers of participants may be given: - The BLF leaflet: Looking after someone with a lung condition booklet (code BK21) - TANDEM hand-outs
Item 4. What (procedures): Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities	HCPs will receive a 3-day training course with between session practice. During delivery of the intervention HCPs will receive fortnightly supervision. Participants in the intervention arm receive between 5 and 8, 30-40 minute long, one to one visits by the TANDEM trained health care professional. The content of the intervention, and skills to deliver it are described in detail in the TANDEM manual.
Item 5. Who provides: For each category of	The CBA facilitator training will be delivered by a team of a Consultant Respiratory nurse and Health Psychologist with

intervention provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given	extensive experience of delivering psychological interventions to COPD patients and a Clinical psychologist with expertise in CBT. CBA facilitators (trained health care professionals who are experienced in dealing with people with COPD e.g. respiratory nurses, physiotherapists, occupational therapists or health psychologists). They will all have attended the three day TANDEM intervention training, practiced the skills and demonstrated competence. They will receive ongoing supervision from a senior clinical psychologist.
Item 6. How: Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group	Facilitator training will be face-to-face group based, with on-going telephone supervision and supported by a written manual. The patient intervention will be individual, face to face sessions followed by phone support and reinforced by written materials.
Item 7. Where: Describe the type(s) of location(s) where the intervention occurs, including any necessary infrastructure or relevant features	The facilitator training will take place in a university or suitable training location. The patient CBA sessions will take place in study participants' own homes or in a local health care setting (e.g. community respiratory clinic, primary care clinic), according to patient preference.
Item 8. When and how much: Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose	Participants in the intervention arm receive between 5 and 8 (depending on individual patient need) 30-40 minute long, weekly, one to one visits by a TANDEM trained health care professional. Following this, participants are given a date to commence routine pulmonary rehabilitation (PR) at their local service. In the gap between the intervention being finished and pulmonary rehabilitation commencing participants receive one to one phone calls by the TANDEM trained health care professional on a weekly basis (duration of each call 10-15 minutes). Weekly phone calls continue whilst the participant is attending PR and for 2 weeks after the completion of PR.
Item 9. Tailoring: If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how	The intervention is tailored to the participants' problems, i.e. depression or anxiety or both, and degree e.g. mild or moderate. Intrinsic to cognitive behavioural approaches is working with individuals' specific problem presentations, thoughts and behaviours. See TANDEM manual for full details.
Item 10.	Not applicable

Modifications: If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)	
Item 11. How well (planned): If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them	Intervention fidelity will be maintained by assessment and selection of facilitators who demonstrate competence at the end of training as well as providing ongoing clinical supervision by a clinical psychologist. Using a manual with structured intervention sessions and standardised self-completion leaflets will also help to promote fidelity.
Item 12: How well (actual): If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned	Intervention fidelity will be addressed in the process evaluation see Section 9.4. Adherence to content will be assessed through CRFs and competence through the adapted CBT Techniques for Palliative Care Practitioners Rating Scale (Mannix)

Criteria for discontinuing or modifying allocated interventions for a given trial participant (which may be reported as an adverse event)

The CBA intervention and pulmonary rehabilitation are tried and tested evidence-based interventions, though they have not previously been evaluated in combination. We will be alert to the possibility that, due to the progressive nature of COPD, there is potential for patient participants to become increasingly distressed by their situation and their condition. We do not envisage this happening but there is a small risk that some participants may become much more anxious or depressed, or (very unlikely but more seriously) may express suicidal intent such that they were at risk of harm to themselves or to others. Throughout the study the CBA facilitators will all receive ongoing supervision from a senior clinical psychologist to help them identify and respond appropriately to this possibility. In addition, they are all health care professionals experienced in the management of people with moderate to severe COPD and will already have been trained to recognise and respond appropriately to the signs and symptoms of severe anxiety or depression.

The development of much worse depressive or anxious symptoms, or suicidal ideation, would be criteria for discontinuing the allocated (CBA) intervention. These will be reported as adverse events which will be recorded and reported in line with ethics committee's and sponsor's requirements. Risk protocols will be followed by CBA facilitators and researchers involved in data collection (see Section 10.3). Only as a last resort where the participant and/or others were in danger would confidentiality be compromised.

Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence

Adherence to intervention protocols among the CBA facilitators will be conducted through fidelity assessment (explained in Section 9.5). The patient attendance and completion rates for the CBA intervention, and for the subsequent routine PR are study outcomes (see Section 7.4).

Relevant concomitant care and interventions that are allowed

The clinical care provided to study participants outside of the study for the management of their condition/s will continue as normal e.g. attending scheduled health care appointments, taking prescribed medications, including any anxiolytics or antidepressants.

7.3.2 Usual care/practice

Usual care will follow local arrangements for provision of PR to people with COPD referred to the service, and patients will attend the usual multidisciplinary PR course (including any psychological treatment provided routinely in that service). In agreement with the local service (who may prefer to use their own materials), we will provide the British Lung Foundation (BLF) DVD on living with COPD, and booklets on COPD (code BK31) and pulmonary rehabilitation (code BK27) http://shop.blf.org.uk/collections/copd Participants will also be eligible e.g. referral for Improving Access to Psychological Therapies (IAPT) services at the discretion of their usual healthcare providers. Referral to these services in both arms of the study will be collected with the heath care resource use data.

7.4 Study outcomes

7.4.1 Trial outcomes

The trial outcomes given in the table below will be used in the internal pilot and feasibility study and the main trial. It is possible that the internal pilot may suggest a change in our choice of primary outcome from within this selection of outcomes, in particular indicating use of the BDI II and BAI rather than the HADS-D and HADS-A. The literature on the optimal measure of anxiety and depression in COPD in studies such as this is inconclusive although HADS-A and HADS-D appear to be most frequently used.

Primary outcome	***Measure***	***Source of data (patient/carer/health care records)***	***Time point collected***	***Participant-level analysis metric***	***Method of aggregation***
Depression and Anxiety (Co-primary outcomes as specified by funder in brief)	HADS-A, HADS-D	Patient	At screening to assess eligibility; 6 and 12 months after randomisation	change from baseline at 6 months	Difference in means
Secondary outcomes	***Measure***	***Source of data (patient/carer/health care records)***	***Time point collected***	***Participant-level analysis metric***	***Method of aggregation***

Depression	BDI-II	Patient	Baseline, 6 and 12 months	Change from baseline	Difference in means
Anxiety	BAI	Patient	Baseline, 6 and 12 months	Change from baseline	Difference in means
Respiratory Health-related quality of life	SGRQ	Patient	Baseline, 6 and 12	Change from baseline	Difference in means
Illness perceptions about COPD	B-IPQ	Patient	Baseline, 6 and 12 months	Change from baseline	Difference in means
Social engagement	heiQ	Patient	Baseline, 6 and 12 months	Change from baseline	Difference in means
Functional/Social activity	Time Use Survey	Patient	Baseline, 6 and 12 months	Change from baseline	Difference in means
Carer Burden Interview	ZBI 22 item	Carer	Baseline, 6 and 12 months	Change from baseline	Difference in means
Carer Mental Well-being	WEMWBS 14 item	Carer	Baseline, 6 and 12 months	Change from baseline	Difference in means

Primary outcomes

The rationale for using the HADS_D and HADS-A as the co-primary outcome measures includes that the HADS is a valid and reliable self-report measure to identify both anxiety and depression in hospital, primary care and community settlings. The measure is preferred by both PR clinicians and patients to the longer BDI/BAI (which is more often used in psychiatric studies). HADS provides clear cut-off scores to indicate the severity of anxiety/depression. It can be used as a screening measure, and is commonly used as such in the PR services involved in this study, and as an index of clinical change, an outcome measure and for research purposes.[43] However, it is possible that the internal pilot and feasibility study may suggest a change in our choice of primary outcome from within this selection of outcomes, in particular indicating use of the BDI II and BAI rather than the HADS-D and HADS-A. The literature on the optimal measure of anxiety and depression in COPD in studies such as this is inconclusive although HADS-A and HADS-D appear to be most frequently used.

Secondary outcomes

The secondary outcomes for patients address the key features of COPD and depression/ anxiety that may be expected to change as a result of CBA/PR:

- Breathlessness: mMRC (modified Medical Research Council) dyspnoea score
- Depression BDI (Beck's Depression Inventory)-II
- Anxiety BAI (Beck's Anxiety Inventory)
- Quality of Life EQ-5D-5L

- Respiratory health-related quality of life SGRQ (St George's Respiratory Questionnaire)
- Illness perceptions B-IPQ (Brief-Illness Perception Questionnaire)
- Social engagement heiQ (The Health Education Impact Questionnaire)
- Social functioning Time Use Survey

The secondary outcomes for carers address aspects of their well-being that may be expected to change by involving them in the CBA sessions and in PR (with patient permission):

- Caring burden ZBI (Zarit Burden Interview)
- Mental well-bring WEMWBS (Warwick-Edinburgh Mental Well-being Scale)

7.4.2 Process outcomes

Outcome	***Measure/ Case report form (CRF)/ topic guide***	***Source of data (patient/carer/health care records)***	***Time point collected***	***Participant-level analysis metric***	***Method of aggregation***
Patient, Carer, study recruitment and retention rates. Reasons for non-participation and dropout	CRF	Patient, Carer	At time of recruitment and over study period	Recruitment: – numbers recruited in study over numbers eligible in study Retention: - numbers completed study over number recruited in study	Proportions
CBA facilitator study recruitment and retention rates. Reasons for non-participation and dropout	CRF	Study team (part of study st-up)	At time of recruitment and over study period	Recruitment: - numbers recruited over numbers considered eligible to join study Retention: - numbers who completed study over numbers who joined study	Proportions
CBA facilitator intervention training attendance and completion rates. Reasons for non-attendance and dropout	CRF	Study team/CBA trainers (part of study set-up)	At time of training delivery	Attendance: - numbers who attended training over numbers eligible for training Completion: - numbers completed training over numbers attended training	Proportions
CBA intervention attendance and	CRF	Study team/CBA facilitators	CBA intervention period	Attendance: numbers attended/received CBA sessions over numbers allocated to intervention	Proportions

completion rates by patient and carer (2 session minimum dose for completer)				Completion: numbers completed felt appropriate by facilitators over numbers who attended/received CBA sessions	
PR attendance and completion rates among patients	CRF	Health care records/PR services	End of study	Attendance: numbers attended PR over numbers referred and deemed suitable to attend PR Completion: numbers completed PR over numbers who attended PR	Proportions
Fidelity assessment among CBA facilitators	Recording of CBA sessions and CBT Techniques for Palliative Care Practitioners Rating Scale	CBA facilitators	Following completion of CBA intervention delivery	See process evaluation section 9.4	Quantitative and Qualitative assessment of audio recordings
Interviews with patients	Topic guide	Patients	After intervention delivery plus at 12 months in main trial	See process evaluation section 9.4	Qualitative
Interviews with Carers	Topic guide	Carers	After intervention delivery	See process evaluation section 9.4	Qualitative
Interviews with CBA facilitators	Topic guide	CBA facilitators	After intervention delivery	See process evaluation section 9.4	Qualitative
Interviews with other stakeholders	Topic guide	Other stakeholders	After intervention delivery	See process evaluation section 9.4	Qualitative

