# STUDY PROTOCOL

## The Gentle Years Yoga Trial

## Individually randomised controlled multi-centre trial to determine the clinical and cost-effectiveness of an adapted yoga programme for older adults with multimorbidity, including an embedded process evaluation

Version 1.3 23 September 2019

**CHIEF INVESTIGATOR (CI):**


| |
|---|
| Associate Professor Garry Tew<br>Associate Professor of Exercise & Health Sciences<br>Department of Sport, Exercise and Rehabilitation |
| **Phone:** 07773310360 |
| **Email:** garry.tew@northumbria.ac.uk |


**SPONSOR:**

| | |
|---|---|
| University of Northumbria at Newcastle | **SPONSOR REPRESENTATIVE:**<br>Mrs Samantha King<br>University of Northumbria at Newcastle,<br>Sutherland Building, Newcastle upon Tyne<br>NE1 8ST |
| | **Phone:** samantha.king@northumbria.ac.uk |
| | **Email:** 01912437108 |


**FUNDING SOURCES:**
National Institute for Health Research, Health Technology Assessment Programme, ref 17/94/36


**REFERENCE NUMBERS**
Sponsor Project Number:
ISRCTN: Registered 18th March 2019
Registration Number: 13567538
IRAS Project ID: 255698
REC Ref: 19/NE/0072
Trial web site:
https://www.york.ac.uk/healthsciences/research/trials/research/trials/gyy-trial/

PROTOCOL AMENDMENT HISTORY

| **Protocol version and date** | **Details of changes made** |
|---|---|
| Version 1.1<br>Date: 25.04.2019 | 1. Added 'adapted' to Bayliss measure reference in section 10.1.2<br>2. Addition of REC reference number, ISRCTN registration number and webpage link<br>3. Updated contact details of trial team<br>4. Updated NIHR logo following new guidelines<br>5. Updated version number and date in text and footer<br>6. Trial Team Configuration updated in Figure 1.<br>7. There was an error relating to the number of GP practices that will be recruited, this was corrected to 36, in section 10.1.<br>8. Added information about the use of Docmail in section 10.1.<br>9. Added that we will send out regular newsletters to trial participants in section 10.2.<br>10. Definition added regarding planned hospitalisation for a pre-existing condition, in section 15.1.<br>11. The procedure for reporting planned hospitalisations and elective surgery unrelated to the intervention was added in section 15.1.1.<br>12. The procedure for reporting extreme anxiety or depression was added in section 15.1.1.<br>13. Added information about Docmail and data confidentiality in section 18.3.<br>14. Updated to clarify that TSC will take on role of DMC in section 19.3.<br>15. Updated to advise that the YTU will send patients randomised to the intervention group the yoga teacher's health questionnaire which the patient will be asked to take to their first yoga class. Sections 7.0 and 10.1.4 |
| Version 1.2<br>Date: 04.06.2019 | 1. Updated to advise that yoga teachers will share details of adverse events with YTU staff in section 15.1.1. |
| Version 1.3<br>Date: 23.09.2019 | 1. Lay summary amended to include that trial staff may be interviewed in section 2.3.<br>2. Exclusion criteria about returning a baseline questionnaire changed to match statement in summary table. Previous statement 'baseline questionnaire not returned' now states 'unable to complete and return a valid baseline questionnaire'. Both section 3.2.<br>3. Statement included to advise that we will also accept ticks in the boxes in place of initials on the participant consent forms in section 10.1.1. |

| | |
|---|---|
| | 4. Statement added to say that allocation will be revealed to a participant's GP in response to an adverse health event if necessary in section 10.1.5.<br>5. Interviews with trial participants: Clarification and timelines around the consent process for interviews in section 10.3.1.<br>6. Section 14.1 now includes a statement that study staff may be interviewed. The rest of this section requires details about the interviews and further details about interviews with the yoga teachers and participants.<br>7. The section on informed consent now includes a statement that we will accepts ticks or crosses or initials on the consent form. Also, further details are provided about consent for interviews. Both section 18.2. |

# STUDY SUMMARY

| | |
|---|---|
| **Lay Title** | Yoga for older adults with long-term medical conditions: The Gentle Years Yoga Trial |
| **Official Title** | Individually randomised controlled multi-centre trial to determine the clinical and cost-effectiveness of an adapted yoga programme for older adults with multimorbidity, including an embedded process evaluation. |
| **Study type and phase** | Non-CTIMP. Phase III |
| **Study design** | Pragmatic, multi-site, two-arm, parallel-group, individually-randomised controlled trial with internal pilot and economic and process evaluations |
| **Chief Investigator** | Associate Professor Garry Tew, University of Northumbria at Newcastle |
| **Study population** | Adults aged 65 years or over, community dwelling, with two or more chronic medical conditions |
| **Condition** | Two or more chronic conditions from a predefined list (see eligibility criteria below) |
| **Study groups** | Intervention and control |
| **Eligibility criteria** | **Inclusion criteria**<br>• Aged 65 years or older<br>• Community dwelling (inc sheltered housing living with support)<br>• Two or more chronic medical conditions from the following list:<br>○ Arthritis: including osteoarthritis, rheumatoid arthritis, and history of shoulder, hip or knee arthroplasty for arthritis<br>○ Asthma or chronic obstructive pulmonary disease (COPD)<br>○ Atrial fibrillation<br>○ A diagnosis of cancer within the last 5 years<br>○ Cardiovascular disease (CVD): including coronary heart disease (includes angina, and history of heart attack, bypass surgery or angioplasty) hypertension, heart failure, peripheral arterial disease<br>○ Chronic kidney disease<br>○ Dementia (only if participant retains capacity to provide written informed consent)<br>○ Depression or anxiety<br>○ Diabetes<br>○ Epilepsy<br>○ Fibromyalgia<br>○ Multiple sclerosis<br>○ Osteoporosis or osteopenia<br>○ Parkinson's disease<br>○ Sensory conditions: including hearing loss, macular degeneration, glaucoma<br>○ Stroke during the last 5 years<br>○ Bowel problems: including IBS, diverticulitis, inflammatory bowel disease |
| | **Exclusion criteria**<br>• Inability to attend one of the yoga courses on offer |

| | |
|---|---|
| | • Attended yoga classes twice a month or more in the previous 6 months<br>• Contraindication(s) to yoga participation (as identified by the patient's GP)<br>• Severe mental health problem (Schizophrenia, bipolar affective disorder or other psychotic illness)<br>• Learning disability<br>• Unable to read or speak English<br>• Unable to provide consent<br>• Unable to complete and return a valid baseline questionnaire<br>• Currently enrolled in another research study for which concurrent participation is deemed inappropriate (by GP or clinical co-investigator)<br>• No more than one patient per household |
| **Target number of participants** | 586 (293 in each group) |
| **Interventions** | Control and intervention groups: Will receive usual care which will comprise unrestricted care from primary, secondary, community and social services.<br><br>Intervention group: In addition, the intervention group will receive the offer of a 12-week Gentle Years Yoga (GYY) programme. The yoga programme will involve weekly group-based sessions and self-managed yoga practice. |
| **Criteria for evaluation** | **Primary outcome measure(s)**<br>Health-related quality of life measured using the EQ-5D-5L; the primary endpoint being the overall difference over 12 months. |
| | **Secondary outcome measure(s)**<br>Depression (PHQ-8), anxiety (GAD-7), PROMIS-29, loneliness (The ULCA 3-Item Loneliness scale and an additional item used in the English Longitudinal Study of Ageing (ELSA)), incidence of falls, adverse events and healthcare resource use including prescriptions. |
| | **Other outcome measure(s) if applicable**<br>A process evaluation will be conducted to explain determinants of delivery (including treatment fidelity), describe experience of intervention, and identify optimal implementation strategies for wider roll-out.<br><br>An economic evaluation will be undertaken from the perspectives of (a) NHS and personal social services (PSS) and (b) society. |
| | **Additional information collected**<br>Socio demographics; and, beliefs and preferences for the GYY programme and usual care.<br><br>Adherence to the intervention will be assessed using class registers. Treatment fidelity will be assessed via observation of a yoga session at each site, and through discussions with yoga teachers as part of the process evaluation. |

| | |
|---|---|
| **Embedded studies** | **Four methodological sub-studies:**<br>1. What is the concurrent validity of the PROMIS-29 with the EQ-5D-5L? [*NOTE: This SWAT is a non-randomised study. PROMIS-29 to be sent to all trial participants]*.<br>2. Does including £5 and/or a pen in the recruitment pack enhance recruitment?<br>3. Does sending a pen with a follow-up questionnaire enhance return rates?<br>4. Evaluation of a waiting list design: In the control arm, does offering a free session of yoga versus nothing after the 12-month follow-up assessment enhance retention and reduce contamination? |
| **Sources of funding** | NIHR Health Technology Assessment programme |
| **Start date:** | 1 January 2019 |
| **Anticipated finish date** | 31 December 2022 |

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| BWY | British Wheel of Yoga |
| CRF | Case Report Forms |
| DMC | Data Monitoring Committee |
| ELSA | English Longitudinal Study of Ageing |
| GAD-7 | Generalised Anxiety Disorder 7-item scale |
| GP | General Practitioner |
| GYY | Gentle Years Yoga |
| ISF | Investigator Site File |
| MD | Mean difference |
| NICE | National Institute for Health and Care Excellence |
| NIHR HTA | National Institute for Health Research Health Technology Assessment |
| PHQ-8 | 8-item Patient Health Questionnaire |
| PROMIS-29 | 29-item Patient-Reported Outcomes Measurement Information System |
| SE | Serious Event |
| SAE | Serious Adverse Event |
| SMD | Standardised mean difference |
| SMS | Short Message Service |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UCLA | University of California, Los Angeles |
| YTU | York Trials Unit |

# 1.0 Roles and Responsibilities

## 1.1 Chief Investigator responsible for the study

| |
|---|
| Associate Professor Garry Tew |
| **Phone:** 07773310360 |
| **Email:** garry.tew@northumbria.ac.uk |

## 1.2. Co-investigators (named funding applicants)

| | |
|---|---|
| Laura Bissell | Caroline Fairhurst |
| **Phone:** [To be inserted] | **Phone:** 01904 321513 |
| **Email:** laurabissell16@hotmail.com | **Email:** caroline.fairhurst@york.ac.uk |

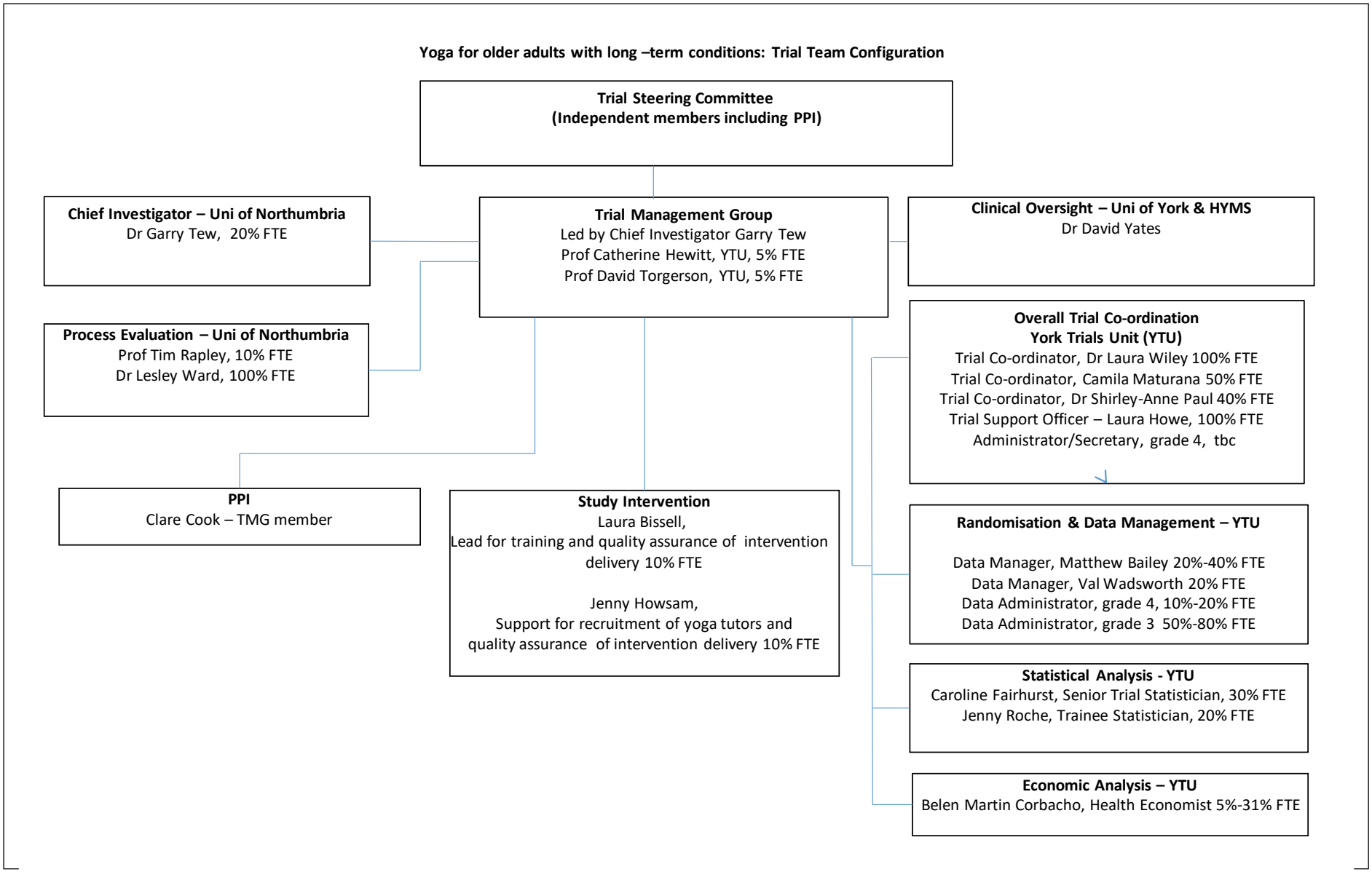
| | |
|---|---|
| Professor Catherine Hewitt | Jenny Howsam |
| Phone: 01904 321374 | **Phone:** 01405 860793 |
| Email: catherine.hewitt@york.ac.uk | **Email:** jenhowsam@hotmail.co.uk |

| | |
|---|---|
| Belen Corbacho Martin | Professor Tim Rapley |
| **Phone:** 01904 321852 | **Phone:** 0191 2156136 |
| **Email:** belen.corbacho@york.ac.uk | **Email:** tim.rapley@northumbria.ac.uk |

| | |
|---|---|
| Helen Tilbrook | Professor David Torgerson |
| **Phone:** 01904 321668 | **Phone:** 01904 321340 |
| **Email:** helen.tilbrook@york.ac.uk | **Email:** david.torgerson@york.ac.uk |

## 1.3 Trial Management

The Chief Investigator (GT) will have overall responsibility for the conduct of the trial. He will chair the Trial Management Group (TMG), which will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to, and take appropriate action to safeguard participants and the quality of the trial. The TMG will comprise the co-applicants, a member of the public, a clinician, and a representative of the British Wheel of Yoga (BWY). A Trial Steering Committee (TSC) will also monitor trial progress and conduct, and advise on scientific credibility. The TSC will comprise researchers, clinicians and patients who are independent of the investigators and who have expertise or knowledge relevant to the trial. It will meet at least every six months. The trial management and co-ordination, statistical evaluation, health economic evaluation, and data management will be conducted by staff in York Trials Unit (YTU), University of York. The process evaluation will be led by staff at the University of Northumbria (Figure 1). Laura Bissell and Jenny Howsam, the originators of the GYY programme, will oversee the delivery of the yoga intervention. Financial management will be undertaken through well-established systems at the Universities of Northumbria and York.


Yoga for older adults with long –term conditions: Trial Team Configuration
Trial Steering Committee
(Independent members including PPI)
Chief Investigator – Uni of Northumbria
Dr Garry Tew, 20% FTE
Trial Management Group
Led by Chief Investigator Garry Tew
Prof Catherine Hewitt, YTU, 5% FTE
Prof David Torgerson, YTU, 5% FTE
Clinical Oversight – Uni of York & HYMS
Dr David Yates
Process Evaluation – Uni of Northumbria
Prof Tim Rapley, 10% FTE
Dr Lesley Ward, 100% FTE
Overall Trial Co-ordination
York Trials Unit (YTU)
Trial Co-ordinator, Dr Laura Wiley 100% FTE
Trial Co-ordinator, Camila Maturana 50% FTE
Trial Co-ordinator, Dr Shirley-Anne Paul 40% FTE
Trial Support Officer – Laura Howe, 100% FTE
Administrator/Secretary, grade 4, tbc
PPI
Clare Cook – TMG member
Study Intervention
Laura Bissell,
Lead for training and quality assurance of intervention delivery 10% FTE
Jenny Howsam,
Support for recruitment of yoga tutors and quality assurance of intervention delivery 10% FTE
Randomisation & Data Management – YTU
Data Manager, Matthew Bailey 20%-40% FTE
Data Manager, Val Wadsworth 20% FTE
Data Administrator, grade 4, 10%-20% FTE
Data Administrator, grade 3 50%-80% FTE
Statistical Analysis - YTU
Caroline Fairhurst, Senior Trial Statistician, 30% FTE
Jenny Roche, Trainee Statistician, 20% FTE
Economic Analysis – YTU
Belen Martin Corbacho, Health Economist 5%-31% FTE

**Figu**

### 1.3.1 Contact Details

**York Trials Unit**
ARRC Building, Lower Ground Floor
University of York
Heslington
York
YO10 5DD

**Chief Investigator:** Associate Professor Garry Tew, garry.tew@northumbria.ac.uk

**Director of YTU:** Prof David Torgerson, david.torgerson@york.ac.uk

**Deputy Director of YTU & Senior Statistician:** Prof Catherine Hewitt, catherine.hewitt@york.ac.uk

**Clinical oversight:** Dr David Yates, drdavidyates@gmail.com

**Trial Coordinator:** Dr Laura Wiley, laura.wiley@york.ac.uk

**Trial Coordinator**: Dr Shirley-Anne Paul, Shirley.paul@york.ac.uk

**Trial Coordinator**: Camila Maturana, camila.maturana@york.ac.uk

**Trial Support Officer:** Laura Howe, laura.howe@york.ac.uk

**PPI TMG Representative:** Clare Cook, clare.cook8@btinternet.com

**Yoga intervention oversight:**
Laura Bissell, laurabissell16@hotmail.com
Jenny Howsam, jenhowsam@hotmail.co.uk

**Quantitative Analysis**
Caroline Fairhurst, caroline.fairhurst@york.ac.uk, Senior Statistician, YTU
Jenny Roche, jenny.roche@york.ac.uk, Trainee statistician, YTU

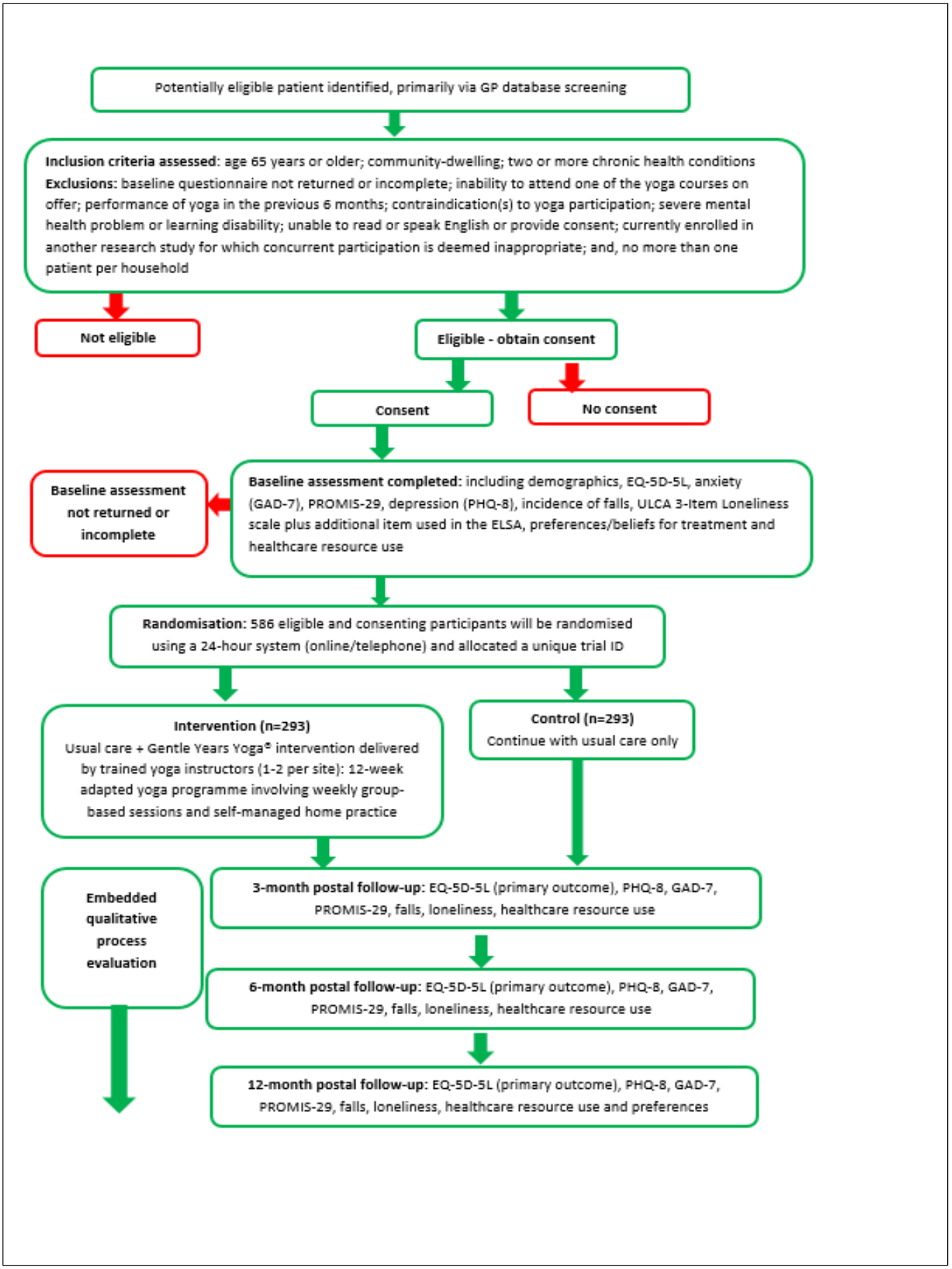
**Health Economic Evaluation**
Belen Corbacho, belen.corbacho@york.ac.uk, Health Economist, YTU

**Process Evaluation**
Prof Tim Rapley, tim.rapley@northumbria.ac.uk, Professor of Applied Health Research, Department of Social Work, Education & Community Wellbeing, University of Northumbria
Dr Lesley Ward, lesley.ward@northumbria.ac.uk, Research Fellow, University of Northumbria

**Trial Steering Committee**
Chair:
Prof Andrew Judge, Andrew.judge@bristol.ac.uk, Professor of Translational Statistics, University of Bristol

# 2.0 STUDY SUMMARY & SCHEMA

2.1 Participant Flow Diagram



## 2.2 Intervention & Assessment Schedule

| | | | | Month | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Recruitment | 1 month pre-randomisation | Randomisation | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Screening CRF | ✓ | | | | | | | | | | | | | | | |
| SWAT - £5 and/or a pen to be included in recruitment pack | ✓ | | | | | | | | | | | | | | | |
| Baseline CRF | | ✓ | | | | | | | | | | | | | | |
| Baseline collection of prescription data from GP records (max 100 participants) | | | ✓ | | | | | | | | | | | | | |
| Randomisation – Main trial | | | ✓ | | | | | | | | | | | | | |
| SWAT – half of control group randomised to be offered one-off class after 12-month follow-up | | | ✓ | | | | | | | | | | | | | ✓ |
| Intervention | | | | ✓ | ✓ | ✓ | | | | | | | | | | ✓ |
| Treatment fidelity conducted by Yoga Teacher Trainers | | | | ✓ | ✓ | ✓ | | | | | | | | | | |
| SWAT – The intervention group to be randomised to receive a pen in the 3-month follow-up pack | | | ✓ | | | ✓ | | | | | | | | | | |
| 3 months postal follow-up[1] | | | | | | ✓ | | | | | | | | | | |
| 6 months postal follow-up[1] | | | | | | | | | ✓ | | | | | | | |
| 12 months postal follow-up[1] | | | | | | | | | | | | | | | ✓ | |

| | | | | Month | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Recruitment | 1 month pre-randomisation | Randomisation | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| 12 month collection of prescription data from GP records (max 100 participants) | | | | | | | | | | | | | | | ✓ | ✓ |
| Participant diary to record health service use | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Qualitative interviews (trial participants – accepted randomisation)[2] | | | | ✓ | ✓ | ✓ | | | ✓ | | | | | | ✓ | |
| Qualitative interviews (trial decliners – declined randomisation)[3] | | | | ✓ | ✓ | | | | | | | | | | | |
| Qualitative interviews (instructors)[2] | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Observation (standardisation training sessions and yoga classes)[4] | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |

[1] Post-randomisation follow-up

[2] To be conducted on a sample of trial participants and yoga instructors. Individuals will be interviewed a maximum of two times

[3] To be conducted on a sample of trial decliners. Individuals will be interviewed once (within 2 months of declining)

[4] To be conducted on a sample of standardisation training sessions and yoga classes

## 2.3 Lay Summary

Multimorbidity is common in older adults, and associated with high levels of illness burden and healthcare expenditure. The evidence base for how best to manage older adults with multimorbidity is weak. Yoga might be a useful intervention because it is low cost, simple, and can address several health conditions simultaneously. The British Wheel of Yoga (BWY) Gentle Years Yoga (GYY) programme was developed for older adults with chronic conditions. A pilot trial of GYY demonstrated feasibility and provided encouraging preliminary effectiveness data. The current full-scale trial aims to answer the following research question: what is the clinical and cost effectiveness of the GYY programme plus usual care versus usual care only in community-dwelling older adults with multimorbidity?

We will conduct a randomised controlled trial with an internal pilot phase and nested process and economic evaluations. The project duration is 4 years. The yoga intervention will be delivered in non-medical community-based facilities in at least 12 sites across England, Wales and Scotland. We aim to recruit 586 participants primarily via mail-out from general practices. Eligible participants will be aged 65 years or over, community-dwelling, and have multimorbidity, defined as having two or more chronic conditions from a predefined list. Participants will be allocated to receive usual care and the offer of a 12-week GYY programme (n=293) or usual care only (n=293). The GYY programme will involve weekly group-based sessions and self-managed yoga practice on most days.