7.4.3 Health economic outcomes

Outcome	*Measure/ CRF for study-specific data*	*Source of data (patient/carer/health care records)*	*Time point collected*	*Participant-level analysis metric*	*Method of aggregation*
Quality of life	EQ-5D-5L	Patient	Baseline, 6 and 12 months	Change from baseline	Difference in means and area under the curve

Planning and delivery of one to one CBA sessions	CRF	CBA facilitators	Baseline and across the intervention (5-8 weeks)		Simple descriptive data
Role and grade of CBA facilitators	CRF	Study team	At recruitment		Simple descriptive data
Cost of delivery of training and costs associated with delivery of training such as travel expenses, refreshments, room hire, use of printed materials, use of assistive technology; provision of financial incentive; attending feedback meeting with trainer/clinical psychologist		Study team	Throughout the project		Simple descriptive data
Health care use and societal costs	CRF/health care records	Patient, Primary care, Secondary care/NHS.Data Client service Inventory	(End of study) Baseline, 6 and 12 month follow up		Quantitative

7.5 Potential Participant and Participant timeline/Study Visits

7.5.1 Patient & Carer Potential Participant and Participant Timeline/Study visits

				-3	-2	-1	0	T1 (1-8 weekly sessions)	T2		F1	F2	
Activity/ Assessment	**CRF/topic guide/checklist/Informed consent form**	**Staff**	**Time to complete**	**Pre-study Introduction of study**	**Pre-study Explanation of study**	**Pre-study Screening and Consent**	**Pre-study Baseline /randomisation**	**Study Visit (CBA intervention sessions1-8 as per patient needs)**	**Weekly phone call during PR sessions of 6-12 weeks and 2 weeks after last PR session**	**Interview after CBA intervention**	**F/up 6 mos**	**F/up 12 mos**	**Interview**
Activity	Pre-screening (Identification log): verbal agreement and study introduction CRF for staff member	Clinical staff	10 min	X									
Activity	Researcher explain study and posts study documents CRF to potential patient participant	Researcher	10 min		X								
Assessment and Activity	Screening log, ICF & Enrolment log	Researcher	20 min			X							
Activity	Consent (Carer)	Researcher	10mins			X							
Assessment	Baseline (Patient & Carer)	Researcher	35mins				X						
Intervention activity CBA sessions	CBA case summary research data access part and audio recording of sessions	CBA facilitator	40 mins per session					X X X X X X X X					
Intervention activity phone calls	CBA case summary research data access part	CBA facilitator	10 -15 mins						X X X X X X X X X X X X				
Activity Interview	Topic guide (Patient & Carer)	Researcher	40-60 mins							X			X
Assessment	Follow up (Patient & Carer)	Researcher	35min								X		
Assessment	Follow up (Patient & Carer)	Researcher	35min									X	

7.5.2 CBA Facilitator & other stakeholder Timeline Interviews/ Fidelity Assessment

				-3	-2	-1	0	T1 (1-8 weekly sessions)	T2		F1	F2	
Activity/ Assessment	**CRF (Y/N)**	**Staff**	**Time to complete**	**Pre-study Introduction of study**	**Pre-study Explanation of study**	**Pre-study Screening and Consent**	**Pre-study Baseline /randomisation**	**Study Visit (CBA intervention sessions1-8 as per patient needs)**	**Weekly phone call during PR sessions of 6-12 weeks and 2 weeks after last PR session**	**After CBA intervention**	**F/up 6 mos**	**F/up 12 mos**	**Interview**
Consent	Informed consent CBA facilitator / other stakeholders	Researcher	5 min			**X**							
Interview/ focus group other CBA facilitator	Topic guide	Researcher	40 to 90 min							X			
Interview stakeholder	Topic guide	Researcher	25-30 to 60 min							X(Once during this period)			
Fidelity assessment of a selection of audio recorded sessions	Validated checklist	Researcher	40 min/ session							**X**			

7.5.3 Criteria for discontinuation

7.5.3.1 Decision making criteria for change of pilot from internal to external pilot

Where the pilot process evaluation data indicates that there should be substantial changes to the intervention before the main trial goes ahead the pilot will become an external pilot. There will be an ITSC meeting towards the end of the pilot study where the process data will be considered and a decision on whether the pilot should be classed as an internal pilot or an external pilot will be made.

7.5.3.2 Decision making criteria for discontinuation of study

SAEs associated with the intervention would be discussed by the DMEC and could lead to study discontinuation (see Sections 10.4 & 10.5). Failure to recruit CBA facilitators to deliver the intervention or to recruit sufficient patients may cause the funders to discontinue the study.

7.5.5 End of Study Definition

The end of the study will be marked by completion of the data analysis shown in the Gantt chart (Appendix 16.1).

7.6 Sample size

7.6.1 Trial sample size calculation

Sample size calculations are based on two primary outcomes (HADS-A, anxiety, subscale at 6 months, and HADS-D, depression, subscale at 6 months). Based on a significance level of 2.5% and 90% power, recruiting 153 participants would allow us to detect a difference of 1.7 points on the HADS anxiety subscale, and 1.5 points on the HADS depression subscale (based on an SD of 4.2 for anxiety and 3.6 for depression:[46] these are equivalent to a standardised mean difference of about 0.4, and are similar to the minimum clinically important difference of 1.5 for HADS in COPD.[47] Due to the clustering effect by therapist in the intervention arm, we increased the sample size. Assuming an intra-class correlation coefficient between therapists of 0.01 and 24 patients per therapist leads to a design effect of 1.23, which required increasing the number of participants in the intervention arm to 189 (342 overall) using Moerbeek's method.[48] Assuming a study dropout rate of 20%, we would require 428 participants overall. This has been rounded up to 430. Using an allocation ratio of 1.25 vs. 1, this would lead to approximately 240 participants in the intervention arm and 190 in the control arm. We have chosen this unbalanced allocation ratio as it will maximise power compared to a 1:1 ratio due to the presence of clustering by therapist in the intervention arm only.[48] Whilst we have performed our sample size calculation on the basis of 20% loss to follow up we will be striving for at least 90% follow up rate for our primary outcome; this is consistent with our recent experience of achieving 90% follow up rates for primary outcomes.[49]

7.6.2 Sample size for fidelity assessment

Audio-recordings of all intervention sessions will be made in both internal pilot and feasibility study and main trial evaluations. In the Phase II evaluation a random 25% sample of recorded sessions across all 25 CBA interventions, and a smaller sample of

10% CBA interventions where the entire intervention is considered, will be coded with respect to:

i) HCP adherence to manual (cross-referenced to summary points for each module as presented in the training manual)
ii) HCP competence in trained skills (coded using the CBT Techniques for Palliative Care Practitioners Rating Scale (Mannix) which is an adaptation of Blackburn's Revised Cognitive therapy scale.http://ebbp.org/resources/CTS-R.pdf In addition, for assessment sessions, primarily topic 4 (Mood and COPD), coding may be supplemented with use of the low-intensity well-being practitioner assessment session coding scheme, which also follows but expands the Blackburn Revised Cognitive therapy scale.

In the internal pilot and feasibility study process evaluation, and in the main trial, HCP intervention logs will be completed at the end of each CBA session. This documentation will record length of session, techniques used, home practice given and CBA facilitator self-efficacy (confidence) in intervention delivery.

Fidelity assessment in the main trial will be refined in the light of the experience of the internal pilot work, but we envisage that a random sample of the HCP intervention logs will be examined and a random sample of up to 5% of the intervention patients, stratified to select examples across the HCPs providing the intervention, will be selected for detailed examination of the recorded intervention sessions (with patient permission).

7.6.3 Sampling and sample size for qualitative interviews

Patient & Career Interviews

Semi-structured interviews (phone or face to face) will be conducted with up to 15 (internal pilot and feasibility study) and 24 (main trial) intervention participants and up to 6 (internal pilot and feasibility study) and 10 (main trial) control participants or until data-saturation is reached.

Interviews will be conducted after intervention delivery, i.e. following receipt of CBA and PR sessions to gain perspectives on the intervention (acceptability, reasons for dropout/non-completion etc) and research process as outlined in the above objectives, for both internal pilot and feasibility study and main trial process evaluations but additionally at 12 months for the main trial evaluation.

All participants will be asked at recruitment into the study if they consent to later invitation to interview. For both the internal pilot and feasibility study and main trial process evaluation a purposive sampling strategy will then be adopted to ensure a full range of views, typical of the wider population.[50] Maximum variation samples[51] will be attempted based (as far as possible on) on: patients who have completed, dropped out of the intervention, with different ages, gender, severity of condition (including anxiety and/or depression and who received the intervention from different CBA facilitators.

CBA Facilitator interviews

All facilitators in the internal pilot and feasibility study will be invited for interview. In the main trial process evaluation, up to 12 interviews will be conducted. The interviews will take place at the end of intervention delivery period. The interviews will explore training experience, experience/issues with intervention delivery with particular focus on acceptability and feasibility. This will also be explored in the main trial process evaluation but further consideration of how it will translate and be implemented in practice will be explored.

Other Stakeholder Interviews

In the internal pilot and feasibility study all PR teams and PR managers (some might be site PIs) will be interviewed (face to face interviews or focus group depending on pragmatics of setting up focus groups at the PR sites) about how intervention fitted/worked at the end of intervention delivery (including weekly telephone follow up of patients by CBA facilitators over the PR duration).

In the main trial, PR teams/PR managers, CCGs, GPs, Consultants' perspectives will be explored on implementation of intervention in practice. The sample will be purposive and maximum variation, to include representation from a range of groups and each area. Up to 10 people will be interviewed.

7.7 Recruitment

The participating PR sites (listed in the study collaborators section) were recruited during the study set-up stage and their process of recruitment is not described here.

This section describes the recruitment process of (A) primary care practices, secondary care/outpatient clinics, community clinics, (B) patient and carer recruitment (from primary care, secondary care, community clinics and the study flow illustrated in Figure 1-4) and (C) CBA facilitator recruitment.

A) *Recruitment process of primary care practices, secondary care/outpatient clinics, community clinics to promote/generate PR referrals*

The guidelines[52] recommend that all symptomatic COPD patients should be offered and encouraged to attend PR by health care professionals in the primary, secondary and community care sector. However, referrals and uptake are far lower than this.[53] We will therefore use a range of strategies to (1) recruit these different sectors and to (2) promote PR referrals for eligible patients.

1) Strategies for recruitment of the different sectors

- The study will be promoted among the Clinical Commissioning Groups and NHS Trusts e.g. accessing them through study team networks, email correspondence introducing the study, sending study summary, study newsletter and highlighting support on offer (resources and cost) if they choose to participate
- CRN support (type of support might vary between sites) will be sought whereby they will help to identify research active practices/clinics. A CRN coordinator could help with facilitation of the invitation process
- The research team will approach practices, identified by PR services, with large COPD registers but with disproportionately low PR referrals.