Outcome data will be collected at baseline, and 3, 6 and 12 months post-randomisation using postal questionnaires. If a participant is unable to complete the questionnaire or there are missing data, this may be collected by a researcher over the phone. The primary effectiveness endpoint will be the overall difference in quality of life over 12 months measured using the EQ-5D-5L. Secondary outcome measures will include depression, anxiety, activities of daily living, falls incidence, loneliness, adverse events, and healthcare resource use. Socio demographic data will be collected at screening and baseline. Preferences and beliefs for the yoga programme and usual care will be collected at baseline and at 12 months. Intervention adherence will be assessed using class registers. A subset of participants and yoga teachers will be interviewed to inform intervention implementation. A subset of trial staff may also be interviewed to inform intervention implementation.

# 3.0 Introduction

## 3.1 Background

Multimorbidity, defined as when a person has two or more long-term health conditions, is one of the biggest challenges facing health systems internationally as multiple disease care becomes the norm in an ageing society [1, 2]. It is highly prevalent in older adults, with one study showing 65% of adults aged 65-84 years to be multimorbid [3]. Multimorbidity leads to poorer health outcomes: it is associated with reduced life expectancy, quality of life and physical and mental wellbeing [4, 5]. Multimorbid individuals also consume a disproportionally large share of healthcare resources [6, 7].

The evidence base for enhancing the care of patients with multimorbidity is limited [8, 9]. A recent Cochrane review found only 18 RCTs worldwide evaluating interventions for improving outcomes in patients with multimorbidity in primary care and community settings [9]. In 12 studies, the interventions were primarily organisational, e.g. case management or addition of a pharmacist to the clinical care team. In the other six studies, the interventions were primarily patient-oriented, e.g. self-management support groups. Across all studies there was little or no difference in clinical outcomes (moderate certainty evidence), whereas mental health outcomes improved (high certainty). There was probably a small improvement in patient-reported outcomes (moderate certainty), and two studies that specifically targeted functional difficulties in participants showed positive effects on functional outcomes [10, 11]. There was limited data on costs. This review highlights the need for further research to determine the clinical and cost effectiveness of interventions that are ideally simple, generalisable, and which can address multiple health conditions simultaneously. Yoga is a candidate intervention.

Yoga originated thousands of years ago in India as an integrated physical, mental, and spiritual practice based on ancient Vedic philosophy. During the 20th century, yoga became increasingly recognised outside India, and over the past decades it has continued to grow in popularity worldwide as a system for promoting health and wellbeing. While modern yoga often focuses on physical poses and is sometimes thought of as a type of exercise, the practice usually incorporates one or more of the mental or spiritual elements that are traditionally part of yoga, such as relaxation, concentration, or meditation. For this reason, yoga is considered a mind-body practice. There are currently many different types or schools of yoga, each with a different emphasis on and approach to practice. It is thought that some of these yoga practices may help treat or prevent physical or mental illnesses, and improve overall quality of life [12].

In November 2017, the Cochrane Library published a special collection of 14 systematic reviews that focussed on the effectiveness of yoga for improving physical or mental symptoms and quality of life in a range of health conditions, including musculoskeletal, pulmonary, cancer, cardiovascular, neurological and mental health. A brief summary of four of these reviews follows:

- Yoga for chronic non-specific low back pain [13]: For yoga compared to non-exercise control (9 trials; 810 participants), there was moderate-certainty evidence that yoga produced small-to-moderate improvements in back-related function (SMD -0.44, 95% CI -0.66 to -0.22) and pain (MD -7.81, 95% CI -13.37 to -2.25) at 6 months. "There is a need for additional high-quality research to improve confidence in estimates of effect, to evaluate long-term outcomes…"
- Yoga for asthma [14]: There was some evidence that yoga may improve quality of life (MD in Asthma Quality of Life Questionnaire score per item 0.57 units on a 7-point scale, 95% CI 0.37 to 0.77; 5 studies; n=375) and symptoms (SMD 0.37, 95% CI 0.09 to 0.65; 3 studies; n=243), and reduce medication usage (risk ratio 5.35, 95% CI 1.29 to 22.11; 2 studies) in people with asthma. "RCTs with a large sample size and high methodological and reporting quality are needed to confirm the effects of yoga for asthma."
- Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer [15]: Seventeen studies that compared yoga versus no therapy provided moderate-quality evidence showing that yoga improved health-related quality of life (SMD 0.22, 95% CI 0.04 to 0.40; 10 studies, n=675), reduced fatigue (SMD -0.48, 95% CI -0.75 to -0.20; 11 studies, n=883) and reduced sleep disturbances in the short term (SMD -0.25, 95% CI -0.40 to -0.09; six studies, n=657). Investigators reported no serious adverse events. "…future trials should assess medium-term and long-term effects of the intervention."
- Yoga for primary prevention of cardiovascular disease [16]: Yoga was found to produce favourable changes in diastolic blood pressure (MD -2.90 mmHg), triglycerides (MD -0.27 mmol/l) and high-density lipoprotein cholesterol (MD 0.08 mmol/l). There was no clear evidence of a difference between groups for low-density lipoprotein cholesterol, although there was moderate statistical heterogeneity. Adverse events, occurrence of type 2 diabetes and costs were not reported in any of the studies. "No study reported cardiovascular mortality, all-cause mortality or non-fatal events, and most studies were small and short-term."

Elsewhere, studies have sought to determine the health benefits and harms of yoga in older populations specifically. For example, a 2012 systematic review of 16 studies (n = 649) [17] and a more recent trial of 118 participants [18] demonstrated that yoga may provide greater improvements in physical functioning and self-reported health status than conventional physical activity interventions in older adults. More recently, a systematic review of six trials (n=307) of

relatively high methodological quality reported that yoga interventions had a small beneficial effect on balance (SMD 0.40, 95% CI 0.15–0.65, 6 trials) and a medium effect on physical mobility (SMD 0.50, 95% CI 0.06–0.95, 3 trials) in people aged 60 and over [19].

In summary, the data presented above offers support for the beneficial effects of yoga in older adults and for several age-related health conditions. However, many of the previous studies had limitations, including small sample sizes, a single yoga teacher delivering the programme, and short-term follow-up. Robust economic evaluations of yoga are also limited, although a recent systematic review concluded that "medical" yoga is likely to be a cost-effective option for low back pain [20]. Of particular relevance is that very little research has specifically focussed on older adults with multimorbidity.

In 2009, the British Wheel of Yoga (BWY) Gentle Years Yoga© (GYY) programme was developed by the Yorkshire Yoga & Therapy Centre to cater specifically for the needs of people with age-related health conditions such as osteoarthritis, hypertension, and cognitive impairment. A standardised GYY teacher training programme has been manualised with quality-assured training courses being delivered by the BWY, which is the National Governing Body of Yoga with a nationwide network of 5,000+ qualified yoga teachers. GYY is based on standard Hatha Yoga, incorporating traditional physical poses and transitions as well as breathing exercises, meditation and relaxation. Adaptations to challenging Hatha Yoga poses have been made so that inactive older adults with multimorbidity can safely participate whilst still reaping the fitness, health and wellbeing benefits of yoga. Each programme involves one 75-minute group-based yoga session per week for 12 weeks and promotion of regular self-managed home yoga practice.

In a pilot trial of the GYY programme [21], 82 potential participants (community-dwelling inactive older adults) expressed an interest within a 2-month recruitment period, of which 52 (mean age 75 years) were recruited and randomised. Participants had up to 6 chronic health conditions, the most common of which were osteoarthritis, hypertension, and depression. The programme was delivered across 4 different community venues by yoga instructors who were specifically recruited and trained for the study. 67% of participants recorded acceptable attendance of 8 or more sessions (out of 10). Feasibility was demonstrated, with potential for a positive clinically important effect on health status (EQ-5D-5L utility score) at 3 months post-randomisation (MD 0.12, 95% CI 0.03 to 0.21). The current study is a much larger study over a wider geographical area to ascertain the clinical and cost effectiveness of the intervention in older adults with multimorbidity.

If demonstrated to be clinically and cost effective, this yoga programme should be feasible for widespread delivery within the NHS. The integration of yoga into the NHS is gradually happening already, championed by bodies such as the Yoga in Healthcare Alliance, with some areas of the UK offering staff yoga classes and yoga programmes for specific conditions (e.g. low back pain) [22]. A process evaluation will help identify optimal implementation strategies for embedding and normalising the programme beyond the study. The focus of this study is consistent with the current NIHR themed call on complex health and care needs in older people; specifically the part on testing interventions that are focussed on promoting healthy ageing and preventing ill health.

## 3.2 Rationale and justification for study

Multimorbidity is common in older adults, and associated with high levels of illness burden and healthcare expenditure. The evidence base for how best to manage older adults with multimorbidity is weak. Yoga might be a useful intervention because it is low cost, simple, and can address several health conditions simultaneously. However, many of the previous research studies on yoga have limitations, including small sample sizes, a single yoga teacher delivering the programme, and short-term follow-up. In addition, few studies have focussed on older adults with multimorbidity. We have successfully completed a pilot trial that demonstrated the feasibility and acceptability of the GYY programme in this population. The current full-scale trial will build on this previous work by evaluating the clinical and cost effectiveness of this intervention.

The research proposal was developed by an experienced group of applied health researchers and trialists, with the input of yoga experts and patient and public representatives. It has been reviewed and approved by the NIHR HTA Funding Board.

Justification for study design: A RCT with embedded economic evaluation is the optimal study design for quantifying the clinical and cost effectiveness of the intervention. The appropriateness of this design is supported by the feedback obtained from the NIHR Board and our PPI group, and the findings of our pilot RCT. All participants will have unrestricted access to usual care during the trial, so the participants allocated to the control condition will not have any existing NHS treatments withheld from them.

We will include people aged 65 years and over (no upper limit) who are community-dwelling, and who have two or more chronic conditions from a pre-specified list. In order to maximise generalisability of the study findings and avoid unfair exclusion, the exclusion criteria have been kept to a minimum. Therefore, the very elderly and people with several comorbidities will be included.

The exclusion criteria will be: unable to complete and return a valid baseline questionnaire. inability to attend one of the yoga courses on offer; performance of yoga in the previous 6 months (defined as twice per month or more); contraindication to participation (as identified by the patient's GP); severe mental health problem (e.g. Schizophrenia) or learning disability; unable to read or speak English or provide written informed consent; and participation in another trial for which concomitant participation is deemed inappropriate. Additionally, only one person in a household will be eligible to take part.

We expect the yoga intervention to be safe, and this will be supported by the use of yoga teachers who have good experience and training in adapting yoga activities to suit an individual's needs. Nevertheless, we will have a safety monitoring expert as part of the research team. The postal follow-up strategy poses minimal risk to participants.

We will adhere to the "Caldicott Principles" and General Data Protection Regulations in relation to the use of personal identifiable data.

# 4.0 Hypothesis and Objectives

## 4.1 Hypothesis

The Gentle Years Yoga programme plus usual care will improve the health-related quality of life of community-dwelling older adults with multimorbidity relative to usual care only.

## 4.2 Primary objective

To establish the effect of the Gentle Years Yoga programme plus usual care in patients with multimorbidity on health-related quality of life over 12 months from randomisation, measured using the EQ-5D-5L utility index score. The EQ-5D-5L will be assessed at baseline and 3, 6 and 12 months after randomisation.

## 4.3 Secondary objectives

- To establish the effect of the intervention on depression (PHQ-8), anxiety (GAD-7), loneliness (ULCA 3-Item Loneliness scale and an additional item used in the English Longitudinal Study of Ageing (ELSA)), and the incidence of falls at 3, 6 and 12 months
- To evaluate the safety of the intervention, relative to control, in terms of the occurrence of adverse events
- To establish whether the intervention is cost-effective, measured using differences in cost of health resource use between groups and the incremental cost effectiveness ratios using quality-adjusted life years derived from the EQ-5D-5L measured at 3, 6 and 12 months
- To explain determinants of implementation, describe experience of intervention, and identify optimal implementation strategies for embedding and normalising the yoga intervention in preparation for wider roll-out.

Internal pilot objectives:

- To assess whether the provision and acceptability of the intervention meet the predefined progression criteria thresholds, via the proportion of participants receiving their first yoga session within three weeks of randomisation and retention of intervention participants respectively.
- To assess whether recruitment and 6-month follow-up rates meet the pre-defined progression criteria thresholds, measured by recruitment and EQ-5D-5L completion data.

# 5.0 Study Design

A pragmatic, multi-site, two-arm, individually-randomised, controlled trial with an internal pilot with progression criteria, an embedded process evaluation and parallel cost-effectiveness evaluation. The trial also includes four embedded methodological studies.

# 6.0 Study Population

## 6.1 Setting and locations

The target population is patients with multimorbidity defined as having two or more chronic health conditions. Patients will be recruited from primary care and the community in at least 12 sites across England, Wales and Scotland. General practices will search patient databases using READ codes to identify potentially eligible patients who will be invited via mail-out. Local media advertising will also be used to recruit participants. We may also invite participants who meet the eligibility criteria and who have previously participated in trials coordinated by the York Trials Unit (YTU). The intervention will typically be delivered in a non-medical community-based facility (e.g. yoga centre, community hall, leisure centre). The study aims to recruit 586 participants (293 intervention and 293 control).

## 6.2 Eligibility criteria

### 6.2.1 Inclusion criteria

Patients will be eligible to join the study if they meet all of the following inclusion criteria:

- Aged 65 years or older
- Community dwelling (including sheltered housing living with support)
- Have two or more chronic health conditions from the following list:-
    - Arthritis: including osteoarthritis, rheumatoid arthritis, and history of shoulder, hip or knee arthroplasty for arthritis
    - Asthma or chronic obstructive pulmonary disease (COPD)
    - Atrial fibrillation
    - A diagnosis of cancer within the last 5 years
    - Cardiovascular disease: including coronary heart disease, hypertension, heart failure, peripheral arterial disease
    - Chronic kidney disease (CKD)
    - Dementia (only if patients have capacity to provide written informed consent)
    - Depression or anxiety
    - Diabetes
    - Epilepsy
    - Fibromyalgia
    - Multiple sclerosis
    - Osteoporosis or osteopenia
    - Parkinson's disease

- Sensory conditions: including hearing loss, macular degeneration, cataracts, glaucoma
- Stroke within the last 5 years
- Bowel problems: including IBS, diverticulitis, inflammatory bowel disease

### 6.2.2 Exclusion criteria

Patients will not be eligible for the study if they meet one of the exclusion criteria:

- Inability to attend one of the yoga courses on offer
- Attended yoga classes twice a month or more in the previous 6 months
- Contraindications to yoga participation (as identified by the patient's GP)
- Severe mental health problem (Schizophrenia, bipolar affective disorder or other psychotic illness)
- Learning disability
- Unable to read or speak English
- Unable to provide consent
- Unable to complete and return a valid baseline questionnaire
- No more than one patient per household
- Currently enrolled in another research study for which concurrent participation is deemed inappropriate (by GP or clinical co-investigator).

## 6.3 Withdrawal criteria

Participants may ask to withdraw from the study at any time without influencing their usual care or treatment. Participants who withdraw will not receive further follow-up but data already supplied will be retained and used in the analysis. Participants may also withdraw from receiving the intervention but may choose to remain in the trial for follow-up of data.

## 6.4 Participant replacement

Participants who withdraw from the study will not be replaced.

# 7.0 Intervention

## 7.1 British Wheel of Yoga Gentle Years Yoga© programme

The GYY programme is an adapted yoga programme for older people with chronic medical conditions. Each course involves twelve 75-minute, group-based classes (usually 1 class per week, but allowance for a gap if there is a holiday or teacher illness). The programme introduces participants to the foundational elements of yoga adapted appropriately for older adults, including *asana* (posture), *pranayama* (breath work), relaxation techniques, *dharana* (mental focus), and philosophy. Classes consist of an introduction to the weekly theme, joint mobilisation, pain-relieving or settling-in relaxing poses, a programme of seated and standing practices, educative postural advice, breath work, concentration activities, and 5–15 minutes of relaxation. After the class there is an opportunity for people to chat over refreshments. Postures target stiff, weak, and untrained areas of the whole body, with the intention of improving mobility, strength, balance and posture and reducing pain. Yoga teachers are specifically trained to appropriately modify the yoga classes to meet individual needs, ensuring that participants can always adopt a safe variation of the postures and sequences that will not compromise their health. Once the teachers are satisfied that the participants know how to adapt the exercises for their medical conditions, self-practice sheets are distributed and the participants are encouraged to practice selected yoga activities at home for 15 minutes each day. As the supervised work in class becomes progressively more challenging, students are given new information sheets to allow them to develop their home yoga routine.

The GYY programme is copyrighted by the British Wheel of Yoga and since 2017 has been providing training in GYY to qualified yoga instructors. Training takes place over approximately 12 months and covers the physiology of ageing and common chronic conditions, and how to modify yoga for different health states. After distance learning modules and face-to-face instruction, the instructors demonstrate their understanding through multiple choice questions, two case studies, designing and teaching a 10-week yoga plan for a GYY class, and being observed and assessed on their teaching of GYY sessions on two occasions.

To minimise inter-teacher variation and enhance fidelity, the yoga teachers in this trial will receive additional intervention standardisation training in interactive workshops. Training will be delivered in regional sessions by members of the study team with experience in delivering teacher training for the GYY programme. This additional training will be limited to a single workshop given the teachers'

prior training in GYY. Ongoing training and support will be provided as required, and will be documented. The training will include clinical reasoning for the GYY programme contents, strategies and practical delivery of the programme including intervention progression and when to hand out the personalised home practice sheets. It will also stress the importance of avoiding access to the intervention to control participants (usual care).

Participants will receive personalised GYY home practice sheets, which will provide details of underpinning yoga principles, monitoring, and progression, which GYY trained instructors will support the implementation of. Details of training provision, including content, attendance, duration, and training providers will be documented. In line with standard practice, the participants will be asked to complete the yoga teacher's Health Questionnaire which we will mail out with the randomisation letter. Participants will be asked to take this questionnaire along to their first yoga class. The Health Questionnaire is required so that the teachers are fully informed of participants' conditions which will enable them to tailor the yoga practice for the individual to ensure safety. The Health Questionnaire is also a policy requirement for the teacher's British Wheel of Yoga insurance. The Health Questionnaire will not be available to the research team for analysis. The yoga teachers will have access to an intervention supervisor who will also be one of the co-tutors on their GYY teacher training course. The intervention supervisors, who successfully oversaw the delivery of the pilot study's intervention in 2016, will be responsible for supporting intervention delivery and sharing of best practice.

## 7.2 Intervention group

The intervention group will receive usual care and the offer of a 12-week course of Gentle Years Yoga in a group class of around 10-15 participants and will be given a programme of yoga activities to perform at home for about 15 minutes each day.

## 7.3 Control group

The control group will receive usual care only. Usual care is defined as 'The wide range of care that is provided in a community whether it is adequate or not, without a normative judgment' [23]. Usual care will be provided by primary care, secondary care, community and social services and will be available to both intervention and control participants.

Also, following random allocation to the control group, the control group will be immediately randomised again and half will receive the offer of a single free session of Gentle Years Yoga after

final follow-up questionnaire has been completed (see section 12.3.2 for further details of this methodological sub-study).

# 8.0 Outcome Measures

## 8.1 Primary outcome measure

The EQ-5D-5L utility score, which will be assessed at baseline and 3, 6 and 12 months after randomisation; the primary endpoint being the overall difference over the 12 months.

## 8.2 Secondary outcome measures

EQ-5D-5L utility score at each of the individual time points (3, 6, and 12 months); depression (PHQ-8) at 3, 6, 12 months and overall, anxiety (GAD-7) at 3, 6, 12 months and overall, health-related quality of life (PROMIS-29) at 3, 6, 12 months and overall, loneliness at 3, 6, 12 months and overall (UCLA 3-Item Loneliness scale and direct loneliness question used in the ELSA), incidence of falls over the 12 months, adverse events, and healthcare resource use including prescriptions.

## 8.3 Other outcomes

Adherence to the intervention will be assessed using class registers. We will also ask participants to report any yoga practice in the follow-up questionnaires. Treatment fidelity will be assessed via observation of a yoga session at each site by the intervention supervisors Laura Bissell and Jenny Howsam and through discussions with instructors as part of the process evaluation.

An economic evaluation will be undertaken from the perspectives of (a) NHS and personal social services (PSS) and (b) wider perspective

A process evaluation will be conducted to explain determinants of trial delivery (including treatment fidelity), describe experience of intervention and identify optimal implementation strategies for wider roll-out. (See section 14 for further details)

## 8.4 Additional information collected

We will collect data on socio demographics; and, beliefs and preferences for the GYY programme and usual care.

## 9.0 Study Timeline

See Appendix 1

# 10.0 Methods and Assessments

## 10.1 Recruitment to main trial

We propose to recruit 586 participants. The main method of recruitment for the trial will be from general practice databases (approximately 36 GP practices) but we will also include other methods as required:

- placing advertisements in local media
- recruitment from patient networks
- inviting potentially eligible patients from previous studies that have been co-ordinated by YTU. We will target individuals who appear to match our eligibility criteria, are in the catchment area of one of the study sites, and who previously consented to being contacted about other studies.

Recruitment from GP database screening

Participating GP practices will search their databases using Read Codes. The research team will work with GP practices to identify Read Codes that can be used to conduct the search. Identified patients who appear to meet the inclusion criteria will be sent a recruitment pack, which will be made up by staff in the YTU and will include:

- a covering invitation letter (on GP headed paper if required)
- a participant information sheet (PIS; we will also refer participants to an audio recording of the PIS on the trial web-site)
- a consent form
- a screening questionnaire
- two prepaid envelopes
- a random sample of packs will also include £5 and/or a pen as part of the methodological sub-study testing strategies to aid recruitment (see section 12)

GP practices wishing to using Docmail (a third party information handler) to mail out the invitation packs to patients, will use a secure method of transfer to transfer details to Docmail. Docmail will produce the invitation packs according to YTU's specification.

For GP practices wishing to mail out the invitation packs themselves, the YTU will supply postage stamps to enable the GP practices to mail out the packs. GP practices will be required to place the stamps on the envelopes and to address the packs to the patients that they have identified as potentially eligible for the trial. GP practices will be given the option to place the invitation letter to

participants on their own letter headed paper. If this is not requested, the invitation will be on the University of York's letter headed paper.

Recruitment from advertisements in local media

Posters and flyers advertising the trial will be placed in the local media and/or participating and non-participating GP practices, other NHS sites and patient groups and societies. Patients wishing to take part will be asked to contact the YTU for a recruitment pack. The recruitment pack will include the same content as described above. In addition it will include a form for the patient to provide their GP's details.

Recruitment from previous trial participants

Potentially eligible patients that have previously taken part in other research in the YTU and who have given consent to be contacted about other research, will be sent an invitation letter from the YTU together with a recruitment pack.

### 10.1.1 Informed consent – main study

Patients who are interested in participating will be invited to complete the consent form and the screening questionnaire. If recruited via advertisement or participation in previous research they will also be asked to complete a GP details form. They will be asked to post the following to the YTU:

- the completed screening questionnaire in one of the supplied freepost envelopes
- the completed consent form in the other supplied freepost envelopes. Here, participants will be asked to initial boxes next to statements they agree to, but we will also accept ticks in the boxes in place of initials. We will accept crosses (i.e., X) where participants have consistently placed only crosses in boxes throughout the consent form (for example, if a participant has placed ticks in some boxes and crosses in others, we will not take a cross to mean the participant agrees, as they might be using ticks to say 'yes' and crosses to say 'no').
- the completed GP details form in the same envelope as the consent form (only patients recruited via the media and from previous trials will be asked to complete this form).

### 10.1.2 Screening

The screening questionnaire will seek to obtain the following information which will be used to assess the patient's eligibility: date of birth; residential status (community-dwelling or care home); participation in yoga in the past 6 months; current participation in other research studies; chronic conditions (using an adapted Bayliss measure of illness burden)[24]; and availability to attend one of the yoga courses on offer. Researchers at the YTU will review the screening questionnaire to determine if the patient is eligible to take part in the study.

If the patient is screened as eligible the YTU will write to the patient's GP with a copy of the patient's completed consent form to inform them that their patient has been screened as eligible to take part in the study. The GP will be asked to notify the YTU within a specified period (e.g. 14 days) if the patient should not be entered in to the study.

If the patient is screened as ineligible or the patient's GP notifies the YTU that the patient should not be entered in to the study, the YTU will write to the patient to inform them that they are unable to take part in the study.

### 10.1.3 Baseline

Eligible patients will be sent a copy of their completed consent form, a baseline questionnaire, and a freepost envelope addressed to the YTU. The baseline form will collect data on socio-demographics measures (gender, ethnicity, employment status, smoking status), primary and secondary outcome measures (including health care resource use), and preferences/beliefs for the treatments on offer in the trial. Patients will be advised that they need to return their completed baseline questionnaire in the freepost envelope by a specified date in order to take part. Patients who return a completed baseline questionnaire by the date specified will be entered in to the study and be eligible for randomisation. Patients who are ineligible at this stage will be informed by letter.

### 10.1.4 Randomisation

Participants will have indicated (in the screening questionnaire) their preference and availability for a particular course of Gentle Years Yoga. Once a sufficient number (ideally ≥20) of recruited participants have stated their availability for a particular class they will be randomised collectively using a bespoke randomisation database. Varying allocation ratios will be used to ensure that (no more than) 15 participants are allocated to the intervention group in any one randomisation wave. Ideally, 30 participants will be randomised 1:1 in each wave (15 to the intervention group, and 15 to control). Classes for which fewer than 30 participants express availability will have an allocation ratio favouring the intervention group; conversely, classes for which more than 30 participants express availability will have an allocation ratio favouring the control group.

All eligible participants will be sent a letter informing them of which group they have been randomised to and a participant diary to prospectively record health service use. If they have been randomised to the intervention group they will be sent details of the class that they should attend and the name of the yoga instructor. They will also be sent the yoga teacher's Health Questionnaire, which is in line with usual practice, and asked to complete and take this with them to their first yoga class.

Following randomisation, the research team at the YTU will provide the yoga instructors with the names and contact details of who will be attending their classes. They will require this information so that they can make appropriate arrangements to support intervention delivery, which may involve the instructors contacting the participants. The yoga classes should commence within 3 weeks of randomisation. The importance of intervention delivery timelines will be highlighted to the yoga teachers in the standardisation training, and the yoga participants in treatment allocation notifications.

For randomisation of participants to the methodological studies, see section 12

#### 10.1.5 Blinding

It will not be possible to blind participants or yoga instructors to group allocation. We have considered how knowledge of allocation status could influence participant and clinician behaviour change in relation to usual care, and have incorporated measures to limit these possibilities. We plan to interview a sample of intervention and control group participants to better understand provision of usual care across sites in the process evaluation, including whether knowledge of allocation status may have influenced participant behaviour.

Although GPs will be informed about study participation, they will not be informed about allocation status, reducing the risk of inducing GP behaviour change based on this knowledge. The wider health and social care team will not be informed about study participation or allocation status. However, allocation will be revealed to a participant's GP in response to an adverse health event if necessary.