- The PR services may also help to generate interest about study among practices that need to refer patients to them

These different sectors will be invited to participate in the study using the study invitation and information sheet. Recruitment will be confirmed by receiving written confirmation either electronically or in paper form.

2) Strategies to promote/generate clinically appropriate PR referrals from the different participating sectors

- Encouraging healthcare professionals involved in the clinical care of people with COPD to identify and assess eligibility of patients for PR and (if appropriate) generate a PR referral. This research activity will be supported through provision of CRN service support costs. Some CRNs will be able to monitor practices regarding the number of referrals being made and will help to encourage practices to make referrals.

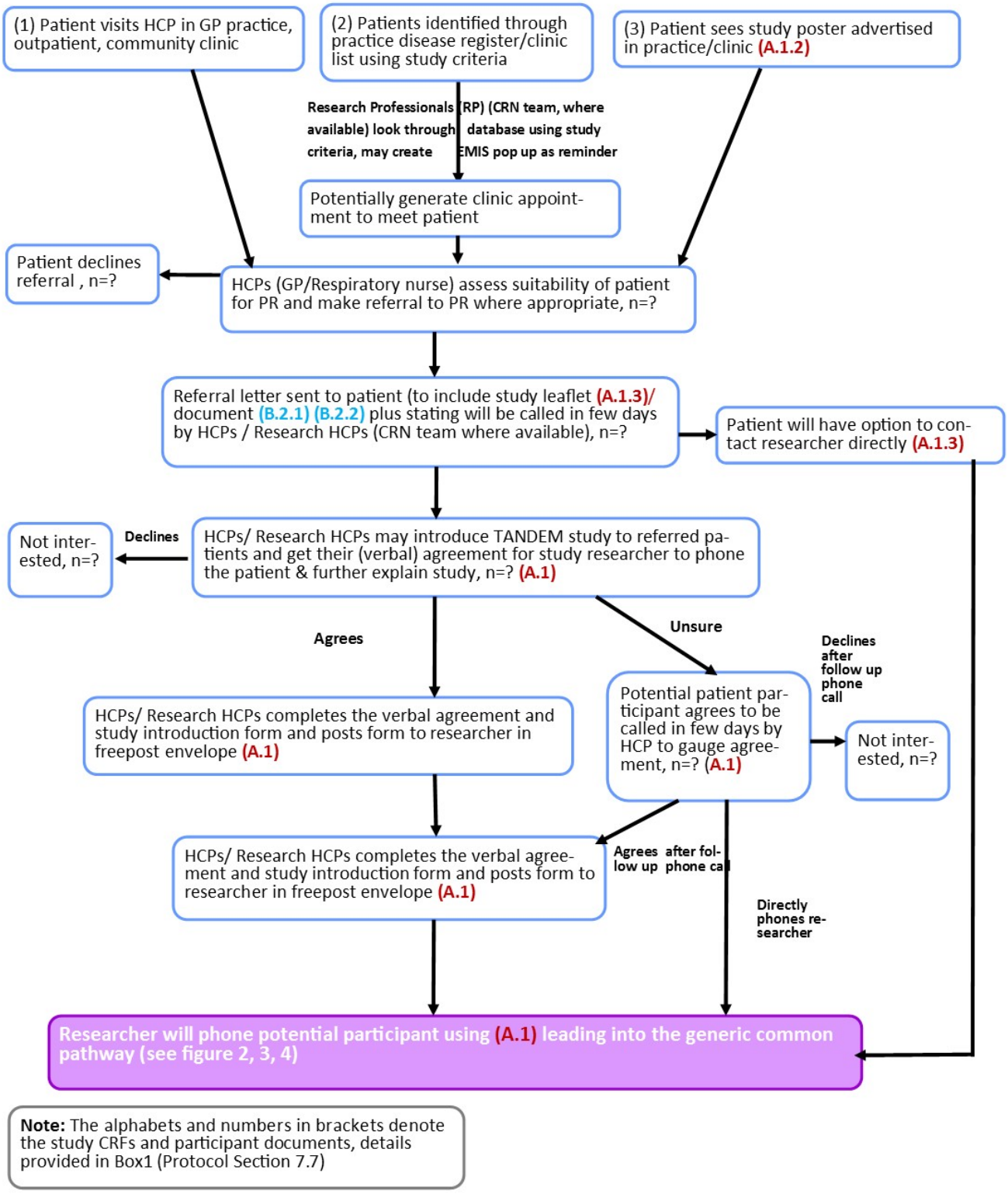
- CRN coordinators (where available), following training by the research team, will search the practice electronic health records, identify patients with a MRC dyspnoea score of 3 or above, moderate to severe COPD diagnosis (these are routinely recorded Quality and Outcome Framework data) who do have PR attendance recorded in the last 12 months. The list of these identified patients will be left with the GP or respiratory nurse who will review the list and (if appropriate) review the patient and make a referral to PR. The latter research activity will be supported through provision of CRN service support costs. Note: The staff will make a note if patient refuses PR referral (i.e. part of routine care).

- Following patient referral, GP or respiratory nurse (or on their behalf CRN coordinators, where available) will introduce the study to patients either by phone or face to face, give/post the study leaflet, and obtain verbal agreement for their contact details to be passed to the study researcher. If a potential patient is unsure but willing to receive some study information and to be followed up, the professionals will give/post study leaflet and arrange to follow up with a phone call after a few days to discuss whether, after time for reflection the patient agrees for their contact details to be passed to the study researcher. Patient agreement will be noted in the study CRF and professionals' own records so patients are not approached twice. This information will also be passed by professionals to PR service clinicians in case patient accepts referral to PR but not in study. This will prevent PR service clinicians to approach these patients about the study.

- Study posters or information for electronic display boards in waiting rooms will be used to inform patients about the study. People with COPD who are interested in the study will be advised to ask their GP or respiratory nurse if they are eligible for, and would benefit from, a referral to PR. The healthcare professional would decide on clinical grounds whether a referral to PR was appropriate.

The strategy to approach patients for the study from primary/secondary/community sector is illustrated in Figure 1. The illustrated flowchart will be adapted for each site prior to study start as each site might vary in the way patients might be identified and approached for the study among these different sectors.

FIGURE 1. GENERATING PR REFERRALS & PATIENT APPROACH FROM PRIMARY/SECONDARY CARE/COMMUNITY



Note: The alphabets and numbers in brackets denote the study CRFs and participant documents, details provided in Box1 (Protocol Section 7.7)

B) *Generic final common pathway: introduction of the study to potential patient participants referred to PR, study screening of potential patient participant (and their carer), recruitment of potential patient participant (and their carer)*

Potential patient participant identification, introduction of study by PR service clinicians and approach by study researcher

1. Potentially eligible patient participants will be identified by PR service clinicians (or on their behalf by CRN coordinators, where available) from people referred to participating PR services (from primary, community or secondary care). PR service clinicians (or on their behalf CRN coordinators, where available) will introduce the study to patients either by phone or face to face, give/post the study leaflet, and obtain verbal agreement for their contact details to be passed to the study researcher.

If a potential patient is unsure but willing to receive some study information and to be followed up, the PR service clinician will give/post study leaflet and arrange to follow up with a phone call after a few days to discuss whether, after time for reflection the patient agrees for their contact details to be passed to the study researcher.

This step is illustrated in Figure 2 and the flowchart will be adapted for each site as mentioned above.

Strategy to facilitate and optimise this step: This strategy of patient identification and introduction of study has been used previously in another COPD study and was instrumental in helping the study reach its recruitment target (personal communication, Dr Patrick White). We have developed this process informed by our preliminary discussions with PR services. This process will be discussed and approved by the clinicians and managers at each participating PR service site; patient referral from primary, secondary care varies and processing of patient referral among PR services varies exemplified in the table below. The research team will provide all training, tools, and study documentation to PR services and schedule regular meetings for PR service clinicians to help facilitate this process.[54] We wish to ensure that the trial is appropriately represented to patients, and that agreement for contact details to be given to researchers is requested properly.[55]

PR Site						
	Pilot trial sites					
		Main trial sites				
	Homerton hospital (east London (EL))	St Mary's hospital (west London (WL))	Glenfield hospital (Leicester (LE))	(south Warwickshire (SW))	Guys and St Thomas hospital (south London (SL))	Atrium (Coventry (CV))
Sources of referral; Assessment of suitability of referral	GP practices, secondary care, self-refer where known. Receive	Clinical team, GP practice; COPD optimisation referral (electronic	GPs, clinical teams, fax, paper, electronic	GPs, clinical teams	primary care outpatient, chest clinic consultation clinics, rest from a mix	GPs, clinical teams

	medical summary (paper +electronic) which is screened and based on screening referrals are accepted or rejected.	) which does not specify that patients are referred for PR. The PR team have to assess if the patients are suitable for PR.			of community nurses, physios in hospital, Integrated Respiratory Team (IRT), oxygen clinic and under a third from admissions.	
Method of processing referral received	Patients are sent an appointment letter with assessment appointment date and leaflet (what PR is), pre-assessment questionnaires are sent - CAT, HADS, PREM (developed locally).	They are sent letters with appointment date. Patients are usually phoned by physio team a week before their assessment to address any queries or concerns.	The senior PR staff review the referrals then log them on a system which then generates an appointment.	Triage prior face to face prior to seeing them at assessment	All referrals are uploaded onto EVS and vetted by one of three PR clinicians electronically. The clinician decides whether to accept the patient for PR at STH, reject as not appropriate, or re-direct to local PR service. The referrals that are accepted for PR at STH are moved within EVS onto a booking list that is accessible by the Physio Referral Management Centre	Phone patients up

					(RMC). The staff in the RMC then book the appointment on PIMS following the Trust Access Policy.	
Time from referral to attendance at PR assessment	8 weeks	4-6 weeks	9 weeks	8 weeks	8 weeks	4-6 weeks
Time from assessment to attendance at PR sessions	8 weeks	4 weeks	0-3 weeks	To confirm	4 weeks	4 weeks

2. The contact details of potential patients will be noted and passed to the researcher following obtaining of verbal agreement. The researcher will phone the potential patient after a few days and provide them with further information about the study, answer any questions they may have. If the patient is potentially interested in participating, the researcher will post the study invitation letter and information sheet and make an appointment to visit them to carry out screening for study eligibility. They will ask the patient if they have a carer who they would also like to involve in the study. The study documentation is theory-based; use of theory to draft study documentation has previously shown to improve attendance in study of cardiac rehabilitation[56] and advice has been sought from patient advisors on the study documentation to make sure the language is clear and easy to understand.

Potential patient screening to assess study eligibility criteria

3. The researcher will visit the patient at a time and place convenient to them, answer any further questions the patient (& carer) may have about the study. If the patient (& carer) is (are) still interested in participating in the trial, the researcher will formally screen the patient (using the HADS score and spirometry) to see if they meet the study eligibility criteria.

The study screening results will be sent via a letter reporting their spirometry results and the HADS to the GP with the patient's written permission. If the HADS indicates possible severe levels of anxiety or depression (score >15) then this will be highlighted so that the GP can arrange further assessment.

Participant (Patient & Carer) recruitment

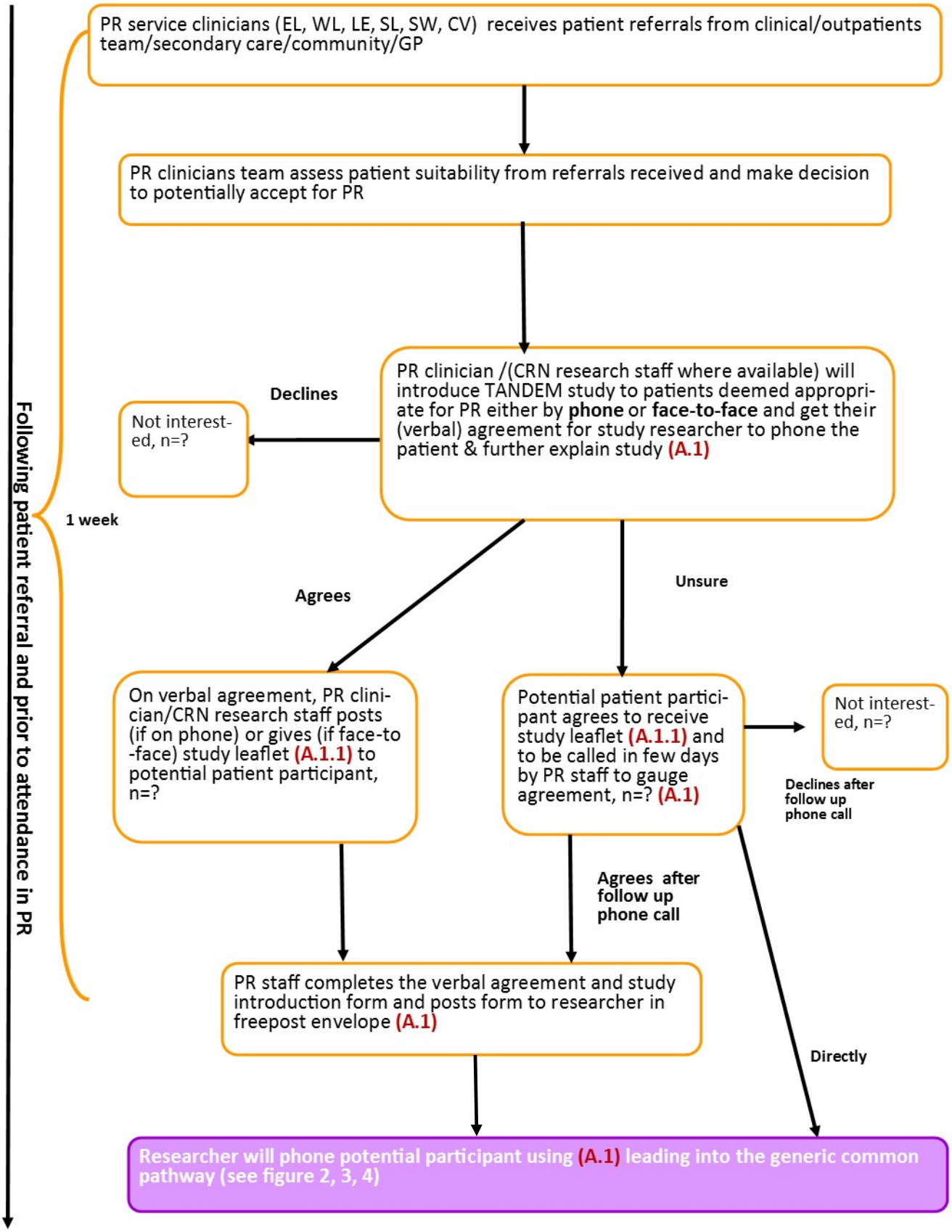
4. If the patient meets the study criteria and is willing to participate in the study, the researcher will take written informed consent from patient (and carer if they wish to participate) and recruit them into trial. If the patient meets the study criteria, but wants time to consider participation, a further appointment will be made.

Recruitment target

In total 45 patients will be recruited for the Phase II study and 430 patients for phase III (if the internal pilot is a success, then the 45 patients will be counted in the main trial and so we will need 385 patients)

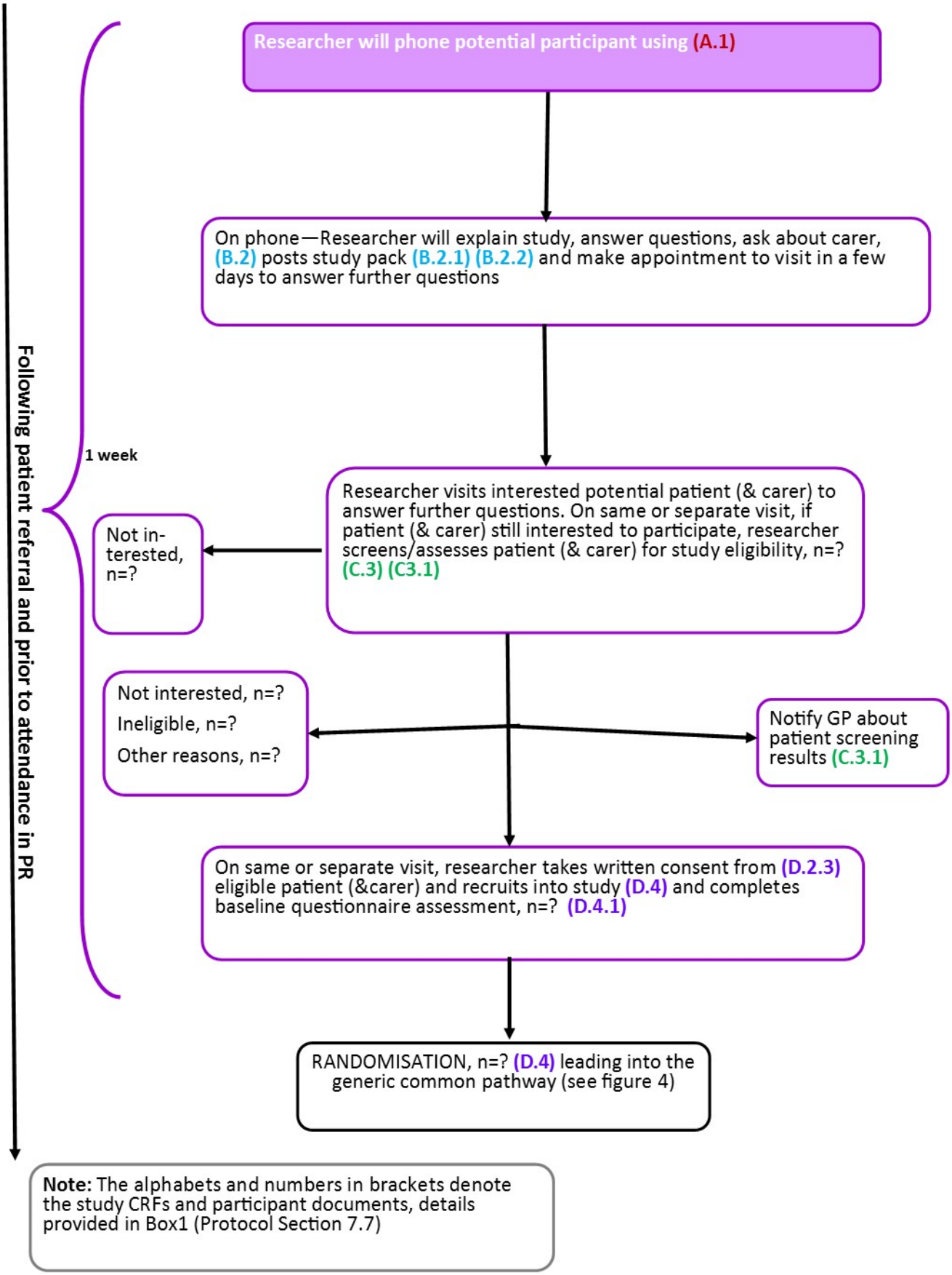
Step 2, 3, 4 is illustrated in Figure 3. Figure 4 illustrates the participant flow in the trial. Box 1 is the key to all flowcharts illustrated (Figure1-Figure 4).

FIGURE 2. PATIENT APPROACH FROM PR SERVICES following their referral



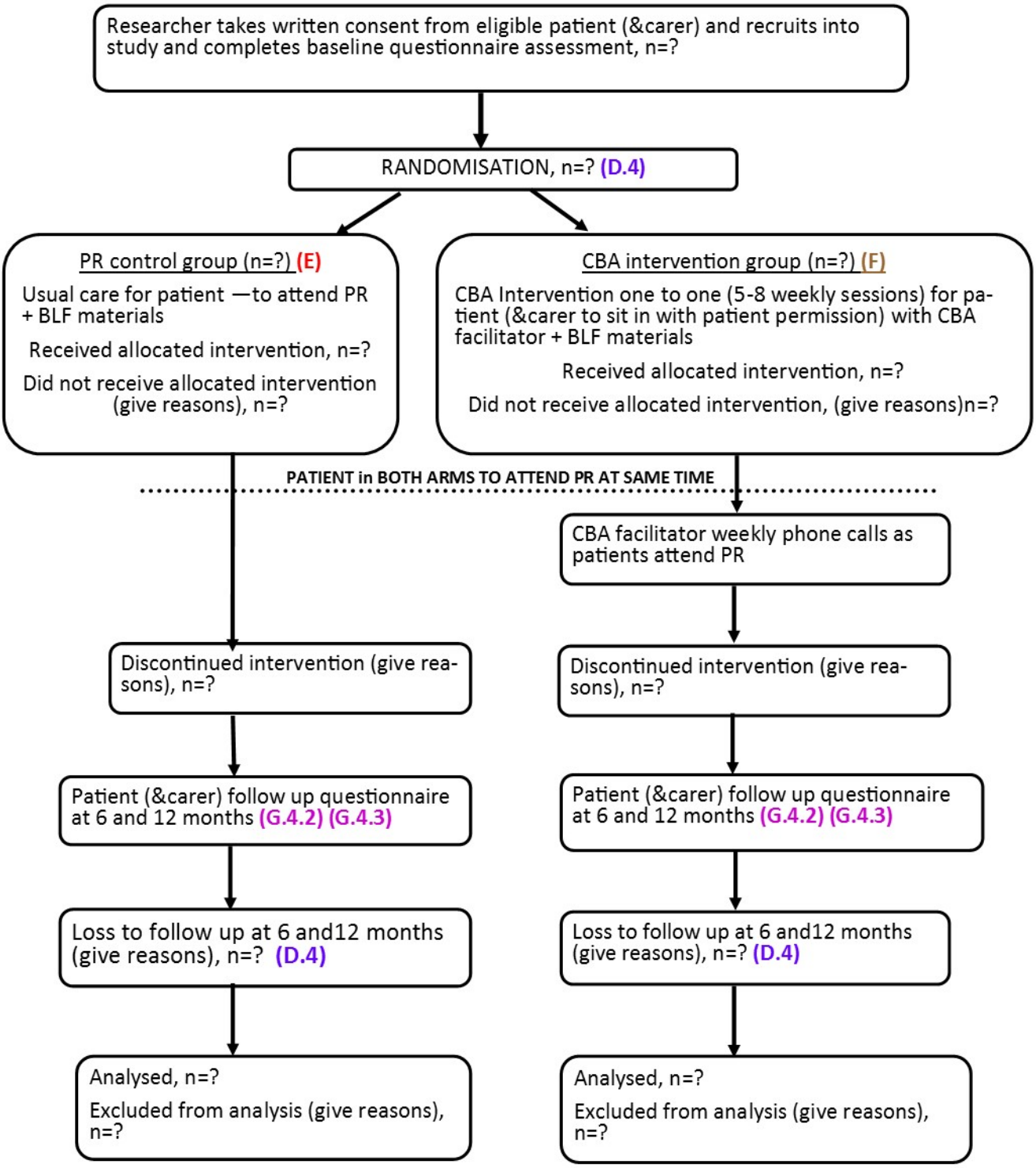
Note: The alphabets and numbers in brackets denote the study CRFs and participant documents, details provided in Box1 (Protocol Section 7.7)

FIGURE 3. PARTICIPANT (Patient & Carer) RECRUITMENT



Note: The alphabets and numbers in brackets denote the study CRFs and participant documents, details provided in Box1 (Protocol Section 7.7)

FIGURE 4. RCT PARTICIPANT STUDY FLOW



Note: The alphabets and numbers in brackets denote the study CRFs and participant documents, details provided in Box1 (Protocol Section 7.7).