Members of the research team collecting the outcome data over the phone will take reasonable steps to ensure that they are blind to the participant's treatment allocation. The method of primary data collection will be recorded (e.g. on paper by the participant or over the phone with a member of the research team). Participants receiving telephone assessments will be advised not to disclose their allocation.

## 10.2 Study visits and follow-up procedures

Participants randomised to the intervention group will receive the offer of 12 weekly yoga classes as described in sections 7.1 and 7.2. Classes will ideally commence in the week following randomisation, and preferably no more than three weeks after. All trial participants, at 3, 6 and 12 months after randomisation, will receive:

- a postal questionnaire collecting primary and secondary outcome measures (including health care resource use), to complete and return in a prepaid (freepost) envelope; at 12 months participants will also be asked about their preferences and beliefs for the treatments that are on offer in the trial;
- £5 with their questionnaire, as a thank you for their continuing participation in the trial;
- a text SMS 1 to 7 days before the questionnaire is sent to advise that they will shortly receive a questionnaire and to complete and return it as soon as possible (this also acts as a prompt for the participant to inform the research team if they have moved address). The text SMS will only be sent to participants who have consented to receive these forms of communication;
- a reminder letter if the questionnaire has not returned to the YTU 14-21 days after it was posted;
- a call from a member of the research team to request the questionnaire if the questionnaire has not been returned 28 days after it was posted. If during the call, the participant advises that they are unable to complete the questionnaire but agrees to provide the information over the phone, primary outcome data will be collected and other outcome data collected that the participant is willing to provide. If the questionnaire is returned to the YTU incomplete or with errors, we will phone participants for clarification or completion of missing data.

We may find that some participants require assistance with completing questionnaires. Therefore, at follow-up, we will advise in the covering letter to participants that they are able to phone a member of the research team if they require assistance who will be able to collect the outcomes over the phone.

We will ask GP practices to provide prescription data for a sample of participants (max n=100 in total) at:

- Baseline for the previous 3 months; and
- 12 months for the previous 12 months (the same sample of participants).

A participant newsletter containing information about trial progress and any relevant updates will be sent out to participants at regular intervals, e.g. every 3 – 6 months.

### 10.2.1 One-off yoga class: after 12 months post-randomisation

Participants in the control group who are randomised to receive the offer of a one-off group yoga class, will be sent a letter after the 12-month follow-up has been completed for all participants in the same geographical area inviting them to attend a yoga class run by a Gentle Years Yoga teacher on a date and time that will be specified in the letter. The yoga teachers will be informed of the names and contact details of trial participants who may attend their class.

### 10.2.2 Availability of Gentle Years Yoga after the trial

All participants will receive details of the nearest Gentle Years Yoga classes and/or Gentle Years Yoga teacher to enable them to attend a local class if they wish. (Our PPI group suggested this idea as they felt some patients may want the opportunity to attend yoga classes that would cater for their particular needs).

## 10.3 Recruitment to qualitative process evaluation

### 10.3.1 Interviews with trial participants

The consent form for the main study (see section 10.1) will contain optional statements about taking part in an interview. Participants can provide consent for:

- Main trial only,
- Main trial and an interview, or
- Interview only

Participants who indicate on the main trial consent form that they are willing to be approached to be interviewed and are chosen by the study team to be approached will be sent a separate, interview-specific Participant Information Sheet and Consent form by the Process Evaluation team within around one month after their main trial consent form being received. A team member will subsequently phone these participants within 10 days of sending these forms, to determine if they would like to take part in the interviews, and to arrange an interview if applicable.

### 10.3.2 Interviews with yoga teachers

Yoga teachers delivering classes to the trial participants will be invited for interview. They will be sent a Participant Information Sheet and Consent Form by the research team. Yoga teachers willing to take part will be asked to complete and return a signed consent form in a freepost envelope provided by YTU.

### 10.3.3 Class observations

For in-depth observations of selected yoga classes by a qualitative researcher; approximately, two weeks before the observation, all the trial participants in the class and the yoga teacher will be sent a Participant Information Sheet and Consent Form asking for their consent for the observation to take place. The yoga teacher and participants willing to be observed will be asked to complete and return a signed consent form in a freepost envelope provided by YTU. The yoga teacher will need to consent to the observation in order for it to take place. However, they will be given the option to decline. If the yoga teacher provides consent but only a proportion of the trial participants in the class provide consent, the observation will proceed but observation notes will only be made of trial participants who have provided consent to the observation.

### 10.3.4 Data sharing for the qualitative process

There will be exchange of personal patient data and yoga teacher data (i.e. name and contact details) between the research team in the YTU and researchers at Northumbria University who are conducting the interviews and observations. Transfer of data of participants and yoga teachers who have consented to take part in the interviews and observations will be by the University of York's DropOff service and the data file will be encrypted.

## 10.4 Intervention/Treatment Fidelity

Treatment fidelity will be assessed via observation of a yoga session at each site by the intervention supervisors (and co-applicants) Laura Bissell and Jenny Howsam. Consent will not be obtained for these observations.

## 11.0 Internal Pilot Study

The design of the internal pilot is based on that used in the NIHR-funded HERO trial: https://doi.org/10.1186/ISRCTN13927531.

The overall recruitment target is 586 participants across at least 12 sites over a total of 24 months. Site set-up will be staggered. The first six months of recruitment and intervention training will take place in 4 sites, and will form the internal pilot phase. Other sites will hopefully be set-up to commence recruiting after the internal pilot, giving a range of 18-24 months per site for recruitment. Data from participants in the internal pilot will be included in the main study analysis.

Descriptive statistics only will be used to evaluate the progression criteria for the four internal pilot sites. The progression criteria will assess the level of recruitment for each site, follow-up rates, and provision and acceptability of the intervention, and will inform study continuation beyond the internal pilot phase. The progression criteria will be assessed using a traffic light system of green (go), amber (review) and red (stop), as follows:

- Intervention provision (assessed 4 months after start of pilot intervention period):
    - Green: 3-4 sites offering their first group yoga session within 3 weeks of participant randomisation
    - Amber: 1-2 sites offering their first group yoga session within 3 weeks of participant randomisation
    - Red: 0 sites offering their first group yoga session within 3 weeks of participant randomisation
- Intervention acceptability (assessed 4 months after start of pilot intervention period)
    - Green: ≥80% retention of intervention participants
    - Amber: <80% but ≥65% retention of intervention participants
    - Red: <65% retention of intervention participants
- Recruitment (assessed at 6 months after start of internal pilot recruitment)
    - Green: 3-4 sites recruited ≥20 patients each within 4 months (based on number of participants needed to allow randomisation and formation of a yoga class)
    - Amber: 1-2 sites recruited ≥20 patients each within 4 months
    - Red: 0 sites recruited ≥20 patients each within 4 months
- Six month follow-up (assessed at 8 months after start of pilot intervention period)
    - Green: ≥80% completion of the EQ-5D-5L
    - Amber: <80% but ≥65% completion of the EQ-5D-5L
    - Red: <65% completion of the EQ-5D-5L

If any criteria are graded as amber, a rescue plan will be developed outlining steps to be taken to improve intervention provision, recruitment, retention and/or follow-up (as appropriate), and will be approved by the Trial Steering Committee before submission to the HTA. If all the progression criteria are failed (red), then the internal pilot will not progress to the definitive study. If the progression criteria are met by the end of the internal pilot then the study will continue and outcome data from participants in the internal pilot will be included in the main study analysis.

# 12.0 Methodological Studies

## 12.1 Concurrent validity of PROMIS-29

Research question: What is the concurrent validity of the PROMIS-29 (evaluated against the EQ-5D-5L)?

Both the EQ-5D-5L and PROMIS-29 will be delivered to all participants at baseline and 3, 6 and 12 months post-randomisation to the main study. The concurrent validity of the PROMIS-29 will be measured relative to the EQ-5D-5L to see how well this test compares to the well-established EuroQoL test. Correlation between the two measures will be calculated. Concurrent validity is demonstrated when a test correlates well with a measure that has previously been validated.

12.2 Incentives to enhance recruitment: a 2x2 factorial trial

Fundamental to health research is the testing of interventions through RCTs. Achieving high participation and retention of participants in RCTs has traditionally been difficult. Published data show that a minority of RCTs recruit successfully [25, 26]. Problems with trial recruitment can limit the internal and external validity of a study and the overall sample size and statistical power. There is therefore a need to develop and test interventions to improve recruitment and retention of participants. One method is to 'nest' trials of recruitment and retention interventions in ongoing randomised trials. Testing interventions in ongoing trials ensures causality of intervention effectiveness is assessed [27] and avoids limitations associated with testing in a quasi-randomised controlled trial, or non-randomised setting such as the feasibility of intervention implementation.

We shall embed a factorial trial into the main trial to test two interventions: financial incentives, and pens. Potentially eligible patients, mailed out to via the GP or cohort mailouts, will receive one of these, both or neither. Patients recruited via local media advertising will not be included in this embedded trial for logistical reasons since they are likely to be recruited in a more ad-hoc way.

**Objective of this methodological study**: To evaluate the effects of offering a small, unconditional financial incentive and/or a pen in the recruitment pack which is posted to potential trial participants, on recruitment rates.

### 12.2.1 Financial incentives to enhance recruitment

Financial incentives are often used to encourage individuals to take part in a trial. In the UK, the size of the incentive is generally modest for publicly-funded trials, generally in the order of £10-£20. There is evidence that providing a financial incentive improves recruitment. The Cochrane Methodology Review on recruitment interventions found that financial incentives increased recruitment by 4% (95% CI -1% to 8%) [28, 29]. However, there was inconsistency between the studies included in the meta-analysis and the confidence interval does leave open the possibility for reducing recruitment. Moreover, most of the studies included in the review used an incentive of £100, which is larger than that generally used in publicly-funded trials. There remains, therefore, uncertainty as to whether the intervention is one that should be widely used, or how much the incentive should be.

**Intervention**: £5 cash

### 12.2.2 Pen incentive to enhance recruitment

There is some evidence that using a pen as a nonmonetary incentive increases response rates and time to response for trial follow-up questionnaires [30, 31]. The theoretical basis underlying the use of pen incentives is that of *reciprocation*, where people feel obligated to respond with positive behaviour received, with positive behaviour in return [32-35]. In the context of trial recruitment, offering a potential participant a gift such as a pen may make the person more likely to take up the trial invitation to enrol. It is also possible that the convenience of having a pen to hand upon receipt of the invitation may increase the likelihood of the forms being completed. One trial in the U.S. embedded in an observational study, showed that including a pen with the study logo to a questionnaire mailed to women who had previously not responded significantly improved recruitment rates [36]. However to our knowledge, there have been no trials which have evaluated the impact of using a pen to increase recruitment.

**Intervention**: Pen printed with the trial or university logo

### 12.2.3 Method of random allocation in this factorial trial

Block randomisation using a block size of 4 will be used to generate an allocation sequence to assign recruitment packs 1:1:1:1 to one of four groups: no pen and no £5; £5 only; pen only; or pen and £5.

### 12.2.4 Outcome measures

The primary outcome is the proportion of embedded trial participants who are randomised into the GYY main trial. Secondary outcomes are:

a. proportion of participants who return a screening form;

b. time to return screening form.

The cost per participant recruited will be calculated for each intervention.

### 12.2.5 Sample size calculation

Due to financial restrictions, we anticipate involving a sample size of approximately 850 patients in this embedded factorial trial. This sample would give 80% power (two-sided $\alpha$=0.05) to detect a difference in recruitment rate of 4% (increase from 3% to 7%) for either of the interventions, relative to not receiving that intervention.

### 12.2.6 Analysis plan

Randomisation rates will be calculated for each intervention (pen and £5). A logistic regression model containing the two interventions will be performed. Adjusted odds ratios and corresponding 95% confidence intervals (CI) will be obtained from this model. The presence of an interaction between the two interventions will be tested by introducing the interaction term of the interventions into the logistic model. The proportion of participants who return a screening form will be similarly analysed. Time to return the screening form will be calculated as the number of days from the date the recruitment pack is sent out to the date it is returned. A Cox proportional hazards regression model containing the two interventions will be performed and hazard ratios and corresponding 95% CIs will be presented. For the time-to-event analysis, screening forms that are not returned will be treated as censored.

## 12.3 Incentives to enhance retention and reduce contamination

### 12.3.1 Offer of a one-off yoga class to enhance retention and reduce contamination

The main trial PIS will make patients aware that some participants in the control group will be randomised to receive a one-off yoga class. After randomisation to the main trial, participants allocated to the control group will be randomised again to receive: the offer of a one-off group yoga class which will take place when final follow-up is completed; or no offer. Participants randomised to receive the offer of a one-off class will be informed immediately after randomisation.

**Objective of this methodological study**: To evaluate the effects of offering a free yoga class versus nothing after the 12-month follow-up assessment on rates of retention and contamination in the control group participants.

**Intervention**: Offer of a free group yoga class

**Comparator**: No offer of a yoga class

**Method for allocating to intervention or comparator**

Simple 1:1 randomisation will be used to allocate control participants to receive, or not to receive, the offer of a free yoga session at the end of their participation in the trial.

**Outcomes**

Primary outcome: The proportion of participants in each group who return at least one questionnaire (3, 6 or 12 months).

Secondary outcomes: The proportion of participants who return all three questionnaires (3, 6 and 12 months), and the proportion of control participants who report use of Yoga throughout the trial follow-up.