Box 1. Key of study CRFs and participant (patient & carer) documents illustrated in flowcharts (Figure 1-4) and other participant documents not illustrated in figures but related.

- Coloured outline denotes **ROLE OF PR service clinician/(CRN research staff** where available) (before randomisation)
- Coloured outline denotes **ROLE OF STUDY RESEARCHER** (before randomisation)
- Coloured outline denotes **ROLE HCPs (GP/Respiratory nurse) or (CRN Research professionals** (before randomisation)
- Coloured outline denotes **study participant flow and ROLE OF STUDY RESEARCHER** (after randomisation)

(A) Potential participant identification and TANDEM introduction pack
- Preamble document for participating site teams to introduce study
- **(1)** Pre-screening (Identification log): verbal agreement and study introduction CRF for staff member
- **(1.1)** Study leaflet for PR site, **(1.2)** Study poster for other health care sectors, **(1.3)** Study leaflet for other sectors
- Freepost envelope, Spare freepost label

(B) TANDEM study invitation pack for potential participant
- **(2)** Researcher explain study and posts to potential patient participants:
- **(2.1)** (Patient & Carer) Study invite letter
- **(2.2)** (Patient & Carer) Study information sheet
- Freepost envelope, spare freepost label

(C) TANDEM screening of potential participant for study eligibility
- **(3)** Screening log for researcher
- Screening equipment for researcher
- **(3.1)** Notify GP by letter of screening results (done by patient/researcher)

(D) TANDEM participant enrolment/recruitment & baseline assessment post randomisation
- **(2.3)** Patient (& Carer) informed consent form
- **(4)** Enrolment log, Randomisation log & Withdrawal log for researcher
- **(4.1)** Patient (& Carer) participant baseline questionnaire with researcher

(E) PR Control group
- Control materials- BLF materials

(F) CBA Intervention group
- Intervention materials including BLF materials
- **(5.1)** Contact List of CBA participants given to CBA facilitator by researcher
- **(5.2)** CBA sessions Contact log to make appointments to visit patient
- **(5.3)** PR sessions contact log by CBA facilitator
- **(5.4)** CBA clinical case notes form with **(5.5)** summary of notes for GP/PR team
- CBA facilitator assessment competency/CFARS scoring grid/Treatment competency measure

(G) TANDEM Follow up assessment post randomisation
- **(4.2)** 6 & **(4.3)** 12 month patient (& carer) follow up questionnaire with researcher

PR Sites	Referral to assessment	Referral to attendance	Assessment to attendance
EL (east London)	8weeks	16weeks	8weeks
WL (west London)	4-6weeks	10weeks	4weeks
LE (Leicester)	9weeks	12weeks	0-3weeks
SL (south London)	8weeks	12weeks	4weeks
CV (Coventry	4-6weeks	8weeks	4weeks
SW (south Warwickshire)	8weeks	10weeks (to confirm)	To confirm

Other participant documents:
(6). GP practice/clinic invite letter **(6.1)** GP practice/clinic information sheet
(7) CBA facilitator invite letter **(7.1)** facilitator information sheet **(7.2)** facilitator consent form
(8) Other stakeholder invite letter **(8.1)** stakeholder information sheet**(8.2)** consent

C) *Recruitment process of CBA facilitators*

The CBA facilitators (respiratory health professionals) will be part of the study team. Each facilitator will be asked to sign a contract acknowledging the role and duties involved in the study. The facilitator will be formally invited, via invite letter and information sheet to participate in the study for collection and analysis of interview and fidelity data. Written consent will be taken to confirm participation in the study.

7.8 Retention/ withdrawal from the Study

Study participants may withdraw from the study at any time and without any reason and this will be made clear in all participant study documentation. In addition, we will also ascertain at the time of withdrawal whether participants want previously collected data and routine health care use data to be retained within the study or removed.

A participating site may choose to withdraw from the study at any time. As per the service contracting agreement (the Statement of Activities form) the site will give the study team a written notice if they wish to withdraw from the study so the study team has enough time to close the site and ensure all data have been collected and all formalities e.g. payment, where relevant, can be completed.

8. METHODS: Assignment of interventions in trial

8.1 Allocation

Randomisation will be performed using a central internet or telephone service, using minimisation with a random element, balanced for important participant characteristics to ensure treatment groups are well matched at baseline.
The minimisation factors are:

1) HADS-Anxiety Scale, with categories: 0-7, 8-10, 11-15
2) HADS-Depression Scale, with categories: 0-7, 8-10, 11-15
3) Modified MRC Dyspnoea Scale, with categories: 0-2, 3-4
4) Smoking status, with categories: smoker, non-smoker

Randomisation will be implemented using a central internet service. Allocation concealment will be maintained through the use of the centralised service.

8.2 Blinding

The facilitators delivering the CBA intervention will not be involved in delivering routine PR to control or intervention patients to avoid any contamination. Healthcare providers will be aware that individuals are in the study and, only with patient permission, will be aware of allocation arm if intervention participants allow a brief summary of their CBA intervention sessions to be sent to their GP and to the PR team at the end of intervention delivery, or if there are particular issues related to PR which have been discussed by the patient during the CBA intervention.

We will develop training and quality control measures to try to minimise the risk of outcome collection bias, this will be assisted by the collection of data straight onto tablet computers. Research staff collecting outcome data directly from patients will

not be involved in the delivery of the intervention and we will attempt to maintain blinding. The statisticians/data analysts will be blinded. Data extraction from primary care records will be done by masked study personnel as will data entry.

9. METHODS: Data collection, management and analysis

9.1 Data collection methods

All- Trial (including health economics and process) data			
Type of data	**Time of data collection; and personnel involved**	**Source and method of data collection**	**Outcome Measure**
Clinical: Anxiety/depression, lung function,	Screening; researcher	Potential patient participants; screening log	HADS measure, Spirometry,
Demographics: Date of birth, gender, marital status, postcode, employment, age completed full-time education Clinical: Home oxygen, age when first diagnosed, comorbidities, attendance at PR Breathlessness	Baseline; researcher	Patient participants; supervised self-complete questionnaire	mMRC Breathlessness scale
Clinical: Smoking status	Baseline & 6 and 12 months; researcher	Patient participants; supervised self-complete questionnaire	
Health care use List of current medications All health care contacts (including hospital admissions, A&E attendance, primary care attendance, home visits by GPs etc)	Baseline & 6 and 12 months; researcher	Patient participants; supervised self-complete, questionnaire primary care medical records and NHS.data	Current medications
Health status measures	6 and 12 months; researcher	Patient participants; supervised self-complete questionnaire	HADS-A & HADS-D,
	Baseline & 6 and 12 months; researcher	Patient participants; supervised self-complete questionnaire	BDI II, BAI, IPQ-B, SGRQ, EQ-5D-5L, heiQ, Time Use Survey (adapted)
Carers			

Demographics: Age, gender, relationship to patient	Baseline; researcher	Carer; self-complete questinnaire	
Wellbeing measures	Baseline & 6 and 12 months; researcher	Carer; self-complete questionnaires	ZBI, WEMWBS
Process data			
Participation (i.e. Attendance, completion, withdrawal) Respiratory HCPs recruitment, attendance and completion of training	Part of study set-up; study team	CRFs	n/a
Study participation Patient and Carers	Over the study period; researcher	CRFs	n/a
Intervention participation Patient and Carers	Following allocation to intervention, facilitators and Health care use	CRFs	n/a
CBA sessions log during delivery of sessions	During intervention delivery; facilitator	CRFs	n/a
Fidelity data	During and following intervention delivery; study team/researcher	CRF and sample of CBA sessions audio-recording	CBT Techniques for Palliative Care Practitioners Ratings Scale, low-intensity competency assessment
Interview data	Following intervention delivery and at end of study; researcher	Topic guide	Understanding views and experiences

9.2 Data management

All PCTU SOPs with regard to data management will be adhered to by the study team. A data management plan will be written to cover all aspects of managing the data such as, the CRF design, the data management system for data collected, data entry, data handling processes including data checking, secure integration of pharmacy data, query management and cleaning, data transfer, quality control procedures, processes for interim and final data extractions, the procedures for freezing and locking the databases.

CRF design

The PCTU SOPs including the associated documents on CRF design have been used to design the relevant CRFs for the trial. All the data to be collected on the CRFs has been provided in Section 9.1 The CRF documents contain the Participant ID, Study name, Site number/ID, Visit Details, Date of Visit, Researcher name, CBA facilitator (where appropriate), CRF document name and other relevant information on each page and space to record appropriate signatures. All questionnaires, to be captured in CRFs, will receive all necessary research governance and ethics approval.

Data management system and data storage

All study data will be uploaded onto a dedicated folder on the secure virtualised environment at the Barts Cancer Centre (BCC). This is where all data analysis of the PCTU trial data is carried out. The BCC environment requires dual factor authentication to access the portal via Citrix and the folders where the data are stored are only accessible to the appropriate members of the PCTU and the TANDEM study team.

Tablets (with 3G/4G connection) will be used to carry out the data collection (including the data collected using the EQ-5D-5L measure, following testing because according to Mapi, the VAS scale, part of the EQ-5D-5L measure cannot be digitised for online use because the VAS scale needs to be represented exactly as on the paper. If it cannot be digitised, then the EQ-5D-5L data will be captured on the paper CRF first and then entered onto the database via the tablet). The tablet will be synced with the secure online data management system, OpenClinica database. The database in OpenClinica will mirror the CRFs to ensure the data entry is accurately recorded. The online 3G/4G connection will help to capture data securely and prevent data loss. It will reduce any need for data entry to 'interpret' paper forms. The use of tablet to enter data will be tested prior to start of the study and only authorised members of the study team, who are fully trained, involved in the data collection will be granted database user accounts.

The OpenClinica software is provided by OpenClinica and is hosted by QMUL IT services in the UK.

The data recorded on encrypted audio-digital recorders from interviews and fidelity assessment will be collected by a study researcher and brought back to the host Centre. The data recordings will be uploaded into the PCTU safe haven (SFTP – secure file transfer protocol) which will then be transferred by the data manager into the TANDEM folder within the BCC Citrix environment.

Prior to transfer of data to the PCTU safe haven, all encrypted recorders containing data will be kept in a locked cabinet in a locked room with key access where access is controlled and only available to delegated study staff. The audio-recordings will be deleted from the recorder once the data is in the BCC Citrix server. The transcriber will be trained in information governance and issued with a Citrix account to securely access the sound files for transcription. The transcripts will be saved in Word document format onto the secure environment which will be accessed by the study researcher for analysis. Nvivo software within the secure Citrix environment will be used for the facilitation and analysis of the qualitative data.

The trial statistician will receive an integrated dataset which is blinded to participant allocation.

The method of data collection and data management has been discussed with the PCTU data management team. The TANDEM study team will develop a data management plan in conjunction with the PCTU data management team. This will ensure that data security, quality and accuracy are maintained to a high standard.

Record Retention and Archiving

The internal pilot and feasibility study and main trial is part of the 51month research programme. The data collected over the study time period will be kept in the secure online data management environment called Citrix. The Citrix server can be used for long term backup and storage. When the research programme is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years. For trials sponsored by QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre which is based at 9 Prescot street.

9.3 Statistical methods

All analyses will be by intention-to-treat, and will include all participants for whom an outcome is available, and will analyse them according to the treatment group to which they were randomised. All analyses will account for clustering-by-therapist in the intervention arm, and each analysis will present a treatment effect (difference in means for continuous outcomes, odds ratios for binary outcomes) with a 95% confidence interval and a two-sided p-value. Outcomes at 6 and 12 months will be analysed using a mixed-effects regression model that will account for correlation within CBA facilitators, and correlation between outcomes at 6 and 12 months. This approach will provide unbiased estimates even if some participants only provide data at one of the two time points. Analyses will adjust for the outcome measured at baseline whenever possible.

We expect that participants in both treatment groups will be offered the chance to begin PR within a similar time frame (approximately 3 months from randomisation). If there are systematic differences in the time to begin PR between groups this may lead to better outcomes in the group that begins PR later, as the effects of PR will have had less time to wear off before the 6 month follow-up period. Although every effort will be made to ensure the time from randomisation to offer of PR is the same in both groups, we will perform a sensitivity analysis to assess the impact that this has on results. We will also perform sensitivity analyses to assess the robustness our results to various assumptions regarding missing data, or participants lost-to-follow-up: for this we will assess the feasibility to use a multiple imputation approach (depending on the entity and structure of missingness).

A detailed Statistical Analysis Plan will be prepared by the PCTU Statisticians.

9.4 Process evaluation methods and analysis

The aim of the process evaluation is to examine the processes by which the intervention and trial is conducted and implemented and consider the effect of these on the outcomes of the study. Thus, informing implementation if the trial is successful

or assisting interpretation of findings if not. A process evaluation will be conducted within both the pilot and main trials.

The interviews will be conducted using a semi-structured interview guide.

Phase II – (Internal pilot and feasibility study) PROCESS EVALUATION

Aim

To inform the decision on whether the pilot remains as an internal pilot or moves to an external pilot based on the extent of changes needed to either the intervention or research processes, and to refine the design of the process evaluation for the main trial.

Research objectives and method of data collection regarding:

(A) TANDEM intervention

i) To assess the acceptability of the intervention (CBA, PR & Telephone Session components) to CBA participants including consideration of:

- Content - in session, home practice
- Therapeutic alliance
- Practicalities – location, timing

Indicated through patient interviews and data logs on uptake, attendance, completion of both CBA sessions and PR sessions

ii) To consider the feasibility of implementing the intervention including consideration of

- intervention drop-out/disruption to delivery of the intervention due to health problems

Indicated through data on delivery of CBA sessions, cancelled/re-scheduled appointments

iii) To assess the acceptability of the intervention to HCPs delivering the intervention (CBA facilitators, Supervisor) with consideration of:

- Patient facing intervention – including content, structure, logistics including CBA sessions, telephone support and integration of intervention components
- HCP training – content, logistics, supervision, perceived confidence to deliver intervention
- HCP facilitators management with workload
- Supervisors – training received to provide supervision, workload

Indicated through interviews, CBA facilitator training attendance and completion rates, CBA process logs at the end of each face to face patient session

NB – interview topic guide will be informed by normalization process theory (NPT) key constructs http://www.normalizationprocess.org/

- Coherence – sense- making work that people do individually and collectively when they are faced with the problem of operationalizing some set of practices.

- Cognitive participation – relational work that people do to build and sustain a community of practice around a new technology or complex intervention.

- Collective action – operational work that people do to enact a set of practices, whether these represent a new technology or complex healthcare intervention.

- Reflexive monitoring – appraisal work that people do to assess and understand the ways that a new set of practices affect them and others around them.

iv) To assess the acceptability of the intervention to PR teams within participating sites

- did PR teams within the intervention sites notice any differences, challenges to PR delivery
- to understand any changes that were made to routine PR to accommodate needs of the TANDEM intervention

Indicated through (short) interviews with PR teams.

v) To assess the acceptability and feasibility of control group including materials i.e. DVD, information leaflet

Indicated through interview with control patients, differential drop out between controls and intervention (from PR health service records).

vi) To monitor delivery of the intervention i.e. fidelity assessment to assess whether the intervention was delivered as intended with respect to adherence/competency

Indicated through intervention delivery process logs and audio-recordings of the CBA sessions, participant (patients and CBA facilitators) interviews to assess perceptions of the intervention, e.g. what aspects were helpful (or not)

Structured data collection during intervention delivery

To understand whether delivering the intervention was feasible, the work load required to deliver the intervention, and how this may have varied from the protocol the following will be collected in Phase II and refined as necessary for Phase III process evaluation. N.B. This is separate from the intervention fidelity.

i) contacts made between CBA facilitator and participant client to arrange/rearrange sessions including contact log where all contacts will be recorded. This will allow monitoring of workload as well as tracking number of cancellations, re-arranged sessions etc.

ii) Data on the intervention pathway

Uptake into the CBA intervention (i.e. defined as numbers of people who participate/attend CBA sessions by numbers of people who were allocated to the intervention), intervention drop-out rates (i.e. defined as number of those not completing a minimum of sessions 1-3 by number of people allocated to intervention) and completion of i) the CBA sessions, ii) the PR sessions, iii) the telephone calls

made during PR sessions will be calculated in both Phase II and Phase III evaluations, as will the period over which CBA sessions took place and period between completion of CBA sessions and initiation of PR.

iii) Post CBA session data collection
Data will be collected from the CBA facilitator following each session on whether patients completed homework practice, who was present for sessions and data on time of sessions.

(B) Trial research processes

i) To explore acceptability of recruitment processes from patient perspective e.g. process of recruitment.

Indicated through interviews with both intervention and control participants, data on study enrolment and withdrawal logs

ii) To assess the acceptability of outcome assessment process from patient participant perspective

Indicated through interviews, and completion rates of outcome measures

iii) To explore acceptability of recruitment processes from clinical teams involved in patient approach and logistics of intervention participants attending PR, any evidence of contamination from intervention to control group

Phase III – (Main trial) PROCESS EVALUATION
Aim
To assist in explaining the results of the main trial, particularly where a non-significant effect may have occurred. In addition, providing guidance towards successful implementation of the intervention in to routine clinical practice.

Objectives – Intervention
i) To describe how the intervention was delivered in practice and implications for implementation if successful

ii) To understand whether adaptations to the intervention are necessary depending on the clinical context in which it takes place e.g. if intervention is delivered through primary care, secondary care or solely via PR services.

Fidelity assessment of intervention delivery among CBA facilitators – Phase II and III
Clinical training, supervision arrangements and assessing fidelity
Promoting fidelity
We are providing extensive training and on-going mentoring for the CBA facilitators. All facilitators will receive clinical supervision from a senior clinical psychologist on a monthly basis, principally by phone, Skype or video conferencing facilities. With

consent from participants' audio-recording of intervention sessions will be used to form part of clinical supervision. In addition, facilitators delivering the intervention will be asked to complete a brief process log and checklist after each encounter (without any confidential patient data) which records the elements of the session delivered and homework set. Together with a robust and standardised training package, the clinical supervision, in addition to promoting the safety and quality of the intervention, will promote intervention fidelity.

Assessing fidelity

Fidelity will consider both aspects of facilitator competence in skill delivery and adherence to the prescribed intervention.[81] During the internal pilot and feasibility study the logs kept by the HCPs (described above) will be validated against recordings of the sessions and the documented module in manual. All logs will be scrutinised as part of the assessment of fidelity.

PROCESS EVALUATION ANALYSIS

Qualitative data analysis for the pilot and main process evaluations will use a 'thematic framework' approach[57] aided by use of NVIVO data management software. A multidisciplinary study team work approach will be used to provide validity and reliability in data interpretation.

Data logs and other numerical data will be presented descriptively. A logic model will be developed incorporating hypothesised change mechanisms.[58]

9.5 Health economic methods and analysis

The economic evaluation will be carried out as part of the main trial, with unit costs and instrumentation (i.e. the adapted Client Service Receipt Inventory) required for the measurement of resource use developed during the Phase II. The economic analysis will assess whether the addition of a tailored psychological intervention, combined with the availability of standard PR, is likely to be a cost-effective use of resources. The economic evaluation will take an NHS and Personal Social Services Perspective as currently preferred by the National Institute for Health and Care Excellence (NICE).[59] CBA sessions and subsequent HCP facilitator support will be centrally recorded and the costs of HCP facilitators will be calculated in line with the methods used for production of unit costs by the University of Kent.[60] This source will be used to generate costs of other services recorded in the Client Service Receipt Inventory, supplemented where possible with administrative data through primary care or HSCIC sources.