**Sample size calculations**

All control participants in the host trial will be randomised into this embedded trial. Assuming that the embedded trial begins at the same time as the host trial and that the host trial recruits 586 participants, then the embedded trial will include 293 participants. This sample size would give us 80% power to detect an increase in the percentage of participants returning at least one questionnaire (3, 6 or 12 months) from 85% in the no offer arm to 95% in the offer arm.

**Analysis plan**

Binary data will be compared using logistic regression, time to response by a Cox proportional hazards model, and completeness of response by a linear regression model. All models will adjust for age, gender, and allocation for the factorial trial embedded at the recruitment stage (anyone not randomised into the factorial trial will be considered in the 'no pen and no £5' group).

### 12.3.2 Pen incentive to enhance retention

The background for this intervention is described in section 12.2.1.

**Objective of this SWAT**: To evaluate the effects of providing a pen with the 3-month follow-up questionnaire on retention rates.

**Intervention**: Pen printed with the trial or university logo

**Comparator**: The comparator would be standard practice for the host trial, i.e. no pen.

**Inclusion criteria**

All participants in the intervention arm of the host trial who are due to be sent their 3-month follow-up questionnaire will be included in this sub-study.

**Exclusion criteria**

Participants who withdraw from follow-up before their 3-month follow-up is due, or those who have already received their follow-up questionnaire prior to the start of the pen sub-study will be excluded.

**Outcome measures**

Primary outcome: The proportion of participants in each group who return the 3-month questionnaire.

Secondary outcomes: Time to response (length of time taken to return the questionnaire), completeness of response (the number of questions completed) and whether a reminder notice is required (number of participants requiring a reminder mailing divided by the number of participants who were sent a questionnaire).

**Sample size calculations**

Assuming that the embedded trial begins at the same time as the host trial, that the host trial recruits 586 participants, and that there is a 10% withdrawal rate prior to the 3-month time point, then the embedded trial will include 264 participants (132 in each arm). This sample size would give us 80% power to detect an increase in response rates from 80% in the no pen arm to 92% in the pen arm.

**Method for allocating to intervention or comparator**

Simple 1:1 randomisation will be used to allocate intervention participants to receive a pen with the 3-month postal questionnaire or to receive the questionnaire alone.

**Analysis plan**

Binary data will be compared using logistic regression, time to response by a Cox proportional hazards model, and completeness of response by a linear regression model. All models will adjust for age, gender, and allocation for the factorial trial embedded at the recruitment stage (anyone not randomised into the factorial trial will be considered in the 'no pen and no £5' group).

# 13.0 Economic Evaluation

## 13.1 Process and Analysis

The aim of the economic analysis will be to assess the cost-effectiveness of the GYY programme plus usual care compared with usual care alone. A detailed health economics analysis plan (HEAP) will be drawn up in advance of the analysis. Further details of this analysis are provided in section 17.3

# 14.0 Process Evaluation Research

The process evaluation focuses on three inter-related areas of work:

• The organisation of the trial processes (e.g. concerns about randomisation) and the intervention (e.g. willingness to undertake yoga). It is envisaged that this work will primarily be focused on during study set-up and internal pilot phases. A detailed action plan of any necessary changes will be developed in conjunction with the TMG and PPI representatives.

• The organisation of experiences of the yoga intervention over time, and where appropriate, the trial over time. This work will take place during intervention delivery and follow-up, and offer information around process outcomes, as well as used to inform post-trial implementation work.

• The organisation of the implementation of the yoga intervention beyond the life of the trial. This will include developing a toolkit, which draws on implementation strategies and associated resources to enable the effective embedding and normalising of the yoga intervention.

The process evaluation will be theoretically informed by Normalization Process Theory (NPT) [37, 38]. NPT considers factors that impact on the introduction, embedding and routinisation of interventions in four key areas: how people make sense of a new practice and compare it to existing practices (coherence); the willingness of people to sign-up and commit to the new practice (cognitive participation); the work, trusts, skills and resources required to undertake the practice (collective action); and activity undertaken to monitor, review, adapt and refine the practice and so sustain it over time (reflexive monitoring).

## 14.1 Study Design

This is a qualitative process evaluation drawing on interviews with trial participants, trial decliners, and yoga instructors, as well as observations of standardisation training sessions and yoga classes. A subset of trial staff may also be interviewed to inform intervention implementation.

### 14.1.1 Recruitment

We propose to recruit 18-20 trial participants, 3-4 trial decliners, and 10-12 trial yoga instructors. We may also recruit 1-5 trial staff. Numbers included are to give an indication of the amount of data to be collected, and to enable the study to be appropriately costed. Our sampling strategy is informed by our current and prior experience, our theoretical framework, and what we already know about the study context. In keeping with the principles of rigorous qualitative research, we will be responsive to the study context.

Participant Interviews: YTU will inform the process evaluation team when they receive a consent form from a trial participant or trial decliner who has specifically consented to be invited to take part in an interview. They will provide the names and contact details of the person, whether they have declined or accepted trial participation, and for those that have accepted, which study arm they have been allocated. The process evaluation team requires this information so that they can make appropriate sampling decisions and arrangements to conduct the interview. Not every person that consents will be invited to take part in an interview, and this is made clear to them in the trial PIS. If the process evaluation team decide to interview a participant, they will contact them by telephone to further discuss their participation. If the participant decides to take part in the interviews they will then be offered a choice of location and method (telephone; face to face) of interview.

Yoga Teacher Interviews: Trial yoga teachers will be sent a PIS and consent form and a prepaid envelope. Teachers will be purposively selected to obtain a representative sample of the trial sites (Northern England, Southern England, Scotland, and Wales). If the process evaluation team decide to interview a yoga instructor, they will contact them by telephone to further discuss their participation. They will then be offered a choice of location and method (telephone; face to face) of interview.

Observation: Participants will be sent an information sheet and consent form and a prepaid envelope at least two weeks prior to that meeting. There will be opportunity for them to ask questions prior to the yoga session, either through telephone or via email, as well as prior to the meeting starting. They will be asked to give written consent for the observation of the yoga session.

Trial staff Interviews: Purposively selected trial staff, representative of a range of trial roles, will be sent a PIS and consent form and a prepaid envelope. If they consent to being interviewed they will be contacted by telephone by the process evaluation team, to further discuss their participation. They will then be offered a choice of location and method (telephone; face to face) of interview.

### 14.1.2 Informed Consent

Informed consent procedures will ensure that participants understand that participation is entirely voluntary and that they can withdraw from the interviews or observation at any time without this affecting their trial participation or other medical treatment, and in the case of yoga instructors and trial staff, without this affecting their trial delivery role. Participants can participate in the trial

without participating in the process evaluation; yoga instructors and trial staff can be involved in trial delivery without participating in the process evaluation.

All individuals (participants, yoga instructors, and trial staff) will be asked to provide written informed consent to take part in interviews and observation prior to the start of any interview or observation session. Those participants taking part in two interviews will be asked for verbal reaffirmation of consent prior to the start of the second interview; the qualitative researcher will keep a record of verbal consent for these second interviews.

If a participant of the yoga session does not wish to participate in the observation the researcher would not make any notes about their participation in that session.

In order to respond to unexpected people attending a yoga session, the researcher will wish to be able to consider a staged approach to consent. In the situation where an unexpected member is attending the session, the researcher will be introduced to them at the start of the session. They will briefly introduce the study to them, explain what they are doing and the purpose of it, as well as providing the full written information. The researcher will seek their verbal consent to observe their part in the session. If they do not wish to take part the researcher would not make any notes about their participation. If they are happy for the observation to take place however, verbal consent will be sought, consenting to the observation. The researcher will contact that person in the next few days (at least 24 hours later) to check they still wish to participate, and to gain full written consent for the observation. If they did not wish to participate the researcher will destroy any notes taken regarding that participant in the previous observation.

### 14.1.3 Data Collection

Internal Pilot Phase – Participants: We will undertake interviews with recipients agreeing to (n≤10) and where possible those refusing (n≤4) trial participation. We will focus on trial processes (e.g. initial information provision; recruitment encounter; ideas and/or concerns about randomisation and consent) and the intervention (willingness to undertake yoga; concerns about impact on health and acceptability). Interviews will last between 20-40 minutes. Participants will be given the option to review their anonymised transcript of the interview and remove any data they do not wish to be used in analysis.

Internal Pilot Phase – Yoga Teachers: We will undertake qualitative interviews with yoga instructors at participating sites (n=4-6) during the internal pilot phase. We will focus on views of trial processes and provision of yoga sessions. Interviews will last between 40-60 minutes.

Internal Pilot Phase – Trial Staff: We may undertake qualitative interviews with trial staff (n=1-5) during the internal pilot phase. We will focus on views of trial processes and implementation. Interviews will last between 40-60 minutes.

Post-Pilot Phase – Participants: We will undertake interviews with recipients recruited to trial and providers to identify any areas for further refinement of trial processes and yoga intervention. Those recipients (n≤10) that already took part in interviews during the internal pilot phase (about initial experiences), will be approached at follow-up, at either six or twelve months, in order to understand their experiences of the yoga intervention over time. Additional recipients (n≤10) will also be approached, at various time points, and interviewed once, to understand their experiences of the intervention. They will be sampled to explore, refine or refute emergent issues and findings. Participants will be given the option to review their anonymised transcript of the interview and remove any data they do not wish to be used in analysis.

Post-Pilot Phase – Yoga Teachers: We will undertake qualitative interviews with yoga teachers at participating sites (n=6-8) to explore their experiences of trial delivery. Those that took part in interviews for Internal Pilot Phase (n=4-6) will also be approached for a follow-up interview, to explore changes in experience over time. Interviews will last between 30-45 minutes.

### 14.1.4 Data analysis

Data analysis will be on-going and iterative throughout the trial. Interviews will, with consent, be audio-recorded, transcribed verbatim and edited to ensure anonymity of respondent. Contemporaneous field notes from non-participant observation will be edited to ensure anonymity of participants. The analysis will be theoretically-informed by Normalization Process Theory ([39, 40] and will be conducted according to the standard procedures of rigorous qualitative analysis [41] including open and focused coding, constant comparison, memoing [42], deviant case analysis [43] and mapping [44]. We will undertake independent coding and cross checking and a proportion of data will be analysed collectively in 'data clinics' where the research team share and exchange interpretations of key issues emerging from the data.

## 14.2 Data Handling

The process evaluation will fully comply with the terms of the General Data Protection Regulation (GDPR) and Data Protection Act 2018. When participants have been recruited into the study and given informed consent they will be assigned a non-identifiable code and all data (paper and electronic) will use this code. Identifiable data (e.g. contact details) will be held on a separate database (i.e. will not be linked to any data) and will only be used to contact the participant about the study. Interviews will be digitally recorded and transcribed verbatim in order to ensure fidelity to the views of interview participants is retained in the analysis. In the event that any participant was to withdraw their consent, any of their existing interview data would be destroyed and would not be used in the analysis.

All data will be held on secure, password-protected University of Northumbria servers. The analysis will be undertaken by the process evaluation researchers and they will be the only members of the team who will have access to field notes, audio-recordings and anonymised interview transcripts. The analysis will take place on University computers at the University of Northumbria. The digital voice recordings will be destroyed at the end of the study. All other records will be retained in a secure archive setting for 10 years to facilitate future analysis and publication of the study material.

## 14.3 Ethical issues related to the process evaluation

While every precaution will be taken to preserve patient anonymity and confidentiality there will be limits to this. In the event that the researcher has concerns for the well-being of a participant or others, action would be taken to disclose concerns to a named contact (e.g. the participant's GP) though the researcher would speak to the participant about this first. If a participant were to disclose anything indicating unsafe practices or misconduct, they would be directed to follow the complaints procedures (in PIS).

## 14.4 Relationship between process evaluation and main trial

The process evaluation team will present anonymised emerging findings to the TMG and YTU on the potential determinants of trial set-up and recruitment. These might include site-specific issues, issues across multiple sites, or at the level of the organisation of the trial. We will work with the TMG, YTU and, where appropriate specific sites, to develop a plan of action. We will focus on aspects that are amenable to change. All feedback to trialists and instructors at sites will be supportive and constructive.

# 15.0 Adverse Event Reporting

## 15.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a trial participant which does not necessarily have a causal relationship with the treatment. This could include any unfavourable clinical sign or symptom, any new illness or disease, or the deterioration of an existing disease or illness.

Serious AE (SAE): Any untoward medical occurrence that: a) results in death; (b) is life threatening; (c) requires in-patient hospitalisation or prolongation of existing hospitalisation; (d) results in persistent or significant disability or incapacity; or (e) consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the aforementioned consequences. A planned hospitalisation for a pre-existing condition is not considered to be a serious adverse event.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Related Unexpected SAE: The National Research Ethics Service (NRES) defines related and unexpected SAEs as follows:

- 'Related' – that is, it resulted from administration of any research procedures; and
- 'Unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence.

### 15.1.1 Expected AEs/SAEs

Events such as falls and musculoskeletal injury represent possible (although unlikely) consequences of yoga practice that cannot be entirely avoided. Similarly, in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected. In recognition of this, events fulfilling the definition of an AE or SAE will not be recorded or reported in this study unless they are specified in this section or fulfil the definition of a Related and Unexpected SAE.

The following SAEs are expected within the study population and will be collected from date of consent until 12 months post-randomisation as follows:

- Death – researcher reported, via a check of survival status with the participants' GP if the participant does not respond to one of the follow-up questionnaires
- Falls resulting in hospitalisation – researcher reported via a telephone check with the participant if they indicate that they have experienced a fall on one of the follow-up questionnaires

As these events are expected within the study population they will not be subject to expedited reporting to the main Research Ethics Committee (REC), but will be reported annually to the REC (in routine annual progress reports) and reviewed by the TMG and TSC. Due to the low risk nature of this trial, the TSC will take on the role of the Data Monitoring Committee (DMC). The TSC and sponsor will immediately see all SAEs thought to be treatment related, and the TSC and TMG will see all SAEs not thought to be treatment related at the next scheduled meeting.