Total health and social care costs will be compared between the groups using a regression model with baseline costs controlled for. Cost data are usually skewed and so bootstrapped confidence intervals will be generated around the cost difference. Incremental cost-effectiveness will be evaluated based on the primary outcome measures and on quality-adjusted life years gained (QALYs). The latter will be derived from the EQ-5D-5L using area under the curve methods.[61] Point estimates of cost and outcome differences between the groups will be used to produce incremental cost-effectiveness ratios (ICERs). ICERs will also be evaluated probabilistically using cost-effectiveness planes generated from 1000 bootstrapped re-samples of the data. This will be used to evaluate the probability of the intervention

being dominant in terms of being of lower cost and more effective according to the trial primary outcome measures and QALYs measured within-trial. Further interpretation of the results will use cost-effectiveness acceptability curves (CEACs) which will provide information on the likelihood that the addition of a tailored psychological intervention will offer a cost-effective addition to patient rehabilitation given current incremental cost per QALY threshold (£20k to £30k) used by NICE to determine whether an intervention is a cost-effective use of health care resource. COPD is a chronic condition with the possibility that the intervention could continue to have an impact on costs and clinical outcomes beyond the follow-up period covered by the proposed trial. We will therefore also explore, during the internal pilot and feasibility study phase of the project, the feasibility of combining data from the trial with other existing evidence to model these longer-term impacts which would be used in sensitivity analysis if within-trial based findings relating to cost-effectiveness prove inconclusive. More generally, impact of uncertainty arising from key assumptions and methods (e.g. costing perspectives) will also be explored through sensitivity analysis

10. METHODS: Monitoring

10.1 Data monitoring committee and Independent Trial committees

There is an independent data monitoring and ethics committee (DMEC) comprising three members and an independent trial steering committee (ITSC) comprising seven members (see boxes below). The DMEC includes one clinician experienced in the clinical area and two statisticians.

The first meeting will be scheduled for March 2017 prior to start of the internal pilot and feasibility study. The meeting will comprise all members of the DMEC and ITSC to cover introductions, scheduling of meetings over duration of the study e.g. every 6, 9 months or 12months and discuss the reporting structure using the Damocles Charter (PCTU_SOP TM_02 Associated document A – part of the Oversight External Trial Oversight Committee).

10.2 TANDEM trial management

The TANDEM Study Steering committee comprises of all the co-investigators. Arrangements are in place to meet every 6 weeks for the duration of the study to discuss all aspects of study progress outlined in the Gantt Chart (Appendix 16.1).

The trial/research management meeting will be set up for the study prior to start of the trial. The trial management group (TMG) will comprise the CI, trial manager, trial statistician researchers in the participating study centres and clinical staff of participating study research sites. Regular meetings will be scheduled with this group to discuss training for staff (researchers, clinical staff), trial recruitment, milestones and any issues affecting these. These individuals will also be invited to attend the steering committee meetings.

People on the Data Management and Ethics Committee (DMEC):

Prof	Toby	Prevost	Head of Statistics, Imperial Clinical Trials Unit, Chair in Medical Statistics and Clinical Trials	School of Public Health, Imperial College London, Stadium House, 68 Wood Lane, London W12 7RH

Dr	William	Man	Consultant Chest Physician	Royal Brompton and Harefield NHS Foundation Trust, Hill End Road, Harefield,Middlesex, UB9 6JH
Dr	Sally	Hopewell	Senior Research Fellow	/ Oxford Clinical Trials Research Unit / Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences / University of Oxford / Botnar Research Centre / Windmill Road / Oxford / OX3 7LD / UK

People on the Independent Trial Steering Committee (ITSC):

Prof	Deborah	Fitzsimmons	Dean of Postgraduate Research	Swansea University, Singleton Park, Swansea, Wales SA2 8PP Wales, UK
Dr	Louise	Restrick	Integrated Consultant Respiratory Physician and London respiratory Network Co-Lead	Whittington Hospital, Magdala Avenue, London, N19 5NF
Dr	Shona	Fielding	Lecturer in Medical Statistics	The Institute of Applied Health Sciences, University of Aberdeen, Polwarth Building, Aberdeen AB252ZD
Mr	Chris	Warburton	PPI representative (NOT independent member)	106 Hillfield Avenue, Hornsey, London N8 7DN
Prof	Christopher	Butler	Clinical Professor, Institute of Primary Care & Public Health	Institute of Primary Care & Public Health, Cardiff University School of Medicine, Neuadd Meirionnydd, Heath Park, Cardiff, Wales CF14 4YS
Dr	Robert	Stone	Consultant Physician	Somerset Lung Centre, Musgrove Park Hospital, Taunton TA1 5DA

Interim analysis

We do not foresee the need of an interim analysis (also because multiple analysis of an ongoing study can increase the risk of a false positive error) but if the DMEC/ITSC might require it for a suspect of potential harm and/or suspect of superiority/futility of one intervention (versus the other). An independent statistician, blinded to the intervention allocation, will perform the analyses following the main indications of the overall statistical analysis plan and report the findings to an ad-hoc joint meeting where the interim findings will be discussed and eventual decision on particular stopping criteria agreed.

10.3 Auditing

The study has undergone a risk assessment by the PCTU QA team and has identified the study as low risk. Based on this level of risk, on-site monitoring will not be required for this research project. An annual audit will be conducted by the PCTU QA

manager to ensure compliance with the study protocol, PCTU and sponsor SOPs and research governance requirements.

Personnel from sponsor and JRMO may monitor or audit the study according to the protocol, sponsor's SOPs, GCP and the application regulatory requirement.

Internal audits may be conducted by a sponsor's or funder's representative.

10.4 Safety consideration/Risk protocols

Safety considerations

We do not foresee any risks or burdens for the research participants (patients with COPD, their carers and CBA facilitators) in this study. However, we will be aware of the risk of psychological distress for patient participants. The minimisation of risks and burden on the patient participants including to carers and to professionals has been explained in section 10.4 of this protocol. The intervention and pulmonary rehabilitation are tried and tested evidence-based interventions though they have not previously been used in combination. All adverse events and serious adverse events will be recorded and reported in line with the ethics committees and sponsors requirements. Risk to CBA facilitators and researchers visiting patients' homes to conduct interviews will be minimised by our adoption of the Queen Mary lone worker policy.

Risk protocols

There will be a risk protocol for CBA facilitators delivering the intervention and researchers collecting data if a participant becomes distressed about their situation and their condition; more seriously expresses suicidal intent or is at risk of harm to themselves or others. The protocol has been developed by Dr Sarah Saqi-Waseem, Consultant Clinical Psychologist (study co-investigator). Only where the participant or others were deemed at risk would confidentiality be compromised, this will be discussed with participants at the outset of the intervention. Any possible risks to researchers and CBA facilitators will be minimised by following the steps laid out in the protocol of safety for researchers that has been developed by QMUL. In addition, we will also incorporate local PR services' emergency contacts for risk management (usually a list of relevant local services).

10.5 Harms/Safety reporting

QMUL will act as sponsors of the study and will have systems in place to monitor the progress of the research study and respond to any development of the research that puts the safety of the study team and research participants at risk.

The CI/co-CI and all members of the research team will comply with all current regulations applicable to the performance of the project, including, but not limited to, the NHS Research Governance Framework for Health and Social Care (April 2005), the World Medical Association Declaration of Helsinki (1996), the Human Tissue Act (2004) and the Data Protection Act (1998). JRMO SOP 26b version 2.0 on Pharmacovigilance and Safety Reporting for Sponsored non-CTIMPs will be followed.

Any possible risks and burden to the research participants will be minimised by:

- provision of the participant information sheet which will describe the study aim and purpose, why they have been approached to participate, what their involvement would mean, any risks and benefits of participation, the voluntary nature of participation and that withdrawal from study can be at any time, details about type of data collection, data storage and security, assurance of anonymity and confidentiality, details of study funder, study sponsor and ethics review committee with reference number, who to contact for further information and details on the complaint procedures.
- discussion of the information sheet and consent form prior to obtaining written informed consent for study participation
- deciding the date, time and location to conduct the screening, recruitment, delivery of intervention, data collection according to the participants' convenience
- ensuring each participant is comfortable and relaxed during receipt of all study-related procedures
- being aware that participating in the CBA intervention might require considerable investment of time on the part of the patient, carer participants which might be seen as a burden (even though we hope the participants enjoy and benefit from it)
- being alert to the possibility that due to the progressive nature of COPD and co-morbidity anxiety and depression, there is a potential for patient participants to become upset about their situation and their condition. More seriously if a participant expresses suicidal intent or is at risk of harm to themselves or others, the study team (CBA facilitators delivering the intervention and researchers collecting data) will follow a risk protocol developed for these situations by Dr Sarah Saqi-Waseem, Consultant Clinical Psychologist (study co-investigator). Only as a last resort where the participant or others were in danger would confidentiality be, compromised. The risk protocol will be submitted to the ethics committee for approval.

Any possible risks to researchers and CBA facilitators will be minimised by following the steps laid out in the protocol of safety for researchers that has been developed by QMUL. The protocol will be submitted to ethics committee for approval.

Reporting of Adverse Events/Serious Adverse Events

The CI and Co-CI have overall safety reporting responsibility and will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements. The Site PIs, or the medically qualified delegated team member for the study site, will assess the AE or AR to establish if it should be classified as a SERIOUS AE, they will simultaneously report the AE/AR and their deliberations to the CI and Co-CI. All harms data is considered by the DMEC who meet on a regular basis, in addition the Chair of the study DMEC is also informed of all SAEs and may choose to convene extra DMEC meetings as a result.

If the Adverse Event (AE) is not defined as SERIOUS, the AE will be recorded in the study case report form, and the participant will be followed up by the research team. The AE will be documented in the participants' medical notes (where appropriate).

A Serious Adverse Event (SAE) occurring to a research participant will be reported to the Chair of the study DMEC (as part of the routine report produced to DMEC) and to the main REC where in the opinion of the CI/Co-CI 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.

SAEs that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. Guidance will be sought from the HRA website (http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/#safetynonCTIMPSAEs), JRMO SOPs (http://www.bartshealth.nhs.uk/research/strategy-and-policy/standard-operating-procedures/)

Safety form will be completed for each event, signed by the P.I or appropriate staff before forwarding the scanned copy to sponsor. JRMO uses e-reporting for safety reporting to Sponsor (QMUL) Research.Safety@bartshealth.nhs.uk
Fax: 0207 882 7276

11. ETHICS

The CI/co-CI will ensure that the study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements.

Research ethics approval

A detailed review of the ethical issues arising in regard to this study will be provided in the research ethics committee application form and the participant study information sheets and consent forms will be submitted to an ethics committee for review. The participant documents will cover the process of obtaining written consent, the access, storage, and use of data collected.

The study start will be following receipt of REC ethics approval, HRA approval and local NHS permissions.

Protocol amendments

Any protocol amendments will be submitted and conducted in accordance with the Research Governance Framework for Health & Social Care, Second Edition, 2005, and the current applicable regulatory requirements.

Consent

Consent materials comprise a Participant Information Sheet and an Informed Consent Form. We made particular effort to use clear, accessible language in these forms and have received advice on them from our study patient advisors. We have produced:

- a GP practice/outpatient clinic/community clinic information sheet. It covers the study purpose, why have they been approached, what it would mean if they

chose to participate, details of the support (resources and cost) offered if they chose to participate, how patients from their practice might be involved in the study, participation is voluntary and withdrawal from study can be at any time.

- patient and carer information sheet and consent form and CBA facilitator information sheet and consent form. It covers the study purpose, why they have been approached to take part, what would it mean for them if they chose to participate, participation is voluntary and withdrawal from study can be at any time, details about type of data collection, data storage, confidentiality, security, who is the study funded, reviewed and sponsored by, who to contact for further information and details on the complaint procedures.