Planned hospitalisations and elective surgery unrelated to the intervention will be recorded but will not be reviewed by the TSC and TMG. Nor will they be reported to the main REC. Should any patient report being extremely anxious or depressed in the EQ-5D-5L, the Trial Manager or Trial Coordinator will report this to the patient's GP.

We will also record and report all non-serious adverse events that are deemed to be related to being in the study or to the trial intervention. Participants will be asked (in the randomisation notification letter and at follow-up) to contact the YTU if they experience and untoward medical occurrence that they think is related to the study. Yoga teachers will share details of any adverse events that occur in the yoga class with trial staff at York Trials Unit by e-mailing or phoning staff in the first instance.

### 15.1.2 Related and Unexpected SAEs – expedited reporting

All Related and Unexpected SAEs occurring from the date of consent up to 12 months post randomisation will be recorded on a SAE form by a member of the research team at YTU within 24 hours of the YTU becoming aware of the event. The following information will be collected: date of SAE; full details in medical terms with a diagnosis, if possible and applicable; its duration (start and end dates; times, if applicable); action taken; and outcome. Events will be followed up until the event has resolved or a final outcome has been reached, and a copy of the SAE form will be stored in the Trial Master File. All Related and Unexpected SAEs will be reviewed by the Chief Investigator and trial clinician and subject to expedited reporting to the Sponsor and the main REC by the YTU on behalf of the Chief Investigator within 15 days.

## 15.2 Reporting to External Bodies

Safety issues will be reported to the REC in the annual progress report. A summary of all events will also be reported to the TSC. Expedited reporting of events to REC and the Sponsor will be subject to current NRES guidance, YTU standard operating procedures and Sponsor requirements.

## 15.3 Responsibilities

In this study, the relatedness and expectedness of AEs will be determined by the Chief Investigator and the trial clinician. In the event of a disagreement between Chief Investigator and trial clinician, additional clinical opinion will be sought and the event upgraded or downgraded prior to reporting to the main REC.

The YTU is responsible for:

- Forwarding AEs to the Chief Investigator and trial clinician for review
- Completing and storing AE/SAE forms with input from the Chief Investigator and trial clinician
- Expedited reporting of Related and Unexpected SAEs to the REC and Sponsor within required timelines
- Checking the survival status of participants with GPs for those participants who do not respond to postal follow-up
- Checking the cause and outcome of falls with participants who report as having had a fall on a follow-up questionnaire
- Preparing annual safety reports to main REC and safety reports for the TSC and TMG.

The TSC are responsible for:

- Periodically reviewing safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.
- Consideration of study continuation in light of safety concerns, and taking appropriate action to escalate issues of concern.

# 16.0 Data Monitoring and Quality Assurance

## 16.1 Audits and inspections

The study may be subject to inspection by any of the funding organisations. The study may also be subject to inspection and audit by the University of Northumbria under their remit as sponsor.

## 16.2 Data quality assurance

The University of Northumbria at Newcastle is the legal sponsor for this study. The study will be fully compliant with the Research Governance Framework.

Data monitoring will be conducted within the YTU on an 'as-needed' basis and dependent on factors such as recruitment rate and any concerns. Audits of enrolment, participant retention and outcome assessment will be performed by a trial co-ordinator and/or monitor from YTU. Written reports will be produced for the TSC (TSC to take the role of the DMC) informing them of any corrective action that is required.

## 16.3 Data entry, data management and storage

Participants' contact details, baseline data and outcome data will be entered on an electronic databases held in the YTU. Consent forms and patient questionnaires (CRFs) will also be stored as hard copies.

Data entered onto a database will be stored on a private network protected by a firewall at the YTU at the University of York. Access to the database is restricted to trial staff by login and password. All paper records will be securely archived by the YTU in a separate storage facility within the University of York initially and then at an approved off-site location. The trial database will be securely archived for a minimum of 10 years on the YTU computer network with restricted access to YTU staff. Access to the archived data will be restricted to YTU staff and named individuals but will be retrievable at the request of the sponsor or investigators.

# 17.0 Statistical Consideration

## 17.1 Determination of sample size

Walters and Brazier [45] in a review paper of the EQ-5D-3L found a difference of 0.074 (mean) or 0.081 (median) to be a minimum clinically important difference (MCID) among a variety of patients, whilst McClure and colleagues found a difference of 0.063 (mean) or 0.064 (median) for the EQ-5D-5L using simulated data [46]. To be conservative, we took the lowest estimate (0.06) with an estimated standard deviation of 0.20 [21]. Accounting for loss to follow-up of 20%, we need to recruit and randomise 586 participants for the study to have 90% power (2p = 0.05).

Although this is an individually randomised trial, there is a possibility of potential clustering within the intervention arm by yoga class. If we assume an ICC of 0.04 and average class size of 13 in the intervention arm, then, with the proposed sample size we would still retain 83% power to detect the same magnitude of effect (ceteris paribus). In this calculation we considered the level of clustering at the yoga class level, rather than at the level of the yoga teacher, since we believe this will be the most influential level of clustering. Accounting for potential clustering within the intervention arm only leads to small reductions in power, which could potentially be recovered in the analysis of the repeated measures which is not currently accounted for in the sample size calculation.

## 17.2 Main Analysis

Statistical analyses will be described in detail in a Statistical Analysis Plan (SAP) drafted by the trial statisticians and will be signed off by the Chief Investigator in agreement with the TSC. Analyses will be conducted in accordance with YTU SOPs. This trial will be reported according to the CONSORT guidelines for clinical trials (http://www.consort-statement.org/). Baseline data will be summarised using descriptive statistics with no formal statistical comparisons of the baseline data undertaken. Analyses will be conducted using intention-to-treat with patient's outcomes analysed according to their original, randomised group irrespective of deviations based on non-compliance, unless otherwise stated.

### 17.2.1 Primary outcome analysis

The primary outcome will be analysed using a linear mixed model, including all available follow-up time points. The model will adjust for EQ-5D-5L at baseline and include as fixed effects: time point, trial arm, arm by time interaction and other important covariates. Patient (to account for the repeated measures) and site will be included as random effects. The overall difference between the two groups over the 12 months from randomisation will be the primary endpoint, but differences at

each time point will be extracted for secondary investigations aimed at determining the potential pattern of improvement. Adjusted mean differences will be presented with an associated 95% confidence interval (CI) and p-value. Different covariance patterns for the repeated measurements will be explored and the most appropriate pattern will be used for the final model. Data will be assumed missing at random. Model assumptions will be checked, and if they are in doubt transformations of the outcome data will be considered.

Analyses to account for possible clustering by yoga class will also be undertaken by including the class as a random effect, nested within treatment arm.

Complier average causal effect analyses for the primary outcome will be undertaken to explore the impact of non-compliance on treatment effect estimates. Three analyses are proposed. The first CACE analysis will be conducted on the data of participants who are fully compliant, defined as attendance of at least three of the first six sessions and at least three other sessions. The second CACE analysis will define compliance as attendance of one yoga session or more (i.e., any compliance), which will include participants who are fully and partially compliant. The final CACE analysis will include the number of sessions attended in its continuous form.

#### 17.2.2 Secondary outcome analysis

The PHQ-8, GAD-7, loneliness scale, and PROMIS-29 data will be analysed in the same way as described for the primary outcome. The number of falls experiences by participants over the 12 months will be analysed using a Poisson, or negative binomial, regression model.

The number and type of serious and non-serious adverse events will be summarised descriptively by randomised group.

## 17.3 Health economics analysis

Economic analyses will be described in detail in a Health Economics Analysis Plan (HEAP) drafted by the trial health economist and will be signed off by the Chief Investigator in agreement with the TSC. A cost-effectiveness analysis will be undertaken to evaluate the cost-effectiveness of the yoga intervention plus usual care compared with usual care alone. The primary analysis will be conducted using a NHS and personal social services perspective in accordance with NICE reference case standards [47]. The primary outcome for the economic analysis will be the additional cost per quality-adjusted life year using EQ-5D-5L data. The analysis will be conducted following an intention-to-treat approach and will cover a time horizon of one year (e.g. the length of trial follow-up).

Data on resource use and health outcomes will be collected during the trial using self-reported questionnaires at baseline, 3, 6 and 12 months. Costs components will comprise (i) primary and social care consultations (e.g. GP, nurse, occupational therapist, physiotherapy, mental health services and mindfulness therapy); (ii) hospital visits (e.g. inpatient episodes, outpatient visits and A&E admissions); (iii) and medications. An intervention form will be specifically designed for the trial to collect costs related to the yoga intervention (e.g. yoga teaching and equipment). We will also collect data on personal expenses (e.g. private treatments) and productivity losses that will be used for a secondary analysis on a societal perspective. Unit costs will be derived from established national costing sources such as NHS Reference Costs, PSSRU Unit costs of health and social care, and the British National Formulary. Unit costs will be multiplied by resource use to obtain a total cost for each patient. The EQ-5D-5L health states will be valued using the mapping function developed by van Hout et al. [48] using a UK-based social tariff according to a NICE position statement [49]. QALYs will be calculated by plotting the utility scores at each follow-up point and estimating the area under the curve [50].

For the analysis, regression methods will be used to allow for differences in prognostic variables. Incremental cost-effectiveness ratios and net-benefit statistics will be calculated. The pattern of missing data will be analysed and handled by means of multiple imputation [51]. Sensitivity analyses will be conducted to test the robustness of the results, including probabilistic sensitivity analysis. A cost-consequence analysis will also be conducted in order to capture the wider consequences of the yoga intervention in terms of the full breath of outcomes measured in the trial.

# 18.0 Regulatory Considerations

## 18.1 Ethical and research governance approval

We will seek ethics approval through the NHS Research Ethics Committee before the trial commences. The trial will also be reviewed by the University of York's Health Sciences Research Governance Committee. Before any site can enrol participants in the trial the site must HRA approval for the study.

The trial will be conducted to protect the human rights and dignity of the participant as reflected in the 1996 version of the Helsinki Declaration.

## 18.2 Informed consent

Main Study: Potential participants will receive an invitation letter along with a patient information sheet, screening questionnaire and a consent form for the main trial. Patients wishing to take part in the trial will be asked to read through the information sheet and complete and send the consent form to the YTU. Here, participants will be asked to initial boxes next to statements they agree to, but we will also accept ticks in the boxes in place of initials. We will accept crosses (i.e., X) where participants have consistently placed only crosses in boxes throughout the consent form (for example, if a participant has placed ticks in some boxes and crosses in others, we will not take a cross to mean the participant agrees, as they might be using ticks to say 'yes' and crosses to say 'no').The patient information sheet will give the details of the research team members that they can contact if they have any questions.

The original main trial consent form will be kept by the trial team in the YTU, one copy will be posted to the trial participant and another copy will be sent to the participant's GP.

Interviews – trial participants: On the consent form for the main study, patients will be given the option to indicate if they are willing to take part in an interview. Patients can also indicate that they are willing to take part in an interview only and not the main study. A sample of patients indicating that they are willing to take part in an interview will be sent an information sheet and consent form specifically about the interviews, detailing what would be involved. Participants who are willing to take part in the interview, will be asked to provide written informed consent for the interviews prior to the interviews being conducted.

Interviews – yoga teachers: Yoga teachers will be sent a consent form and information sheet about the interviews being conducted by the process evaluation team. Yoga teachers who wish to give consent will be asked to provide written informed consent prior to the interviews being conducted.

A copy of the consent form for the interviews with trial participants and yoga teachers will be kept by the trial team in the YTU and a copy provided to the participant.

Observations (participants in the intervention group only): A consent form and an information sheet about observations that will made for the process evaluation will be given to all participants allocated to a class that is to be observed. Participants who agree to take part in the observation will be asked to provide written informed consent prior to the class observation. If some participants in the class do not provide consent, the observation will take part but notes will not be made about non-consenting participants.

Observations (yoga teachers): A consent form and an information sheet about observations for the process evaluation will be given to the yoga teachers in the trial. Yoga teachers who wish to consent will be asked to provide written informed consent prior to the class observation. If a yoga teacher does not provide consent then their class will not be observed.

A copy of the consent form for the observation of the yoga teachers and trial participants will be kept by the trial team in the YTU and a copy provided to the participant.

## 18.3 Confidentiality of data and patient records

Data will be handled in accordance with the Data Protection Act 2018 and GDPR legislation.
Some trial data including participants contact details, random allocation, yoga class details will be stored on the password protected trial database held by YTU to enable mail out of questionnaires and other trial related correspondence, and to manage yoga class attendance. The data will be accessed by the Trial Team in the YTU and the qualitative researcher at the University of Northumbria. Follow-up outcome data and baseline data to be used in the trial analyses will be identified only by a unique reference number and will be stored in a separate password protected database so that outcome data is anonymised.

Docmail which may be used by some or all of the GP practices for mailing out invitations to patients are also bound by the same GDPR leglislation. Docmail will be information handlers, and not information processors in the context of this trial, and patient data will be securely transferred from GP practices to Docmail using a password protection system.

Yoga teachers delivering the intervention will be given the names and contact details of patients randomly assigned to their classes and patients randomly allocated to the one-off class 12 months after randomisation. (We will obtain consent from trial participants to do this in the main consent form). Information will be transferred in an encrypted file via the University of York's DropOff system or via registered mail. Yoga teachers will send class registers to the YTU using the same methods. In the intervention standardisation training yoga teachers will be given advice on storing and transferring information in line with Data Protection legislation.

For the qualitative study, all personal identifiers will be removed from interview transcripts and observation field notes.

## 18.4 Potential risks and benefits

Potential adverse events associated with participating in yoga: cardiovascular event, musculoskeletal injury. The likelihood based on experience and previous research is very low [52].

Measures taken to minimise risk include exclusion of high-risk patients; all yoga sessions will be taught by an experienced teacher; gentle warm-ups at the start of each class include performance of joint mobilisation activities; and activities in the class with be adapted to meet individual needs.

Risk is related to the disclosure of identifiable data: patients will be asked to return their consent form containing their contact details in a separate envelope from their eligibility questionnaire which will contain medical information. Two prepaid envelopes will be provided and in the Patient Information Sheet we will ask patients to send the consent form and eligibility questionnaire to the YTU in separate envelopes

All participant data used by the Trial Team will be kept strictly confidential, in accordance with the Data Protection Act 2018 and GDPR legislation.

## 18.5 Indemnity

The University of Northumbria at Newcastle will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the management of the research. The University of Northumbria at Newcastle will provide indemnity and compensation in the event of a claim by, or on behalf of participants for negligent harm as a result of the study design and/or in respect of the protocol authors/research team. The University of Northumbria at Newcastle will provide indemnity with regards to the conduct of the research.

# 19.0 Trial Oversight

## 19.1 Trial Management Group (TMG)

The Chief Investigator, Garry Tew, will be supported by trial coordinators and other Investigators namely the co-applicants, a clinician, a patient representative, and a British Wheel of Yoga representative. Data managers and the trial coordinators will establish systems of data collection and data checks as well as data monitoring. Tim Rapley will oversee the process evaluation of the trial. Tim Rapley and a researcher, who will conduct the majority of the process evaluation aspect of the trial, will be members of the TMG. The main worker conducting the health economic analysis is a co-applicant and will also be a member of the TMG. The TMG will generally meet on a monthly basis but more frequently or less frequently as the trial requires.

## 19.2 Trial Steering Committee (TSC)

The TMG will be supported by the Trial Steering Committee (TSC).

The TSC will be made up of an independent chair Professor Andrew Judge and other independent members including two patient representatives. The Chief Investigator, trial manager and/or trial co-ordinator and trial statistician will present updates to the TSC. Other members of the TMG may join TSC meetings from time to time to provide updates as required.

Members of the TSC will provide input and advice on the trial design, will assist with modifications to the study protocol and will monitor and provide overall supervision for the trial. The TSC will meet approximately every 6 months but more often if required.

Members will be required to sign up to the remit and conditions as set out in the TSC charter.

## 19.3 Data Monitoring Committee (DMC)

The TSC has agreed to take on the role of the DMC. As this is a low risk 'open' study a separate DMC, which would have a role in looking at unblinded data, is, we believe, not necessary. Instead, we propose that independent members of the TSC meet separately with the study statistician, to discuss emerging data with a particular reference to any issues affecting participant welfare.

## 20.0 User and Public Involvement

Most of the participants in the pilot continued in the classes on a self-pay basis after the pilot ended, which confirmed that they found the programme to be of value. They have been actively involved (participating in a focus group) in this trial's plans and they are committed to continuing their support and help with this study. One of the pilot trial participants, Clare Cook, is a member of the TMG and two other participants are members of the TSC.

## 21.0 Publications

The study protocol and results will be reported and disseminated in the HTA final report and a peer reviewed journal for publication. The trial results, whether negative or positive, will be disseminated using peer reviewed publications and presentations. The final trial paper will be submitted to a peer-reviewed journal within 12 months of the results being available to the study team. The anonymised dataset for the quantitative analysis will be available to external researchers three years after the trial end via the lead investigators.

Care will be taken to ensure no participant is identified on any publications. The names of participants or any other identifying details will not be used when publishing quotes from qualitative research.

We will produce a short summary of the results of the study which can be distributed to trial participants and participating sites.

## 22.0 Retention of Trial Documents

Essential trial documentation (i.e. documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced) will be kept with the electronic Trial Master File. Hard copy questionnaires and consent forms will be stored separately and in a secured area in locked cabinets. There will be notes in the e-TMF to say where hard copies are stored. The documents will be retained for a minimum of 10 years after completion of the trial in order to comply with standards of Good Clinical Practice. All electronic records will be stored on a password protected server.

The digital voice recordings, obtained for the process evaluation research, will be destroyed at the end of the study. The anonymised transcripts will be retained in a secure archive setting for five years after the end of the study to facilitate future analysis and publication of the study material.

## 23.0 Study Closure/Definition of End of Trial

The end of the study is defined as the date when the last randomised participant has attended the one-off yoga class offered to the control group.

The trial will be stopped early if:

- Funding for the trial ceases
- The Trial Steering Committee recommends it
- It is mandated by the Research Ethics Committee, University of York's Research Governance, or the sponsor.

## 24.0 References


1. Mangin, D., I. Heath, and M. Jamoulle, *Beyond diagnosis: rising to the multimorbidity challenge.* BMJ, 2012. **344**: p. e3526.
2. Goodwin, N., et al., *Providing integrated care for older people with complex needs Lessons from seven international case studies*. 2014, King's Fund: London.
3. Barnett, K., et al., *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study.* Lancet, 2012. **380**(9836): p. 37-43.
4. Wolff, J.L., B. Starfield, and G. Anderson, *Prevalence, expenditures, and complications of multiple chronic conditions in the elderly.* Arch Intern Med, 2002. **162**(20): p. 2269-76.
5. Salisbury, C., et al., *Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study.* Br J Gen Pract, 2011. **61**(582): p. e12-21.
6. McPhail, S.M., *Multimorbidity in chronic disease: impact on health care resources and costs.* Risk Manag Healthc Policy, 2016. **9**: p. 143-56.
7. Eckardt, M., et al., *Analysis of Health Care Costs in Elderly Patients with Multiple Chronic Conditions Using a Finite Mixture of Generalized Linear Models.* Health Econ, 2017. **26**(5): p. 582-599.
8. Excellence, N.I.o.H.a.C., *NICE guideline [NG56]. Multimorbidity: clinical assessment and management*. 2016.
9. Smith, S.M., et al., *Interventions for improving outcomes in patients with multimorbidity in primary care and community settings.* Cochrane Database Syst Rev, 2016. **3**: p. CD006560.
10. Garvey, J., et al., *OPTIMAL, an occupational therapy led self-management support programme for people with multimorbidity in primary care: a randomized controlled trial.* BMC Fam Pract, 2015. **16**: p. 59.
11. Gitlin, L.N., et al., *A randomized trial of a multicomponent home intervention to reduce functional difficulties in older adults.* J Am Geriatr Soc, 2006. **54**(5): p. 809-16.
12. Woodyard, C., *Exploring the therapeutic effects of yoga and its ability to increase quality of life.* Int J Yoga, 2011. **4**(2): p. 49-54.
13. Wieland, L.S., et al., *Yoga treatment for chronic non-specific low back pain.* Cochrane Database Syst Rev, 2017. **1**: p. CD010671.
14. Yang, Z.Y., et al., *Yoga for asthma.* Cochrane Database Syst Rev, 2016. **4**: p. CD010346.
15. Cramer, H., et al., *Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer.* Cochrane Database Syst Rev, 2017. **1**: p. CD010802.
16. Hartley, L., et al., *Yoga for the primary prevention of cardiovascular disease.* Cochrane Database Syst Rev, 2014(5): p. CD010072.
17. Patel, N.K., A.H. Newstead, and R.L. Ferrer, *The effects of yoga on physical functioning and health related quality of life in older adults: a systematic review and meta-analysis.* J Altern Complement Med, 2012. **18**(10): p. 902-17.
18. Gothe, N.P. and E. McAuley, *Yoga Is as Good as Stretching-Strengthening Exercises in Improving Functional Fitness Outcomes: Results From a Randomized Controlled Trial.* J Gerontol A Biol Sci Med Sci, 2016. **71**(3): p. 406-11.
19. Youkhana, S., et al., *Yoga-based exercise improves balance and mobility in people aged 60 and over: a systematic review and meta-analysis.* Age Ageing, 2016. **45**(1): p. 21-9.
20. Andronis, L., et al., *Cost-Effectiveness of Non-Invasive and Non-Pharmacological Interventions for Low Back Pain: a Systematic Literature Review.* Appl Health Econ Health Policy, 2017. **15**(2): p. 173-201.
21. Tew, G.A., et al., *Adapted yoga to improve physical function and health-related quality of life in physically-inactive older adults: a randomised controlled pilot trial.* BMC Geriatr, 2017. **17**(1): p. 131.

22. Mason, H., N. Schnackenberg, and R. Monro, *Yoga and Healthcare in the United Kingdom.* Int J Yoga Therap, 2017. **27**(1): p. 121-126.
23. Smelt, A.F., et al., *How usual is usual care in pragmatic intervention studies in primary care? An overview of recent trials.* Br J Gen Pract, 2010. **60**(576): p. e305-18.
24. Bayliss, E.A., J.L. Ellis, and J.F. Steiner, *Seniors' self-reported multimorbidity captured biopsychosocial factors not incorporated into two other data-based morbidity measures.* Journal of Clinical Epidemiology, 2009. **62**(5): p. 550-557.e1.
25. Bower, P., S. Wilson, and N. Mathers, *how often do UK primary care trials face recruitment delays?* Family Practice, 2007. **24**(6): p. 601-603.
26. McDonald, A.M., et al., *What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies.* Trials, 2006. **7**(1): p. 9.
27. Bowling, A., *Research methods in health: investigating health and health services*. 2014: McGraw-Hill Education (UK).
28. Treweek, S., et al., *Strategies to improve recruitment to randomised controlled trials.* The Cochrane Library, 2010.
29. Treweek, S., et al., *Strategies to improve recruitment to randomised trials.* Cochrane Database of Systematic Reviews, 2018(2).
30. Brueton, V., et al., *Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis.* BMJ open, 2014. **4**(2): p. e003821.
31. Bell, K., et al., *Enclosing a pen reduced time to response to questionnaire mailings.* Journal of clinical epidemiology, 2016. **74**: p. 144-150.
32. Gouldner, A.W., *The norm of reciprocity: A preliminary statement.* American sociological review, 1960: p. 161-178.
33. Cialdini, R.B., et al., *Reciprocal concessions procedure for inducing compliance: The door-in-the-face technique.* Journal of personality and Social Psychology, 1975. **31**(2): p. 206.
34. Regan, D.T., *Effects of a favor and liking on compliance.* Journal of experimental social psychology, 1971. **7**(6): p. 627-639.
35. Falk, A. and U. Fischbacher, *A theory of reciprocity.* Games and economic behavior, 2006. **54**(2): p. 293-315.
36. White, E., P.A. Carney, and A.S. Kolar, *Increasing response to mailed questionnaires by including a pencil/pen.* American journal of epidemiology, 2005. **162**(3): p. 261-266.
37. May, C. and T. Finch, *Implementing, Embedding, and Integrating Practices: An Outline of Normalization Process Theory.* Sociology, 2009. **43**: p. 535-554.
38. May, C.R., et al., *Evaluating complex interventions and health technologies using normalization process theory: development of a simplified approach and web-enabled toolkit.* BMC Health Serv Res, 2011. **11**: p. 245.
39. May, C. and T. Finch, *Implementing, embedding, and integrating practices: an outline of normalization process theory.* Sociology, 2009. **43**(3): p. 535-554.
40. May, C.R., et al., *Evaluating complex interventions and health technologies using normalization process theory: development of a simplified approach and web-enabled toolkit.* BMC health services research, 2011. **11**(1): p. 245.
41. Rapley, T., *Some Pragmatics of Qualitative Data Analysis*, in *Qualitative Research: Theory, Method and Practice*. 2017, SAGE Publications Ltd. p. 273-290.
42. Glaser, B.G., *The constant comparative method of qualitative analysis.* Social problems, 1965. **12**(4): p. 436-445.
43. Seale, C., *Quality in qualitative research.* Qualitative inquiry, 1999. **5**(4): p. 465-478.
44. Charmaz, K., *Constructing grounded theory: A practical guide through qualitative analysis*. 2006: Sage.
45. Walters, S.J. and J.E. Brazier, *Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D.* Qual Life Res, 2005. **14**(6): p. 1523-32.

46. McClure, N.S., et al., *Instrument-Defined Estimates of the Minimally Important Difference for EQ-5D-5L Index Scores.* Value Health, 2017. **20**(4): p. 644-650.
47. Excellence, N.I.f.H.a.C., *Guide to the methods of technology appraisal*. 2013.
48. van Hout, B., et al., *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets.* Value Health, 2012. **15**(5): p. 708-15.
49. Excellence, N.I.f.H.a.C., *Position statement on use of the EQ-5D-5L valuation set*. 2017.
50. Billingham, L.J., K.R. Abrams, and D.R. Jones, *Methods for the analysis of quality-of-life and survival data in health technology assessment.* Health Technol Assess, 1999. **3**(10): p. 1-152.
51. Manca, A. and S. Palmer, *Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials.* Appl Health Econ Health Policy, 2005. **4**(2): p. 65-75.
52. Cramer, H., T. Ostermann, and G. Dobos, *Injuries and other adverse events associated with yoga practice: A systematic review of epidemiological studies.* Journal of Science and Medicine in Sport, 2018. **21**(2): p. 147-154.

# Appendix 1: Gantt Chart - Timelines