There is a legal requirement for research data to be archived for a set period (explained in Section 9). Apart from the practice/clinics invited, participants will be given a copy of their signed consent form at the time of their recruitment into the study.

The process of taking consent has been detailed in Section 7.7. All research team members have received appropriate training including good clinical practice training and are experienced in the process of taking consent.

Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

The participant information sheets will set out arrangements relating to confidentiality, security, storage of data and accessibility of data only to the study team. They will also be informed about transfer of any hard copy data about them to the host centre/s for secure and confidential storage. All documentation containing identifiable participant data such as in informed consent forms and contact details logs, will be stored separately from case report forms (CRFs), adverse event logs, in a locked cabinet, in locked room with key code access at the host centre/s. The researcher will add to the informed consent form, the TANDEM study unique ID. All participants will be assigned a unique TANDEM study ID. The CRFs will be pseudo-anonymised with the TANDEM study unique ID. For details of data transfer, data management and data access, see Section 9.

All participants will have the opportunity to contact the study research team if they require more information and the Patient Advice and Liaison Service (PALS) or local Public Health department.

Ancillary or post-trial care

The PR component of the intervention and the PR in the control arm is standard NHS care however for the trial to be viable we need a waiting list for PR of around 3 months, where if it is much longer we propose to purchase additional PR slots so that study participants all have around a three month wait without disadvantaging study non-participants and the participating PR services. We believe this constitutes an excess treatment cost.

Delivery of the CBA intervention by trained professionals, supervised by Dr Sarah Saqi-Waseem, Consultant Clinical Psychologist (study co-investigator) may lead to improvements in the well-being of patient and, indirectly, their carers which is the ultimate aim of the TANDEM trial. The delivery of the psychological components of the intervention during the main trial may become standard care and will be considered an excess treatment cost dependent on the results of the trial. Therefore, the intervention does not pose any specific ethical concerns. All complaints and compensation procedures for any trial-related harms will be outlined in the participant information sheet.

There are no conflicts of interest among the research study team.

12. FINANCE AND FUNDING

The study is funded by the NIHR Health Technology Assessment Programme 13/146/02.

13. INDEMNITY

Queen Mary University of London will be the study sponsor. The sponsorship will be given on the basis of meeting the 'Conditions of sponsorship' which means that the research should be conducted and managed as per the Research Governance Framework for Health and Social Care 2005 and/or the Medicines for Human Use (Clinical Trials) Regulations 2004.

Queen Mary University of London has a no fault indemnity insurance policy for research participants. These compensation arrangements apply where harm is caused to a participant that would not have occurred if they had not taken part in the study. These arrangements do not affect participants' rights to pursue a claim through legal action.

14. DISSEMINATION POLICY

The dissemination of the study results will be by the following means:

1) Through the NIHR Collaboration for Leadership in Applied Health Research and Care collaboration (CLAHRC) East Midlands and the NIHR CLAHRC North Thames, and through these CLAHRCs to CLAHRCs nationwide.

2) To study participants and advisors (patients and carers) through a dedicated study website and hard copy newsletters produced at the end of Phase II and at the end of the whole study. These will be sent to the lay members by email or post according to their preference. Our lay advisors and the CLAHRC North Thames and CLAHRC East Midlands Patient Public and Involvement experts will advise on dissemination to patients and carers.

3) To participating health care professionals through a dedicated study website and an electronic newsletter.

4) To people with COPD and their carers via the British Lung Foundation.

5) To professional groups (e.g. respiratory clinicians, GPs, psychologists, psychiatrists) via papers in peer review journals and at local, national and international scientific meetings.

6) To health service providers and commissioners via the dedicated study website and an electronic newsletter describing our findings to PR services and GP commissioning groups.

7) To the wider public through local and national media and via the dedicated study website.

Anticipated research outputs:

1) **Peer reviewed publications – advancing scientific understanding of the area**. We anticipate at least four peer-reviewed scientific publications from this project (the protocol, feasibility and acceptability of the intervention, the clinical effectiveness of the main trial, the health economic analyses of the main trial).

2) **Development of a training programme to deliver the intervention**. In conjunction with Education for Health we will have developed a proven, documented training module for delivery of the intervention which could be readily disseminated through Education for Health, should the intervention prove effective and cost-effective.

3) **A treatment package that links into, and enhances, established NHS care.**

4) **Communicating research findings to Trusts and commissioners.** By communicating our results directly to Trusts and commissioners we will promote implementation of our findings.

5) Communicating research findings to patients and their carers, and to patient support groups. We are committed to feeding back our learning not only to study participants, their carers, and groups which lobby on behalf of patients, such as the British Lung Foundation, but to the wider population with COPD - not only in respect of social justice but also because patients and carers can themselves help to promote change and service developments.

Reproducible research/Data sharing

In line with the PCTU Data sharing policy v2.0, the PCTU will facilitate appropriate data sharing to maximize the value of research data, including for patient and public benefit. Anonymised individual patient data can be shared without specific consent, as anonymised data are not covered by the Data Protection Act 1998. To facilitate data sharing, we have included a statement, stated in the policy and recommended by the HRA, in the participant consent form and the participant information leaflet

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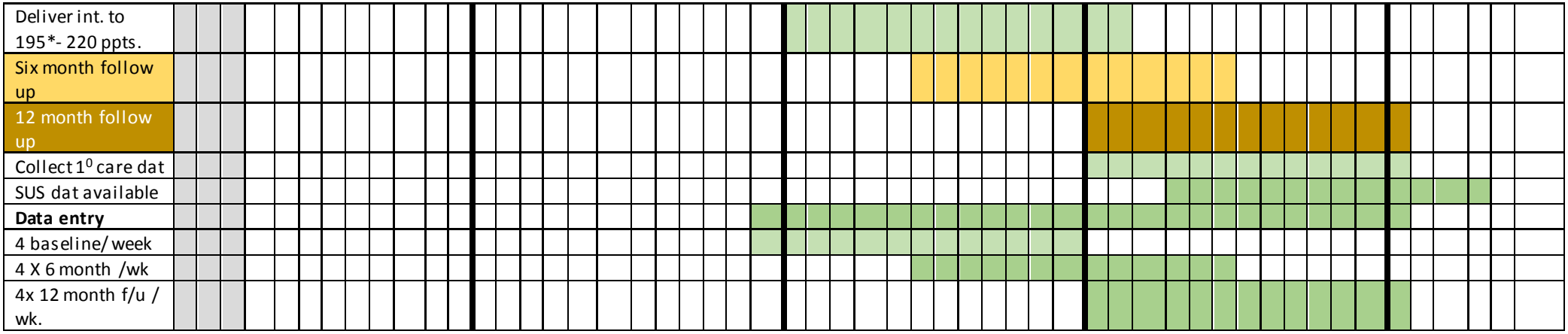
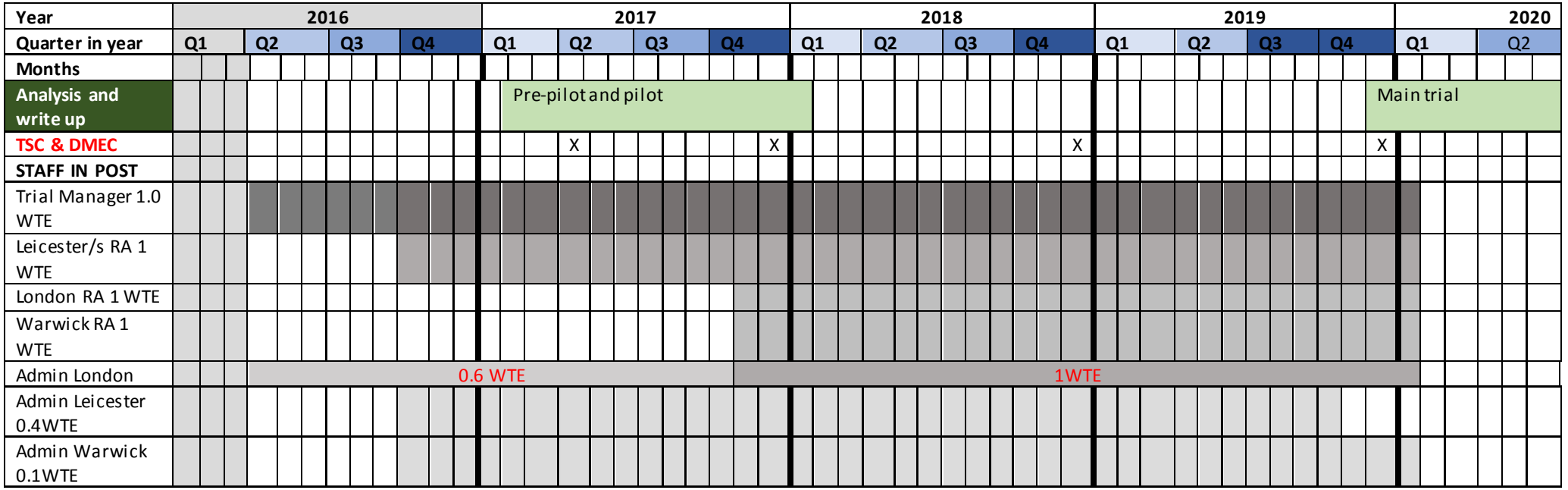
16. APPENDICIES

16.1 Gantt Chart

Year	2016												2017												2018												2019												2020						
Quarter in year	Q1			Q2			Q3			Q4			Q1			Q2			Q3			Q4			Q1			Q2			Q3			Q4			Q1			Q2			Q3			Q4			Q1			Q2		
Months				1											12										24												36												48				51		
				STUDY DURATION																																																				
Study phases				PHASE I & II																					PHASE III																											WRITE UP						
Set up and pre-pilot																																																					
Deliver int.to 6 ppts.																																																					
Ethical approvals																																																					
Pre-pilot																																																					
Pilot & Main trial																																																					
Main trial (amendments?)																																																					
Phase II Internal pilot & feasibility study																																																					
Recruit 45 particpts.																																																					
Deliver intervention																																																					
6 month follow up																																																					
12 month follow up*																																																					
Checkpoint report																																																					
Phase III Main Trial																																																					
Recruit 390*- 430 ppts.																																																					


Deliver int. to 195*- 220 ppts.
Six month follow up
12 month follow up
Collect 1^0 care dat
SUS dat available
Data entry
4 baseline/ week
4 X 6 month /wk
4x 12 month f/u / wk.


Year
2016
2017
2018
2019
2020
Quarter in year
Q1
Q2
Q3
Q4
Months
Analysis and write up
Pre-pilot and pilot
Main trial
TSC & DMEC
X
STAFF IN POST
Trial Manager 1.0 WTE
Leicester/s RA 1 WTE
London RA 1 WTE
Warwick RA 1 WTE
Admin London
0.6 WTE
1WTE
Admin Leicester 0.4WTE
Admin Warwick 0.1WTE

Data entry Clerk 0.4WTE																																																						
PCTU involved																																																						

Plan of investigation and timetable 19 10 16 *assuming Pilot remains internal pilot (study not predicated on this assumption)